NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Eribulin for treating locally advanced or metastatic breast cancer after two or more prior chemotherapy regimens [ID964]

FAD Committee papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Eribulin for treating locally advanced or metastatic breast cancer after two or more prior chemotherapy regimens [ID964]

Contents:

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

Pre-meeting briefing
Eribulin for treating locally advanced or metastatic breast cancer after two or more prior chemotherapy regimens

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

List of abbreviations	
AE	Adverse event
CI	Confidence Interval
CR	Complete response
ER	Oestrogen receptor
ERG	Evidence Review Group
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health Related Quality of Life
ICER	Incremental cost-effectieness ratio
ITT	Intention to treat
LABC	Locally advanced breast cancer
MA	Marketing Authorisation
MBC	Metastatic breast cancer
ORR	Overal response rate
OS	Overall survival
PaR	Partial Response
PFS	Progression-free survival
PPS	Post-progression survival
QALY	Quality-adjusted life year
SMPC	Summary of Product Charactersitics
TPC	Treatment physician's choice

Key decision points

- Is there a high unmet medical need? What are the current options for this population?
- Are the results of the EMBRACE trial generalisable?
- Is the comparator TPC (Treatment physician's choice) used by the company appropriate?
- Is it appropriate to focus on Subgroup 2 of the company submission (previously treated with at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine) or is the ITT population of EMBRACE trial more relevant to the current appraisal?
- What is the Committee's view on the issues around cost-effectiveness?
  - Utility values (mapping algorithm, sources and utility value for progressive disease)
  - Dose calculations for eribulin
  - Administration costs post 6 months treatment
  - Cost calculations for the comparators
  - Cost calculations for subsequent lines of therapy
- What is the most plausible ICER?
- Does eribulin fulfil the end of life criteria?

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Background

- In their submission, the company separated the population of the scope into two subgroups:
  - Subgroup 1: HER2-negative patients with locally advanced or metastatic breast cancer (LABC/MBC), whose disease has progressed after **one prior** chemotherapy regimen in the advanced setting.
  - Subgroup 2: Patients with LABC/MBC whose disease has progressed after at least **two prior** chemotherapeutic regimens for advanced disease **which includes capecitabine** (if indicated).

- The current appraisal will focus on the **review of TA250**, and will consider a population of people with 'locally advanced or metastatic breast cancer that has progressed **after two or more prior** chemotherapeutic regimens for advanced disease (including anthracycline and a taxane, unless these treatments were not suitable)'.

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The approach taken by the company considerably increased the complexity of the appraisal, therefore it was agreed to separate it into two appraisals.

The first (current appraisal), will focus on the review of TA250, and will consider a population of people with 'locally advanced or metastatic breast cancer that has progressed after two or more prior chemotherapeutic regimens for advanced disease (including anthracycline and a taxane, unless these treatments were not suitable)'.

Currently eribulin is available to people with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens via the CDF.

However the interim funding will expire soon, therefore it is important to appraise the CDF indication first and according to the originally set timelines.

TA250 Eribulin for the treatment of locally advanced or metastatic breast cancer

- Previously did not recommend eribulin for the treatment of locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease
- Changes since TA250:
  - The list price of eribulin increased, but the company offered a higher PAS discount, which has been approved by the Department of Health
  - The marketing authorisation for eribulin has been extended and now incudes people with LABC/MBC who have progressed after at least one chemotherapeutic regimens for advanced disease
  - The company presented results for comparing eribulin with TPC instead of individual treatment options as did in the submission for TA250
  - Updated survival results became available from the EMBRACE trial, after 95% of patients had died. In TA250 results after 55% of patients died were available only.
  - Eribulin has been available via the CDF
  - Data are available from audits from 5 hospitals in the UK.

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In TA250, the committee's preferred comparator was TPC, because

- the individual comparisons restricted the population to too small,

- They were based on post-hoc analysis

- the trial was not powered to detect differences between eribulin and individual groups

- the analysis of eribulin vs. individual drugs had been done without appropriate adjustment for multiple testing

In TA250, the committee expressed concerns about the toxicity profile of eribulin and the uncertainties about health-related quality of life

It also considered that the less frequent administration of vinorelbine, the use of generic prices to estimate the price of the comparators and the national discounts available to the NHS for vinorelbine would result in a further increase in the ICER per QALY gained.

Most plausible ICER presented in the ERG exploratory analysis was above £68,600 per QALY gained for eribulin compared with TPC

For further details on the issues raised in TA250 see page 11 of the Company Submission (Executive Summary)

Locally advanced or metastatic breast cancer

- Breast cancer arises from the tissues of the ducts or lobules of the breast. 'Locally advanced' cancer describes tumours that are larger than 5 cm in size, and may have grown into the skin or muscle of the chest or nearby lymph nodes. Metastatic breast cancer describes disease that has spread to another part of the body, such as the bones, liver, or lungs.
- Over 44,800 people were diagnosed with breast cancer in England in 2013, and there were approximately 9800 deaths from breast cancer in 2012
- Approximately 16% of people with invasive breast cancers have locally advanced or metastatic disease when they are diagnosed, and around 35% of people with early or locally advanced disease will progress to metastatic breast cancer
- The estimated patient numbers with locally advanced or metastatic breast cancer which progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated) are between 1125 -1500 patients (see section 2.7 of the ERG report and table 86 of company submission).

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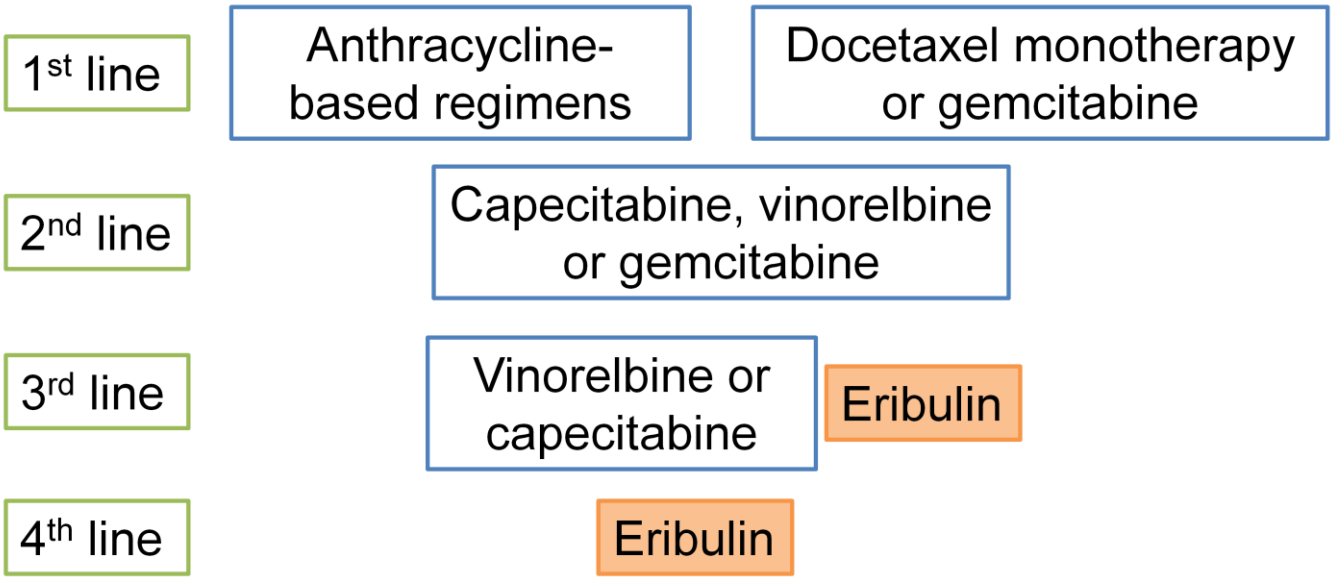
Also see section 3 of the company submission.

Treatment pathway
for people having chemotherapy for advanced breast cancer

NICE Clinical Guideline 81: Advanced breast cancer: diagnosis and treatment



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Recently published data from audits undertaken at three UK hospitals showed that more than 80% of patients had received prior capecitabine when prescribed eribulin under the CDF (as third or subsequent line of treatment).

Eribulin

Marketing Authorisation in the UK (2014)	For the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least **one** chemotherapeutic regimen 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. This appraisal only focuses on the original licence indication: locally advanced or metastatic breast cancer that has progressed after at least **two prior** chemotherapeutic regimens for advanced disease (including anthracycline and a taxane, unless these treatments were not suitable).
Mechanism of action	It is a synthetic analogue of halichondrin B, which inhibits tubulin polymerisation. The destabilisation of tubulin polymers disrupts the assembly and formation of microtubules, which in turn arrests cancer cell division.
Dosage and administration	The recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 which should be administered intravenously over 2 to 5 minutes on days 1 and 8 of every 21-day cycle
Costs	• £361 per 0.88mg/2ml solution for injection vial • £541.50 per 1.32mg/3ml solution for injection vial A Patient Access Scheme has been approved by the Department of Health for eribulin

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The company emphasised in its submission that eribulin is a ready to use solution in a vial, and there is no need for reconstitution or dilution, as it is the case of many IV chemotherapeutic agents.

It is administered as a 2-5 minute IV infusion.

It requires no premedication to prevent hypersensitivity.

The indication in the orange rectangle is identical to the CDF indication and that is what this current appraisal is focusing on (i.e. the review of TA250).

Decision problem

	Final Scope	Company submission
Population	Adults with locally advanced or metastatic breast cancer that has progressed **after at two or more prior chemotherapeutic regimens for advanced disease** (including anthracycline and a taxane, unless these treatments were not suitable)	**Subgroup 2:** Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated)
Intervention	Eribulin	
Comparators	• Vinorelbine • Capecitabine • Gemcitabine	• Treatment of Physician's Choice (TPC), including: Vinorelbine, Gemcitabine, Anthracyclines (Doxorubicin), Taxanes (Paclitaxel and Docetaxel)
Outcomes	• Overall survival • Progression free survival • Response rate • Adverse effects of treatment • Health related quality of life	

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The company also used a mixed comparator, a 'mix of 50% gemcitabine and 50% vinorelbine (including both oral and IV formulation)' in sensitivity analysis in order to reflect the final scope.

Comments from Breast Cancer Now (I)

- Living with MBC is difficult for both the patient and their family
- It is a heavily pre-treated patient population, therefore there is an increased risk for drug resistance
- Many newer, very effective treatment have only been available through the CDF and are currently reappraised by NICE, therefore their future availability is uncertain
- Current treatment options are limited, therefore more options would be appreciated by patients
- Common side effects of these treatments are hair loss, nausea, vomiting and fatigue
- Willingness to accept side effects varies from patient to patient, quality of life is just as important as length of life and being able to spend quality time with their loved ones. Therefore a modest survival benefit might not justify serious side effects for them
- People with triple negative breast cancer would likely to benefit the most from an additional treatment option, as there is no targeted treatment available for the condition, whereas cancers with ER and HER2 receptors have access to some targeted therapies.

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Submission was received from one consultee, Breast Cancer Now, a patient organisation.

Additional comment:

Triple negative patients are also tend to be younger (it is more common in women under 40), who have smaller children

Comments from Breast Cancer Now (II)

- Eribulin is not an expensive treatment and it has been shown in trials that extends life by an average of three months longer than capecitabine
- This survival benefit is greater when looking specifically at patients with HER2- breast cancer, an indication where very little progress has been seen in recent years
- It controls the symptoms of the disease (including pain) better
- Five audits of use of eribulin were carried out at hospitals in England with 270 patients and shown that eribulin:
  - is generally well tolerated
  - performs as well in clinics as it does in trials with similar survival benefits and toxicities, particularly for patients who have previously received more than one previous chemotherapy regimen for metastatic breast cancer
- In addition, the contacted clinicians said that they value having the option of eribulin for patients, particularly at the end of their lives

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Submission was received from one consultee, Breast Cancer Now, a patient organisation.

Clinical-effectiveness evidence

Company submission section 4

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Overview of the clinical evidence

- The company presented the results of 2 RCTs in the submission:
  - EMBRACE trial (Study 305), the pivotal trial for the population of the current appraisal, was the main source of clinical evidence
  - Study 301 trial was used for applying for the licence extension, in the context of this appraisal, this was only used to provide HRQoL data, which was not assessed in the EMBRACE trial.

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Clinical trial evidence – RCT evidence EMBRACE trial

Design	Phase III, open label, multicentre, randomised controlled trial	
Population	N=762, women with locally advanced or metastatic breast cancer, who had received 2 to 5 chemotherapy regimens for advanced disease	
Intervention	n=508; Eribulin mesylate 1.4 mg/m2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle	This is equivalent to the licensed dose specified in the SMPC (1.23 mg/m2 which should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle
Comparator	n=254; TPC (any available single agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer, radiotherapy or best supportive care). The selection of the TPC agent took place prior to randomisation.	
Outcomes	Primary outcome: OS	
	Secondary outcomes: PFS, ORR, safety	
Subgroups	**Previously treated with capecitabine (73.4% of ITT)**	

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Source: Section 4 of company submission

The company's literature search identified one randomised controlled trial, which was relevant to the decision problem. The EMBRACE trial.

This was the primary source of clinical-effectiveness evidence.

The subgroup of LABC/MBC previously treated with capecitabine is referred to as Subgroup 2 in the company submission and that served as a basis for this appraisal.

The selection of the TPC agent took place prior to randomisation and patients were randomised in a 2:1 ratio to receive either eribulin or TPC.

Patient characteristics EMBRACE trial (ITT population)

		Eribulin (n=508)	TPC (n=254)
Median age, years (range)		55.0 years (28–85)	55.0 years (27–81)
Geographic region, n (%)	• **North America, Western Europe**, Australia	**325 (64.0%)**	**163 (64.2%)**
	• Eastern Europe	129 (25.4%)	64 (25.2%)
	• Latin America, South Africa	54 (10.6%)	27 (10.6%)
HER2 status, n (%)	+	83 (18.0%)	40 (17.2%)
	–	**373 (81.1%)**	**192 (82.8%)**
	Unknown	4 (0.9%)	0
Triple negative, n (%)	(ER/PR/HER2-negative)	93 (18.3%)	51 (20.9%)

Abbreviations: ITT, Intent-to-treat; TPC, Treatment of Physician's Choice; HER2, Human epidermal growth factor receptor 2
Source: Table 19 and 20, Company submission

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The majority of the patients were involved in the trial from the North America, Western Europe, Australia region.

More than 80% of the patients had HER2 negative breast cancer and above 18% were in the subgroup of people with triple negative breast cancer, which was identified by the patient organisation as the subgroup with highest unmet medical need.

Prior treatments
EMBRACE trial (ITT population)

		Eribulin (n=508)	TPC (n=254)
No. of prior chemotherapy regimens (adjuvant and LABC/MBC setting), n (%)	1	1 (0.2%)	0
	2	65 (12.8%)	31 (12.2%)
	3	176 (34.6%)	83 (32.7%)
	4	166 (32.7%)	79 (31.1%)
	5	85 (16.7%)	51 (20.1%)
	≥ 6	13 (2.6%)	9 (3.5%)
No. of patients who previously (adjuvant and LABC/MBC setting) received, n (%)	Taxanes	503 (99.0%)	251 (98.8%)
	Anthracyclines	502 (98.8%)	250 (98.4%)
	Capecitabine	**370 (72.8%)**	**189 (74.4%)**

Abbreviations: TPC, Treatment of Physician's Choice; LABC, locally advanced breast cancer; MBC, metastatic breast cancer
Source: Table 21, Company submission

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The majority of the patients had 3 or 4 previous chemotherapy regimens before treatment with eribulin.

Approximately 73% of patients had prior capecitabine, which according to the company and the ERG seems to reflect current clinical practice in the UK.

EMBRACE results

- Comparator was Treatment of Physician's choice (TPC):
  - Chemotherapy (vinorelbine, gemcitabine, capecitebine, taxanes anthracyclines, others)
  - Hormonal therapy (fulvestrant, letrozole, exemestane, tamoxifen)

- The company conducted a primary analysis of overall survival, when the primary endpoint was met, when 55% of patients died
- The company conducted updated analysis when 77% of patients died.
- The company presented the results of a **further updated analysis when 95% of patients died**. The result of this analysis has been used for the cost-effectiveness analysis

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Source: section 4.7 of company submission

EMBRACE results

Survival results (further updated analysis after 95% of patients died)

	ITT population		Subgroup 2	
	Eribulin (n = 508)	TPC (n = 254)	Eribulin (n = 370)	TPC (n = 189)
Overall survival (OS), months (95% CI)				
Median	13.24 (12.06, 14.4)	10.55 (9.23, 12)	13.0 (11.7, 13.8)	10.1 (7.7, 11.4)
Difference in medians	**2.7** (1, 4.4)		**2.9** (CIs N/A)	
Stratified log-rank test	p = 0.011		p = 0.008	
Hazard ratio	**0.815 (0.696, 0.955)**		**0.78 (0.65, 0.94)**	
Progression-free survival (PFS) - investigator review, months (95% CI)				
Median	3.61 (3.29, 3.75)	2.17 (1.97, 2.76)	3.6 (3.3, 3.8)	2.1 (1.9, 2.2)
Difference in medians	**1.4** (CIs N/A)		**1.5** (CIs N/A)	
Stratified log-rank test	p = 0.002		p < 0.001	
Hazard ratio	**0.771 (0.651, 0.913)**		**0.68 (0.56, 0.83)**	

Abbreviations: ITT, intention to treat; TPC, treatment physician's choice; CI, confidence interval; OS, overall survival; PFS, progression –free survival

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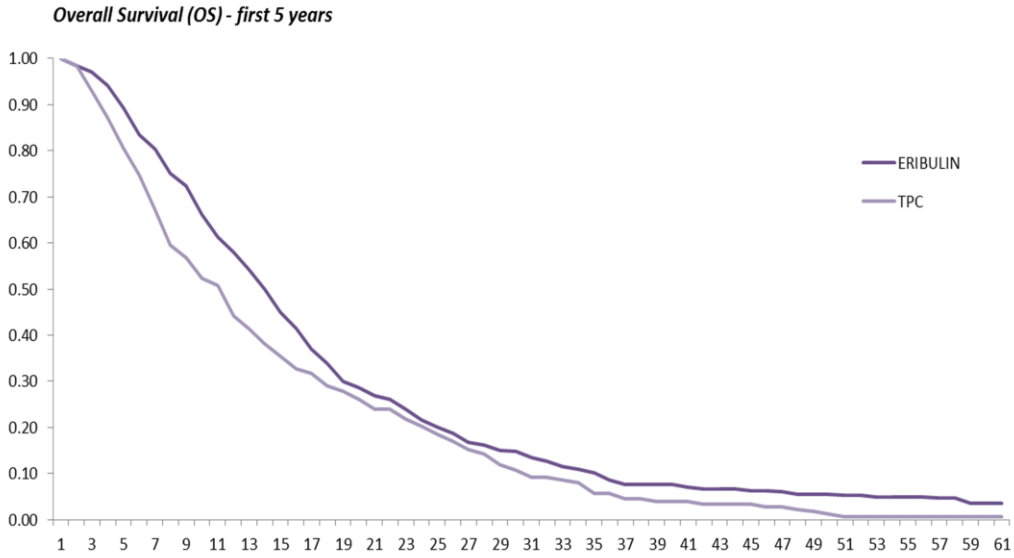
Eribulin was associated with statistically significant improvement in overall survival compared with TPC according to all of the data cuts (after 55%, 77% and 95% of patients died)

And in both the ITT population and in Subgroup 2 according to the latest data cut (after 95% of patients died).

EMBRACE results

Kaplan-Meier analysis of overall survival: EMBRACE, Subgroup 2; further updated analysis after 95% of patients died)



Source: Figure 34 of company submission

Kaplan-Meier results for the ITT population for the further updated analysis after 95% of patients died were not presented in the company submission.

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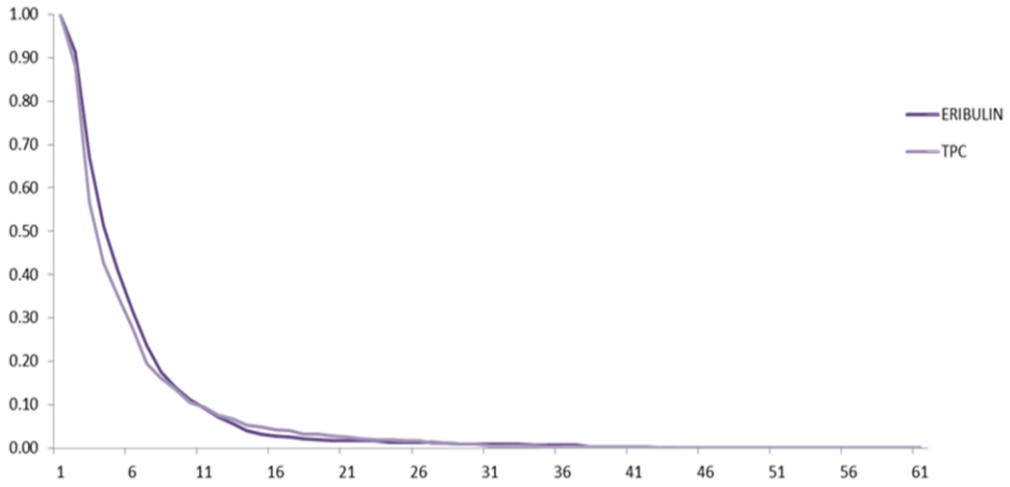
EMBRACE results

Kaplan-Meier analysis of progression-free survival: EMBRACE, Subgroup 2, further updated analysis after 95% of patients died)



Source: Figure 33 of company submission

Kaplan-Meier results for the ITT population for the further updated analysis after 95% of patients died were not presented in the company submission.

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EMBRACE results

Objective response rate results (ITT population, primary analysis after 55% of patients died)

Investigator review		
	Eribulin (n=468) n (%)	TPC (n=214) n (%)
ORR [CR or PaR]	**62 (13.2)**	**16 (7.5)**
95% CI	(10.3, 16.7)	(4.3, 11.9)
p-value	0.028	
CR	1 (0.2)	0
PaR	61 (13.0)	16 (7.5)
Abbreviations: ORR, objective response rate; CR, complete response; PaR, partial response; CI, confidence interval Source: table 27 of company submission		

Objective results rate results for the further updated analysis after 95% of patients died were not presented.
The results of the investigator review have been used in the cost-effectiveness model, because it was considered to represent UK clinical practice.

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Eribulin was associated with a statistically significant improvement in overall response rate (ORR) according to both the independent and the investigator review.

The results by the independent review showed 12.2% ORR for eribulin and 4.7% ORR for TPC.

The majority of this benefit however came from partial response and not complete response.

Health Related Quality of Life evidence – Study 301

- Health-related quality of life data was not collected in the EMBRACE trial
- Therefore the company used HRQoL results from Study 301 in the analysis
- Data from EORTC QLQ-C30 (version 3.0) and the breast module QLQ-BR23 (version 1.0) instruments were collected in Study 301
- For the cost-effectiveness analysis global health status results from the EORTC QLQ-C30 questionnaire were used and was mapped to EQ-5D

design	Phase III, open label, multicentre, randomised controlled trial
population	N=1102, women with locally advanced or metastatic breast cancer, who had received up to 3 chemotherapy regimens, **less than 2 for advanced disease**
intervention	n=554; Eribulin 1.23mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle
comparator	n=548; capecitabine
outcomes	Primary outcome: OS, PFS
	Secondary outcomes: ORR, HRQoL
subgroups	By geographic region and by HER2 status

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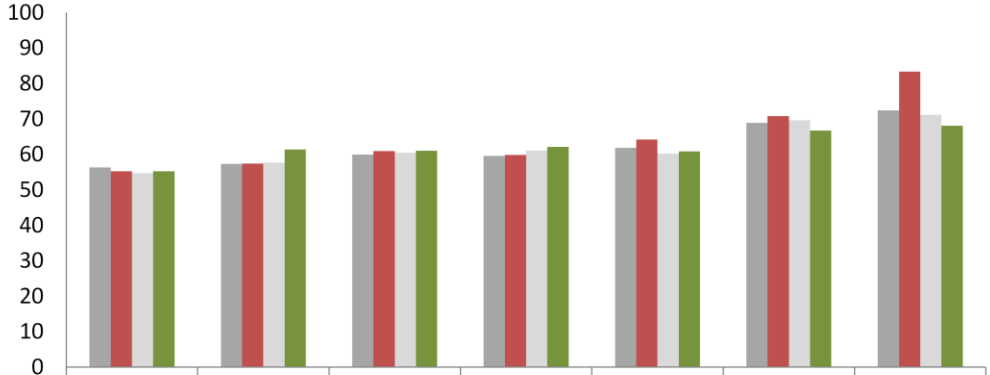
See section 4 of the company submission for the design and results of Study 301 and more specifically section 4.7 on the HRQoL results.

Health-related quality of life results

Global Health Status by Treatment (ITT and 3rd Line Plus)



	Baseline	6 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
Eribulin ITT	56.3	57.3	59.9	59.6	61.8	68.9	72.4
Eribulin 3rd Line Plus (N=158)	55.2	57.4	60.9	59.8	64.2	70.8	83.3
Capecitabine ITT	54.7	57.7	60.5	61.1	60.2	69.6	71.1
Capecitabine 3rd Line Plus (N=151)	55.2	61.4	61	62.1	60.8	66.7	68.1

Eribulin ITT Eribulin 3rd Line Plus (N=158) Capecitabine ITT Capecitabine 3rd Line Plus (N=151)

Source: Figure 18 of company submission

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The population in Study 301 population was different to the population in the EMBRACE trial, and in Subgroup 2 of the company submission.

Therefore the company conducted a sub-analysis of the HRQoL results was conducted for patients that had received at least two prior chemotherapies. According to the company the results are again consistent with those in the overall population.

Adverse events

AEs	EMBRACE trial Eribulin n=503	EMBRACE trial TPC n=247	Study 301 Eribulin n=544	Study 301 Capecitabine n=546
Any AE	497 (98.8%)	230 (93.1%)	512 (94.1%)	494 (90.5%)
Any treatment-related AE	474 (94.2%)	192 (77.7%)	460 (84.6%)	421 (77.1%)
Fatal serious AEs	20 (4.0%)	18 (7.3%)	26 (4.8%)	36 (6.6%)
Any treatment-related serious AEs	59 (11.7%)	17 (6.9%)	7.7%	8.1%
AEs that led to discontinuation	67 (13.3%)	38 (15.4%)	43 (7.9%)	57 (10.4%)
AEs that led to dose interruption	25 (5.0%)	25 (10.1%)	10 (1.8%)	1 (0.2%)
Common AEs				
Asthenia/ fatigue	270 (53.7%)	98 (39.7%)	174 (32%)	163 (30%)
Neutropenia	260 (51.7%)	73 (29.6%)	295 (54.2%)	87 (15.9%)
Alopecia	224 (44.5%)	24 (9.7%)	188 (34.6%)	22 (4.0%)
Peripheral neuropathy	174 (34.6%)	40 (16.2%)	73 (13.4%)	38 (7.0%)
Arthralgia/ myalgia	109 (21.7%)	29 (11.7%)	72 (12.2%)	39 (7.1%)
Febrile neutropenia	23 (4.6%)	4(1.6%)	7 (1.3%)	4 (0.7%)

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Source section 4.12 of company submission, and table 33

	Embrace trial		Study 301	
	Eribulin	TPC	Eribulin	Capecitabine
Any serious AEs	126 (25.0%)	64 (25.9%)	95 (17.5%)	115 (21.1%)
AEs that led to dose reduction	85 (16.9%)	39 (15.8%)	174 (32.0%)	174 (31.9%)
Grade 3 AEs	308 (61.2%)	114 (46.2%)	202 (37.1%)	183 (33.5%)

ERG critique of clinical evidence (I)

- The company's literature search was appropriate
- The EMBRACE trial appears to be of good quality
- For the statistical analysis of the EMBRACE study the results of the latest data cut (after 95% of patients died) should have been presented, instead of the updated data cut (after 77% of patients died); the availability of mature clinical effectiveness data is considered one of the strengths of the EMBRACE trial
- Considered the use of the TPC comparator to be appropriate as it represented 'real life' treatment options for LABC/MBC
- Proportional hazards assumption was not tested by the company, however the HRs only valid if this assumption holds.
  - The ERG tested whether the proportional hazards assumption holds and found that the only reliable HR is for OS in the ITT population for all patients receiving ≥3 chemotherapy regimens for LABC/MBC
  - HRs for OS for Subgroup 2 and for PFS in both populations are derived from K-M data that are not proportional to one another

  Nonetheless, the ERG considers the estimates for median OS and PFS in both populations are valid

Source: Section 4 of ERG report

ERG critique of clinical evidence (II)

- The main difference between the ITT and Subgroup 2 populations is that Subgroup 2 patients appear to be slightly more heavily pre-treated:
  - approximately 64% of Subgroup 2 patients had received 4 or more prior chemotherapy regimens (in any setting) compared with approximately 53% of all patients in the ITT population
  - approximately 65% of Subgroup 2 patients had received 3 or more prior chemotherapy regimens in the LABC/MBC setting compared with approximately 57% of all patients in the ITT population
- Safety data from the EMBRACE trial and from 'real world' observational studies show that eribulin has an acceptable safety profile
- The EMBRACE trial results appear to be generalisable to NHS clinical practice
- The generalisability of HRQoL data from Study 301 (only 28% of patients in this trial had received study treatment as a 3rd line option) compared with the population of the appraisal may be questioned, given the different designs of the EMBRASE and Study 301 trials.

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Cost-effectiveness evidence

Company submission section 5

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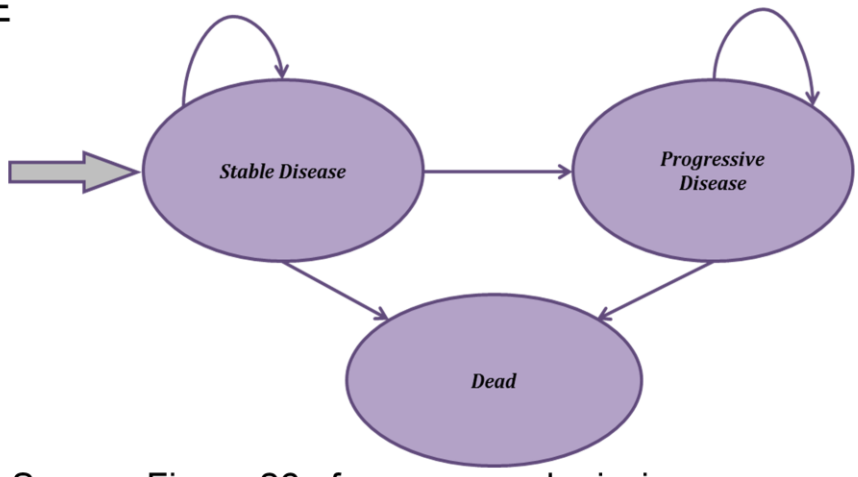
Economic model

- A de novo economic was developed to assess the cost effectiveness of eribulin compared with TPC for people with LABC/MBC whose disease has progressed **after at least two prior chemotherapeutic regimens** for advanced disease which includes capecitabine (if indicated)
- Transition probabilities are based on the patient level data from EMBRACE



Source: Figure 26 of company submission

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The model was developed with 3 health states:

Pre-progression/Stable disease health state

Post-progression/progressive disease health state

Dead

Patients enter the model in the Stable disease health state, where they receive treatment with eribulin or TPC.

Patients stay in SD health state until disease progression or death, when they move on to the progressive disease health state.

Patients stay in PD health state until death

Structure of the model

- 5 year time horizon in the base case
- Clinical-effectiveness data was directly based on the Kaplan-Meier results from EMBRACE (PFS and OS) for the base-case analysis
- Cycle length 30.42 days = 1 months
- Half-cycle correction was not applied
- Outcomes are calculated at the end of each cycle
- NHS and PSS perspective
- Costs and benefits were discounted at the rate of 3.5%

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In deterministic scenario analyses a time horizon of 10 and 20 years have been presented, for which an exponential model has been fitted to the whole data set and used for extrapolation.

Costs (I)

- Body surface area was assumed to be 1.74m^2 (CI 1.72-1.76), based on a study by Sacco et al.
- The PAS discount for eribulin has been incorporated in the model
- The model used the licensed dose of eribulin and the comparators
- A dose intensity of 0.84 was used in both arms based on the dose reduction used for eribulin in EMBRACE
- Drug wastage: The average dose of treatment was calculated based on average body surface area. If the pack sizes of treatments did not account for the exact dose required, doses were rounded to lessen drug wastage
- The treatment duration for 'Stable' and 'Progressive' health states in combination is set to a maximum of 6 months. The treatment duration of secondary treatment following eribulin or TPC in the 'Progressive' state is linked with the treatment duration of the 'Stable' health state
- End of life costs were applied to the 2-week period prior to death
- Resource utilisation was based on NICE CG81 and TA250
- The cost and disutility of common AEs (all grades with a prevalence ≥10%) or serious AEs (≥3 with a prevalence ≥2%) are included within the model (for the full list of included AEs, see table 23 of the company submission)

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Costs (II) - comparators

- Comparator (TPC): The proportions of the different therapeutic options are based on the ITT population in the EMBRACE trial, excluding capecitabine and any treatments that were used as initial treatment in less than 10% of the TPC arm
- These proportions were used for both primary and subsequent lines of treatment

Drug name	Number of patients	Proportion	
		ITT population	Subgroup 2
Vinorelbine	61	24.00%	36.75%
Gemcitabine	46	18.10%	27.71%
Paclitaxel	26	10.20%	15.66%
Doxorubicin	23	9.10%	13.86%
Docetaxel	10	3.90%	6.02%
Total	166	65.30%	100.00%

Source: Table 43 of company submission, Table 21 of ERG report

30

Utilities

- HRQoL data from Study 301 (using the EORTC QLQ-C30 results) was used to estimate EQ-5D utility values, using a mapping algorithm published by Crott and Briggs, 2010 (see section 5.4 of company submission)
- The algorithm was developed using data from people with LABC with good baseline health status
- Disutilities associated with AEs were also calculated using EORTC QLQ-C30 results from Study 301 and a linear mixed-effects model
- Only common AEs (all grades with a prevalence ≥10%) or serious (≥3 with a prevalence ≥2%) were included (for the full list of included AEs, see table 23 of the company submission)

Utility scores per health states	Eribulin	TPC
Stable disease	0.706	0.701
Progressive disease	0.679	0.679
Source: Table 57 of company submission		

31

Reminder: In TA250 a utility value of 0.715 was used for stable disease health state, 0.790 for responsive disease and 0.443 for the progressed disease health state by the company, based on Lloyd et al.

This has been amended by the ERG to of 0.715 for stable disease, 0.823 for responsive disease and 0.496 for progressed disease health state.

Cost-effectiveness results

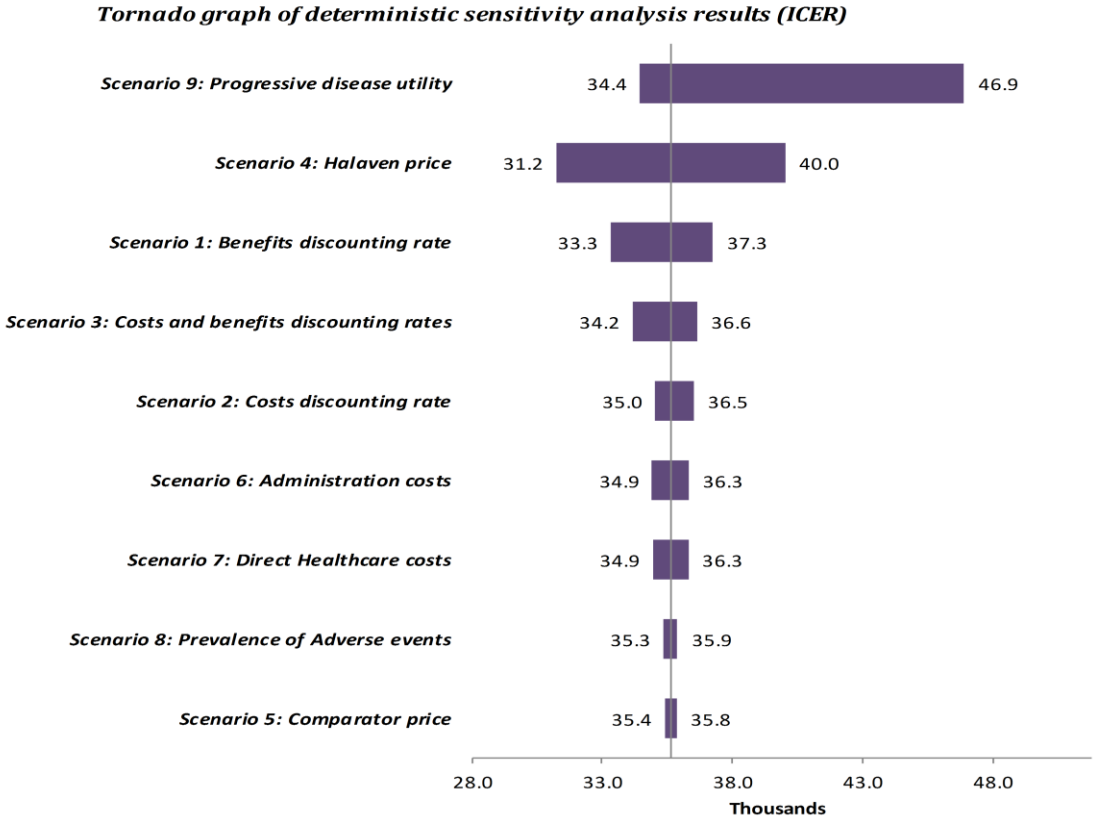
	Total		Incremental		ICER per QALY gained
Technologies	Costs	QALYs	Costs	QALYs	
Eribulin	XXXXX	XXXXX	XXXXX	XXXXX	**£35,624**
TPC	XXXXX	XXXXX			
Source: Table 72 of company submission					

- The PSA results also showed that the ICERs ranged between £20,000 and £60,000 per QALY gained.
- The probability of cost-effectiveness was 30% for eribulin compared with TPC at a cost-effectiveness threshold of £30,000 per QALY gained and a 72% at a cost-effectiveness threshold of £50,000 per QALY gained.

Probabilistic sensitivity analysis results (please note that this graph contains CIC information)

Sources: Figure 45 and 46 of company submission

Tornado diagram



Source: Figure 48 of company submission

33

The results show that the ICER was most sensitive to the utility value applied to the progressed disease health state.

Deterministic scenario analysis

Scenario	Incremental		ICER per QALY gained
	QALY	Cost	
Base case	XXXXX	XXXXX	**£35,624**
Maximum treatment duration threshold of 12 months	XXXXX	XXXXX	£39,164
Excluding wastage	XXXXX	XXXXX	£16,053
Vinorelbine and gemcitabine as comparator	XXXXX	XXXXX	£23,931
Prevalence of AEs Grade ≥3	XXXXX	XXXXX	£35,964
Time horizon 10 years	XXXXX	XXXXX	£32,362
Time horizon 20 years	XXXXX	XXXXX	£32,282

Abbreviation: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year
Source: Table 84 of company submission

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The biggest effect on the company's base case results occurred when the cost of wastage was excluded from the company's base case calculations.

This lowered the ICER per QALY gained for the comparison of eribulin versus TPC to £16,053 per QALY gained (a 54% reduction in the base case result).

ERG critique of cost-effectiveness evidence (I)

- The company's partitioned survival model is structured in an inconsistent manner
- The proportions of the different treatments in TPC are taken from the ITT population in the EMBRACE trial, excluding capecitabine and any treatments that were used as initial treatment in less than 10% of the TPC arm. The proportions are therefore calculated on a subset of the TPC group.
- A weekly or 3-weekly cycle length would be more appropriate than a monthly cycle length, given that all treatments that are included prescribed on a weekly or 3 weekly schedule
- It was not possible to estimate post-progression survival benefit from the data provided by the company
- Censoring survival data on the basis of the last contact with a patient may poorly reflect the true profile of time-to-event data
- For the sensitivity analysis with longer time horizon, extrapolating the results beyond the trial period should have been based on the mortality of the later stage of the of the trial, as that is relevant to future projection

From section 5.5.1 of the ERG report:

The model features individual monthly cycles at the end of which patient status, resource use and costs are updated. 35

All the treatments included in the model are prescribed on either a weekly or 3-weekly basis, therefore it would have been preferable to employ weekly or 3-weekly cycles.

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).

For further details see section 5.5 of the ERG report.

ERG critique of cost-effectiveness evidence (II)

- The way the company models subsequent lines of chemotherapy leads to anomalous results, because it limits the number of cycles of therapy, which ignores that patients who respond better to third-line treatment will continue third-line treatment longer and be more likely to receive additional lines of subsequent treatment
- The ERG identified a number of issues relating to cost calculations in the model, which have been adjusted in its revised analyses (see slide 39)
- For calculating treatment costs time-to-treatment discontinuation data would have been more appropriate, instead of PFS data
- The mapping algorithm that has been used to estimate EQ-5D utility values was based on data from a trial of people with untreated LABC (no MBC has been included) with good performance status, treated with an anthracycline regimen
- Probabilistic ICERs are not calculated in the company's model
- Correlated parameter uncertainty has not been incorporated in the company's model

Revised cost-effectiveness results by the ERG

Model scenario ERG revision	Eribulin		TPC		Incremental		ICER	ICER
	Total Cost	Total QALYs	Total Cost	Total QALYs	Cost	QALYs	Per QALY gained	Change
A. Company base case	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	**£35,624**	**-**
R1) ERG use of K-M PFS data	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£37,182	+£1,557
R2) ERG use of K-M OS data	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£35,425	-£199
R3) Annual discounting applied	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£35,471	-£154
R4) Correct logic error on oral vinorelbine costs	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£31,276	-£4,349
R5) ERG estimated eribulin unit costs	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£45,418	+£9,793
R6) ERG estimated comparator unit costs (combined with R4)	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£30,106	-£5,518
R7) ERG preferred progression utility value	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£46,912	+£11,288
R8) ERG alternative method of costing subsequent lines of therapy	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£45,435	+£9,811
R9) Correct logic error on eribulin administration costs	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£39,737	+£4,113
B. ERG revised base case A+R1 to R9	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	**£62,672**	**+£27,047**

Source: Table 35 of the ERG report

37

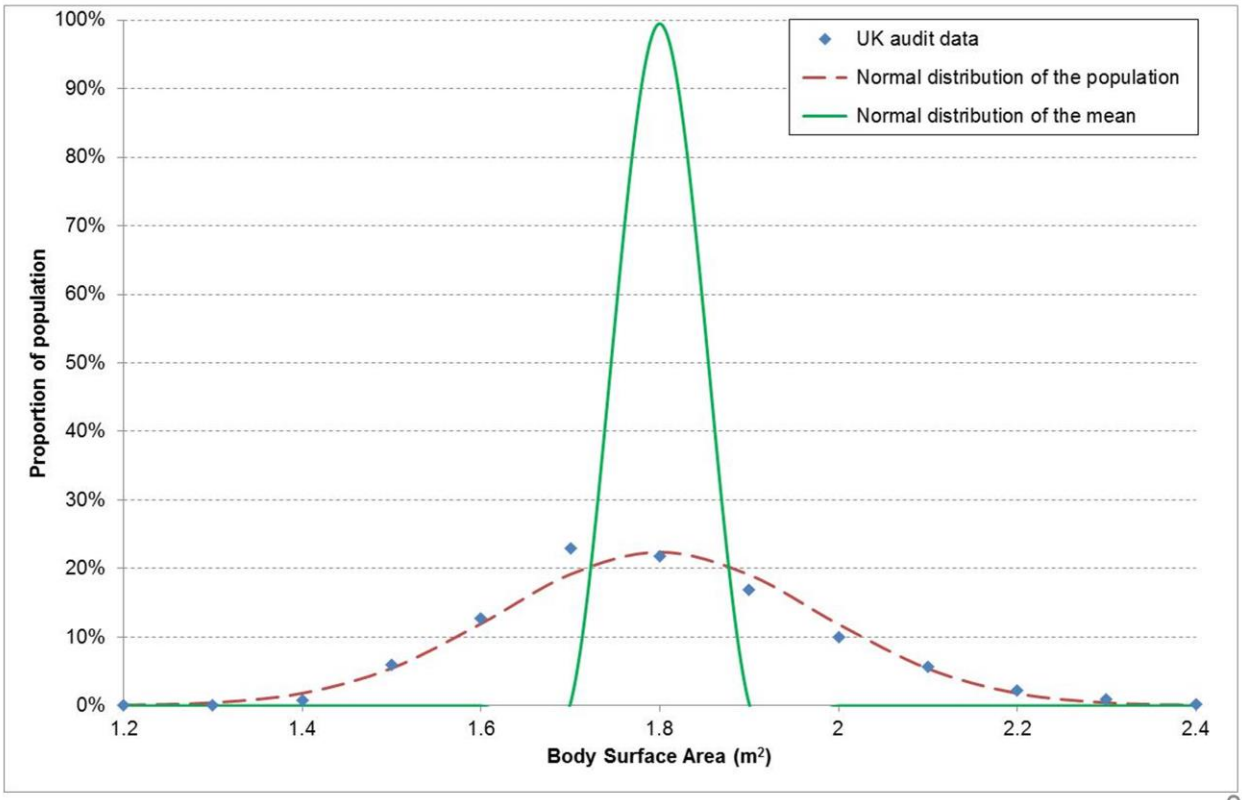
Please note that figures in this table have been updated and are consisted with the latest results presented in the Erratum to the ERG report.

ERG amendments – cost calculations (I)

- The ERG identified six issues relating to the calculations of treatment costs:
  - The estimation of drug use by body surface area for calculating the cost of treatments was incorrect (using the standard error of the mean instead of the standard deviation of the population) – this seriously underestimates treatment costs (see figure on the slide 40). This has been corrected and the unit cost per dose of all chemotherapy agents has been recalculated by the ERG
  - A logic error in the calculation of the cost of treatment which seriously underestimates the cost of oral vinorelbine was corrected
  - The facility to vary dose intensity has no impact on the estimated costs of treatments except when the non-base-case scenario analysis which excludes wastage from drug costs is employed
  - The estimation of the cost of further lines of chemotherapy beyond eribulin or TPC as third-line therapy should not be limited by an arbitrary treatment duration nor assumed not to occur beyond treatment progression. This leads to a bias in favour of eribulin which has been shown to improve post-progression survival time and therefore leads to additional lines of treatment and extra costs
  - The number of patients continuing on therapy is capped by arbitrary limits on the use of PFS data
  - Discounting of costs and benefits was implemented on a continuous rather than an annual basis

38

ERG amendments – calculation of BSA



39

This graph shows the difference between using the normal distribution to model the pattern of BSA in breast cancer and (wrongly) using the standard error of the mean to model BSA. The latter means that all patients are concentrated close to the mean BSA value so they all get the same dose of medication, and there is very little variation or wastage. By contrast when the true normal distribution is used, patients use the quantity of drug greater than or equal to their requirements using the limited dose steps possible with the two vial sizes available. As a consequence there is much greater opportunity for drug wastage and increased cost.

ERG amendments – cost calculations (II)

- Subsequent line of chemotherapy:
  - The company applied a cap on the number of cycle of subsequent treatment with chemotherapy (n=6) which the ERG considered implausible and was removed from the ERG model
  - The company assumed that nobody who progresses alive whilst on eribulin or TPC incurs the costs of subsequent chemotherapy which caps the cost of all subsequent treatments and adds additional PPS time
  - The ERG amended the model to calculate the costs of subsequent care for 60% of the patients still alive in the progressed health state each month (based on Kantar Health data which reports 54%-56% go on to receive an extra course of treatment).
- Eribulin administration costs:
  - The company's model does not calculate with administration costs after 6 months for eribulin.
  - This error has been corrected by the ERG.

40

ERG amendments - Utilities

- The mapping algorithm used by the company (Crott and Briggs, 2010) to estimate EQ-5D values from QLQ-C30 results from study 301 was inappropriate as it was based on trial results from untreated LABC with good performance status
- The ERG considered as an alternative the Standard Gamble mixed model published by Lloyd et al. (2006), which has been used in previous appraisals for advanced breast cancer; this shows a more realistic estimate for patients with progressive disease
- Therefore the ERG updated the utility values to the following values

Utility scores per health states	ERG		Company	
	Eribulin	TPC	Eribulin	TPC
Stable disease	0.706	0.701	0.706	0.701
Progressive disease	0.496	0.496	0.679	0.679
Source: Section 5.5.9 of ERG report and table 57 of company submission				

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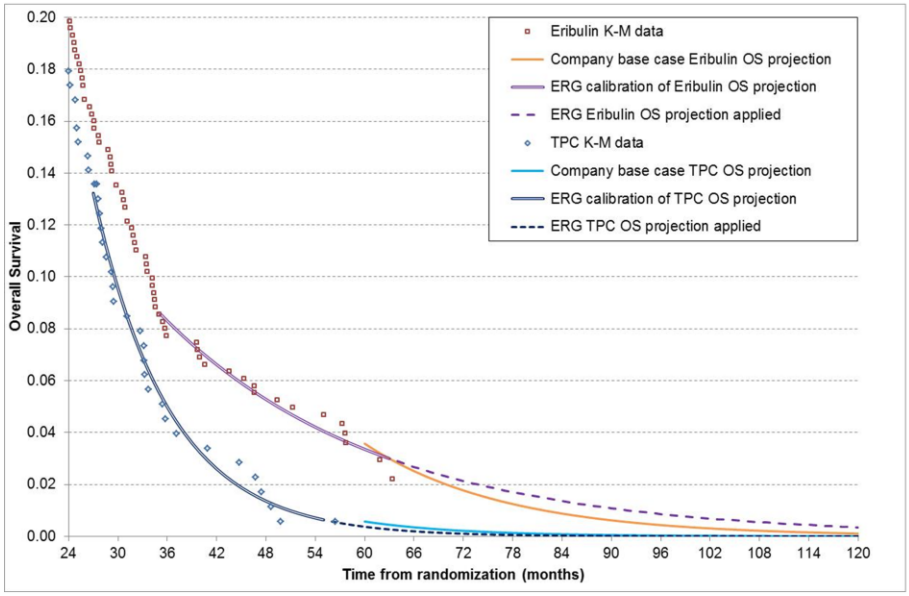
The reason for the difference between the utility values used for the 2 arms, in the stable disease health state is the different response rate, which has been observed in EMBRACE and the disutility values applied for AEs.

ERG amendments - Modelling OS

For the scenario analysis OS KM curves have been replaced by an exponential extrapolation model in the ERG's model after the time point where a long-term exponential trend becomes established in the data

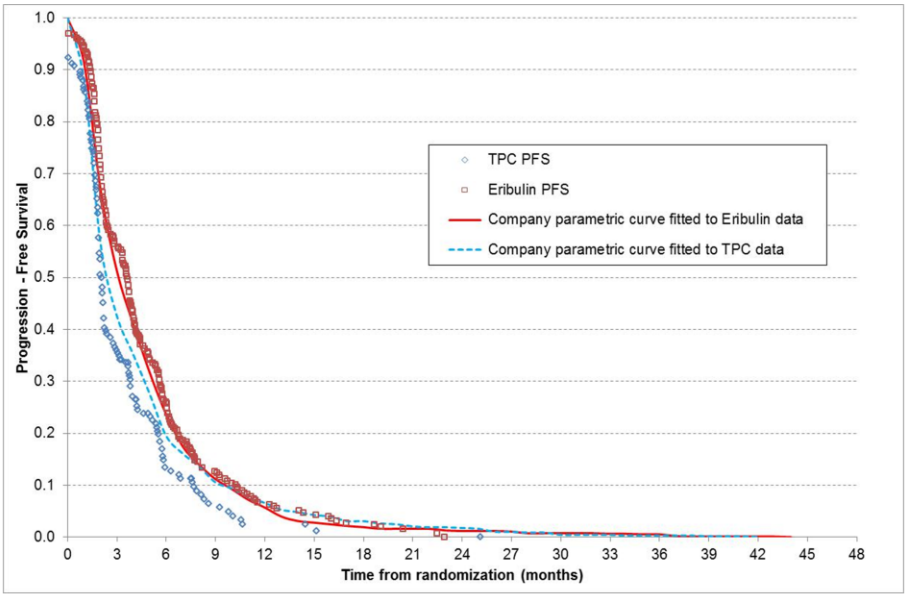
(i.e. month 35 on the eribulin arm and month 27 on the TPC arm)



Source: Figure 5 of ERG report

ERG amendments - Modelling PFS

- For the scenario analysis the company's Weibull curves, were replaced by KM data from the EMBRACE trial
- This results in the model estimated PFS gain increase from 8.2 days in the company's model to 40.2 days (95% CI 13.0 to 67.8 days).



43

Source: Figure 6 or ERG report

ERG amendments - Modelling PPS

- The ERG did not find that the data provided by the company for the ERG's clarification question on PPS was appropriate for modelling PPS
- It included the patients who died without progression, and as a result it is not possible to estimate the extent of any survival benefit after disease progression
- Therefore is was not possible to estimate directly the extent of any survival benefit (or disbenefit) arising after disease progression.

Revised cost-effectiveness results by the ERG

Model scenario ERG revision	Eribulin		TPC		Incremental		ICER	ICER
	Total Cost	Total QALYs	Total Cost	Total QALYs	Cost	QALYs	Per QALY gained	Change
A. Company base case	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	**£35,624**	**-**
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R2) ERG use of K-M OS data	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£35,425	-£199
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R8) ERG alternative method of costing subsequent lines of therapy	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£45,435	+£9,811
R9) Correct logic error on eribulin administration costs	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£39,737	+£4,113
B. ERG revised base case A+R1 to R9	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	**£62,672**	**+£27,047**

Source: Table 35 of the ERG report

45

Please note that figures in this table have been updated and are consisted with the latest results presented in the Erratum to the ERG report.

End of life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months, **and**	TPC arm of the EMBRACE study: **Median OS 10.6 months Mean OS 13.53 months** (95% CI 11.87 to 15.19 months)
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 cost-effectiveness analysis in patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (subgroup 2): • **mean OS benefit of 3.04 months** for eribulin compared with TPC (See table 36 of company submission) The results of the EMBRACE trial show an **extension in median survival of 2.9 months** with eribulin compared with TPC. The **mean OS benefit is 3.39 months** (95% CI 0.83 to 5.96 months) in the ERG's revised model (see ERG report section 7). 46

Innovation

- The company considers eribulin to be innovative because of its mechanism of action and convenient administration method (it is administered as an IV infusion for 2-5 minutes with no special handling or tubing required).

For further details please see section 2.5 of company submission.

Equality

- Company: no equality issues were raised
- Consultees: no equality issues were raised

Authors

- **Boglarka Mikudina**
  Technical Lead
- **Eleanor Donegan**
  Technical Adviser
- with input from the Lead Team (Andrew England, Adrian Griffin and David Thomson)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Eribulin for treating locally advanced or metastatic breast cancer after two or more prior chemotherapy regimens [ID964]

Final scope

Remit

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

Objective

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

Background

Breast cancer arises from the tissues of the ducts or lobules of the breast. 'Locally advanced' cancer describes tumours that are larger than 5 cm in size, and may have grown into the skin or muscle of the chest or nearby lymph nodes. Metastatic breast cancer describes disease that has spread to another part of the body, such as the bones, liver, or lungs.

Over 44,800 people were diagnosed with breast cancer in England in 2013, and there were approximately 9800 deaths from breast cancer in 2012[1,2]. The 5-year survival rate for people with metastatic breast cancer in England is 15%[3]. Approximately 16% of people with invasive breast cancers have locally advanced or metastatic disease when they are diagnosed[4], and around 35% of people with early or locally advanced disease will progress to metastatic breast cancer[5,6].

Current treatments for locally advanced or metastatic breast cancer aim to relieve symptoms, prolong survival and maintain a good quality of life with minimal adverse events. Treatment may depend on whether the cancer cells have particular receptors (oestrogen receptor or HER2), the extent of the disease and previous treatments; options include endocrine therapies, biological therapies and chemotherapy. For advanced breast cancer NICE clinical guideline 81 recommends endocrine therapy.

For people having chemotherapy for advanced breast cancer, NICE clinical guideline 81 (CG81) recommends anthracycline-based regimens as the initial treatment, followed by sequential lines of treatment with docetaxel first line followed by capecitabine and vinorelbine as second or third line. Gemcitabine

monotherapy is also used in clinical practice in the UK. Patients for whom anthracyclines are not suitable (because of contraindication or progression on prior anthracycline treatment) are offered sequential treatment with systemic chemotherapy.

The technology

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

Eribulin has a marketing authorisation in the UK for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen 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.

Intervention	Eribulin
Population	Adults with locally advanced or metastatic breast cancer ~~who have~~ **that has** progressed after ~~at least one~~ **two or more prior** chemotherapeutic regimen**s** for advanced disease (**including** anthracycline and a taxane, unless these treatments were not suitable).
Comparators	• vinorelbine • capecitabine • gemcitabine
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	If the evidence allows, consideration will be given to subgroups according to HER2 status, oestrogen receptor **status** and line of treatment. 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.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (2013) NICE technology appraisal guidance TA295. Review ongoing [ID965], publication date February 2017 Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane (2015) NICE technology appraisal guidance 371. Review date December 2018 Fulvestrant for the treatment of locally advanced or metastatic breast cancer (2011) NICE technology appraisal guidance 239. Review date Nov 2014. Review decision, static list Gemcitabine for the treatment of metastatic breast cancer (2007) NICE technology appraisal guidance 116. Review date, May 2010. Review decision, static list Guidance on the use of trastuzumab for the treatment of

	advanced breast cancer (2002) NICE technology appraisal guidance 34. Review date TBC **Suspended appraisals** Lapatinib for breast cancer (for use in women with previously treated advanced or metastatic breast cancer) NICE technology appraisal guidance. Suspended. **Proposed Technology Appraisals:** Palbociclib for treating metastatic hormone receptor-positive, HER2-negative breast cancer. Proposed NICE technology appraisal [ID915]. Publication date to be confirmed. Etirinotecan pegol (after chemotherapy). Proposed NICE technology appraisal [ID881]. Publication date to be confirmed. Fulvestrant for untreated hormone-receptor positive metastatic breast cancer [ID951]. Publication date to be confirmed. **Related Guidelines:** Familial breast cancer: Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer (2013). NICE guideline CG164 Review date: December 2015 Advanced breast cancer (2009 updated 2014) NICE guideline CG81. Review date December 2015. Early and locally advanced breast cancer (2009) NICE guideline CG80. Review date December 2015. **Related Quality Standards:** Breast cancer quality standard (2011) NICE Quality Standard QS12. **Related NICE Pathways:** Advanced breast cancer (2015) NICE pathway Familial breast cancer (2015) NICE pathway Early and locally advanced breast cancer (2014) NICE

	pathway
Related National Policy	NHS England, Manual for prescribed specialised services 2013/14: Chapter 105. Specialist Cancer services (adults) http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf NHS England (November 2015) Cancer Drugs Fund list version 6.0. See also: decision documents for previously treated and third line indications (May 2015). Department of Health, Improving Outcomes: A Strategy for Cancer, third annual report, Dec 2013 https://www.gov.uk/government/publications/the-national-cancer-strategy-3rd-annual-report--2 Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 1, 2, 4 and 5 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf

References

1. Office for National Statistics (2015) Cancer registration statistics, England, 2013. Accessed February 2016.

2. Cancer Research UK (2014) Breast cancer mortality statistics. Accessed February 2016.

3. Cancer Research UK (2014) Breast cancer survival statistics. Accessed February 2016.

4. Cancer Research UK (2015) Breast cancer incidence statistics. Accessed February 2016.

5. NICE (2009) Costing report for clinical guideline 81: advanced breast cancer. Accessed February 2016.

6. Dewis R and Gribbin J (2009) Breast cancer: diagnosis and treatment, an assessment of need. Cardiff: National Collaborating Centre for Cancer. Accessed February 2016.

APPENDIX C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Eribulin for treating locally advanced or metastatic breast cancer after two or more prior chemotherapy regimens [ID964]

Provisional matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Eisai (eribulin) Patient/carer groups • Black Health Agency • Breast Cancer Care • Breast Cancer Now • Breast Cancer UK • Cancer Black Care • Cancer Equality • Haven • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care • Women's Health Concern Professional groups • Association of Cancer Physicians • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • Cancer Research UK • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Health Forum • United Kingdom Clinical Pharmacy Association • United Kingdom Oncology Nursing Society	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • Accord Healthcare (capecitabine, gemcitabine) • Actavis UK (capecitabine, gemcitabine, vinorelbine) • Dr. Reddy's Laboratories (capecitabine) • Eli Lilly and Company (gemcitabine) • Hospira UK (gemcitabine) • Medac GmbH (capecitabine, gemcitabine, vinorelbine) • Pierre Fabre (vinorelbine) • Roche Products (capecitabine) • Sun Pharmaceuticals UK (capecitabine, gemcitabine) • Zentiva (capecitabine) Relevant research groups • Against Breast Cancer • Breast Cancer Hope • Breast Cancer Research Trust • Cochrane Breast Cancer Group • Institute of Cancer Research • MRC Clinical Trials Unit

Others • Department of Health • NHS East Surrey CCG • NHS England • NHS North Hampshire CCG • Welsh Government	• National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research • Pro-Cancer Research Fund Associated Public Health Groups • Public Health England • Public Health Wales NHS Trust

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

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

The company/sponsor of the technology are invited to prepare a submission dossier, can respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).
All non-company/sponsor consultees are invited to prepare a submission dossier respond to consultations on the draft scope, the Assessment Report and the Appraisal Consultation Document. They can nominate clinical specialists and/or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but are not asked to prepare a submission dossier. Commentators are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies of comparator technologies; Healthcare Improvement Scotland; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.
All non-company/sponsors commentator organisations can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Eribulin for treating locally advanced or metastatic breast cancer after chemotherapy [ID964]

Company evidence submission

April 2016

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Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Tables and figures

Abbreviations

ABC	Advanced breast cancer
AE	Adverse event
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AWMSG	All Wales Medicines Strategy Group
CDF	Cancer Drugs Fund
CBR	Clinical benefit rate
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMBRACE	Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389
EMT	Epithelial-mesenchymal transition
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire with Breast Module
EPAR	European public assessment report
ER	Oestrogen receptor
ESMO	European Society for Medical Oncology
G-CSF	Granulocyte colony stimulating factor
GHS	Global health score
GI	Gastrointestinal
HER2	Human epidermal growth factor receptor 2
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
LABC	Locally advanced breast cancer
LD	Longest diameter
LL	Log logistic

LN	Log normal
LY	Life year
MAA	Marketing Authorisation Approval
MBC	Metastatic breast cancer
MID	Minimum important differences
MRI	Magnetic resonance imaging
N/A	Not applicable
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OLS	Ordinary least-squares
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressive disease
PFS	Progression free survival
PH	Proportional hazard
PM	Parametric
PP	Per protocol
PR	Progesterone receptor
PaR	Partial response
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY(s)	Quality-adjusted life year(s)
QoL	Quality of life
RCT	Randomised, controlled trial
RECIST	Response evaluation criteria in solid tumours
RWE	Real world evidence
SA	Sensitivity analysis
SAE	Serious adverse event
SD	Stable disease
SMC	Scottish Medicines Consortium
SPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event
TNM	Tumour, Nodes, Metastasis
TN	Triple negative
TPC	Treatment of Physician's Choice
TSW	Time to symptom worsening
TTP	Time to progression
TTR	Time to response
VAS	Visual analogue scale

1 Executive summary

Overview

Halaven (eribulin) was reviewed by NICE in 2011 and the current guidance (TA250) is that eribulin is not recommended for the treatment of locally advanced or metastatic breast cancer (LABC/MBC) that has progressed after at least two chemotherapy regimens for advanced disease.

In 2014, the European Medicines Agency (EMA) granted an extension to the above indication for eribulin to be used in an earlier chemotherapeutic line, i.e. following one prior chemotherapy. Therefore, for this single technology appraisal, NICE has proposed a broad remit to include:

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

On the basis of current clinical practice and unmet clinical need, this evidence submission considers two subgroups separately within the above remit, namely: (see further details in Table 1)

Subgroup 1

1. HER2-negative patients with locally advanced or metastatic breast cancer (LABC/MBC), whose disease has progressed after one prior chemotherapy regimen in the advanced setting.

Subgroup 2:

2. Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated).

Two phase III studies (study 305 and study 301) involving more than 1,800 patients form the basis of the current licensed indication for eribulin in breast cancer:

- In the landmark Phase III study 305 (EMBRACE) where the primary endpoint was overall survival (OS), eribulin was the first cytotoxic agent to improve overall survival in heavily pre-treated patients with MBC versus treatment of physicians' choice (TPC). (7)
- This is acknowledged in current ESMO (30) and ASCO (31) metastatic breast cancer guidelines.
- Study 301 (11) provides further supporting evidence for the efficacy and safety of eribulin in MBC against the commonly used agent capecitabine. The duration of OS (in months) was similar to that seen in study 305.
- Importantly, the results of a health-related quality of life (HRQOL) assessment conducted in study 301 show that eribulin does not adversely impact HRQOL (as assessed by EORTC QLQ-C30).
- Eribulin demonstrates a consistent overall survival benefit in both the aforementioned subgroups:

  [redacted]

  - In subgroup 2 in study 305, the median OS was 13.0 months for eribulin (n=370) and 10.1 months for TPC (n=189), an **extension in median survival of 2.9 months** (HR: 0.78; 95% CI, 0.65 to 0.94, p=0.008) (9)

- Eribulin has a predictable and manageable profile of adverse events (AEs) which is similar to those of other chemotherapeutic agents used in this setting:
    - Discontinuations due to AEs were lower in the eribulin group than in the control group for both Phase III studies (13.3% vs. 15.4% in Study 305 and 5.7% vs 6.2% in study 301, respectively) (7,11)
    - Recently published "real world" data from independent audits undertaken in the UK (35,36,37), France (66) and Spain (67) have mirrored the safety results of the phase III evidence and have shown that eribulin is well tolerated in a routine clinical practice setting with AEs that can be adequately managed by clinicians.
    - This is further supported by the fact that in England to date, eribulin is the 7th most prescribed treatment in the Cancer Drugs Fund (CDF) and has been given to more than 2300 patients since it was first made available through the regional CDF panels in April 2011. Since clinicians will not prescribe agents that are not well tolerated by their patients, the CDF usage reinforces the fact that UK clinicians have confidence in using eribulin.
- A de novo cost effectiveness analysis was conducted for eribulin within the two subgroups identified.
    - In comparison to TA250, this economic evaluation of eribulin was based on patient-level data to model the survival functions and within-trial collected patient reported outcomes for the elicitation of the utilities. These two elements are very important in terms of reducing uncertainty around the outcomes.
    - The basecase ICERs were £36,244 per QALY for subgroup 1 and £35,624 for subgroup 2.
    - All the sensitivity analyses conducted strongly indicate that the evaluation is very robust with all the ICER derivatives being a very narrow range from the basecase ICERs.
    - The results of the cost effectiveness analysis indicate that eribulin offers an extension to life of an additional 3 to 4.6 months, compared with current NHS treatment.
    - Therefore, given that eribulin meets the "end of life criteria" (see section 5.11), the cost effectiveness analysis demonstrates that eribulin in the two specified subgroups has been robustly and conservatively demonstrated to meet all the accepted criteria for a cost-effective end of life treatment and could be considered good value for money for adoption by the NHS.

The submission addresses the following key conclusions of the NICE Appraisal Committee in the TA250 final guidance:

1. **"The Committee concluded that eribulin was associated with a less favourable toxicity profile compared with TPC."**

As highlighted above, this evidence submission incorporates "real world" data from independent audits undertaken in the UK, France and Spain which mirrored the safety results of the phase III evidence and have shown that eribulin is well tolerated in a routine clinical practice setting. This is further reinforced by the CDF prescribing figures showing the confidence clinicians have in eribulin in terms of its efficacy and manageable tolerability.

2. **"The Committee concluded that the effects of eribulin on health-related quality of life had not been adequately captured"**

The evidence submission incorporates Health-related Quality of Life data from study 301, which included patients who were treated for first, second and third line MBC. The QLQ-C30 results are converted into EQ-5D utility scores that are used in the economic analysis.

3. **"The Committee was aware that a major stratification factor in the EMBRACE trial was pre-treatment with capecitabine (73.4% of patients) and agreed that this was potentially relevant to clinical practice"**

As stated above, this submission provides evidence for this subgroup of patients from study 305 (EMBRACE) – subgroup 2.

4. **"The Committee agreed that it was more appropriate to use the ERG's exploratory analysis that projected survival trends to the end of life in line with the lifetime horizon recommended in the NICE methods guide"**

The submission incorporates mature data from Study 305 (EMBRACE), increasing the completeness of the study and reducing the uncertainty in the cost effectiveness results related to projected survival. In addition, ten and twenty year time horizons are provided as additional sensitivity analysis scenarios with the latter approximating lifetime horizon.

5. **The Committee agreed with the ERG's approach to:**
   a. **estimating the costs of chemotherapy drugs per cycle by using body surface area values from the Sacco et al study,**
   b. **estimating supportive care and state-based cost as per NICE Clinical guideline 81**
   c. **incorporating costs for IV vinorelbine, chemotherapy day-case unit costs and first administration costs**

The submission incorporates all of the above in the cost effectiveness analysis (see section 5.2 and 5.5)

1.1 Statement of decision problem

The decision problem is presented in Table 1 overleaf.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease (anthracycline and a taxane, unless these treatments were not suitable).	The submission focuses on two subgroups in particular: **Subgroup 1:** HER2-negative patients with locally advanced or metastatic breast cancer (LABC/MBC), whose disease has progressed after one prior chemotherapy regimen in the advanced setting. **Subgroup 2:** Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated).	Although the population described in the final NICE scope reflects in full eribulin's indication, the submission looks at two subgroups in particular. The patient population differs for the following reasons: 1. Eribulin's clinical benefit has been assessed in two phase III pivotal trials, study 305 (EMBRACE) (7) and study 301 (11). However, the two studies included patient populations with different characteristics and focused in slightly different disease settings (see section 4.3). In order to ensure an accurate assessment of eribulin's cost effectiveness, the model includes two specific subgroups allowing the utilisation of exact patient level data without having to pool data from the two studies which would have created uncertainty risks given the aforementioned studies' characteristics. Figure 25 illustrates the overlap between the two trials and how the selection of the subgroups enables accurate cost-effectiveness assessment. Table 40 summarises the methodological issues that would arise by utilising the pooled data from the two studies. 2. Different comparator arms were included in each of the studies - Study 301 included capecitabine whereas Study 305 (EMBRACE) included TPC. The selection of these comparators within the clinical trials was based on the current clinical practice at the time of the studies' design. The assessment of eribulin's cost-effectiveness in two specific subgroups allows for the comparison of eribulin to the most appropriate comparator instead of using a common control arm which would necessitate pooling patient data from the two studies. 3. The specific subgroups identified within the clinical trials are those where eribulin's greatest clinical benefit was observed. 4. Subgroup 2 reflects current clinical practice in England as observed through the usage of eribulin through the CDF. Recently published data from audits undertaken at three UK hospitals (35,36,37) showed that more than 80% of patients had received prior capecitabine when prescribed eribulin under the CDF.

Intervention	Eribulin	As defined by scope	N/A
Comparator (s)	Vinorelbine Capecitabine Gemcitabine	Capecitabine Treatment of Physician's Choice (TPC), including: Vinorelbine, Gemcitabine, Anthracyclines (Doxorubicin), Taxanes (Paclitaxel and Docetaxel)	As indicated in the final scope, NICE clinical guideline 81 (CG81) (29) clearly defines vinorelbine monotherapy and capecitabine monotherapy as potential treatment options for patients with advanced breast cancer who are not suitable for anthracyclines because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting. However, in the UK, there is currently no single pattern of treatment for patients at this stage of the disease and the choice of treatment in real-life clinical practice for LABC/MBC depends on many more factors other than prior chemotherapy exposure and response, including HER2 status, tolerability, patient preference, availability of drugs, the patient's quality of life and performance status. In the absence of a clear standard of care, offering patients a choice of treatment and taking their preferences into account is crucial to this approach, as recognised in CG81 and highlighted by UK clinical experts. Therefore, gemcitabine (as indicated in the final scope), anthracyclines and taxanes (UK clinical experts have confirmed that in the absence of a standard of care, some patients are re-challenged with these agents) are included as comparators in the submission in order to cover not only patients treated following one prior chemotherapy but also in later lines of therapy, as observed in current UK clinical practice and in the composition of treatment of the Treatment of Physician's Choice arm of the phase III EMBRACE clinical study for eribulin. Given this, Eisai have included the following comparators for each subgroup listed below: **Subgroup 1** • Basecase comparator: *capecitabine* To reflect the design of study 301 of which patient level data are used in the model to estimate clinical and cost effectiveness outcomes • Sensitivity analysis scenario comparator – *mix of 50%*

			capecitabine and 50% vinorelbine (including both oral and IV formulation) Selected as an alternative set of comparators for subgroup 1 in order to reflect the final scope and the NICE clinical guideline CG81 (29). Although gemcitabine was included in the final scope, it was not included as a comparator in this subgroup as it is not included in the NICE clinical guideline CG81 (29). Moreover, no clinical evidence exists for gemcitabine in this specific disease setting and a small number of UK clinical experts have validated that it is not currently routinely used in this setting. **Subgroup 2:** • Basecase comparator - *Treatment of Physician's Choice (TPC), excluding capecitabine ie vinorelbine, gemcitabine, doxorubicin, paclitaxel and docetaxel* As described in section 4.3, this is the basis of the approach taken for the comparator arm of study 305 (EMBRACE), and reflects a pragmatic approach to compare eribulin in a disease setting of such late treatments, consisting of a variety of therapeutic options instituted by practicing physicians on a day-to-day basis. The treatments making up the TPC comparator are based on the therapies included in the TPC arm of study 305 (EMBRACE), excluding capecitabine and treatments with less than a 10% share. • Sensitivity analysis scenario comparator - *mix of 50% gemcitabine and 50% vinorelbine (including both oral and IV formulation).* Selected as an alternative set of comparators for subgroup 2 in order to reflect the final scope.
Outcomes	Overall survival Progression free survival Response rate Adverse effects of treatment HRQOL	As defined by scope	N/A

Economic analysis	Incremental cost per QALY Time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	As defined by scope The time horizon in the submission is such that it approximates a lifetime projection in the LABC/MBC patient population. A patient access scheme has been approved by the Department of Health and this has been incorporated into the submission.	The economic evaluation was based on patient-level data from studies 301 and 305. The survival data for the two studies were very close to being complete. Thus, the basecase time horizon was set at five years. In addition, ten and twenty year time horizons are provided as additional sensitivity analysis scenarios with the latter approximating lifetime horizon.
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups according to HER2 status, oestrogen receptor and line of treatment.	The submission considers two separate subgroups according to HER2 status and line of treatment	On the basis of current clinical practice and unmet clinical need, the submission considers two separate subgroups separately, namely: **Subgroup 1** 3. HER2-negative patients with locally advanced or metastatic breast cancer (LABC/MBC), whose disease has progressed after one prior chemotherapy regimen in the advanced setting. **Subgroup 2:** 4. Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated). Further rationale for focusing specifically on these two subgroups is provided in the “Population” section of this table above.
Special considerations including issues related to equity or	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the	As defined by scope	N/A

equality	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.		

Abbreviations: EMBRACE, Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389; HER2, Human epidermal growth factor receptor 2; HRQOL, health-related quality of life; QALY, quality-adjusted life year; LABC, Locally advanced breast cancer; MBC, metastatic breast cancer; TPC, Treatment of Physician's Choice

1.2 Description of the technology being appraised

Table 2 Technology being appraised

UK approved name and brand name	Halaven® (eribulin)
Marketing authorisation/CE mark status	Licensed
Indications and any restriction(s) as described in the summary of product characteristics	Halaven (eribulin) is indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments. Eribulin is contraindicated in breast-feeding and in those patients who have a hypersensitivity to the active substance or to any of the excipients.
Method of administration and dosage	The recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 (equivalent to 1.4mg/m^2 eribulin mesilate) which should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle. Eribulin should only be administered under the supervision of a qualified physician experienced in the appropriate use of cytotoxic medicinal products.

Source: Halaven SPC (Appendix 1)

1.3 Summary of the clinical effectiveness analysis

Background and unmet medical need in metastatic breast cancer

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. (13) However, 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).

There is currently no cure for MBC and the long-term prognosis is poor. The aim of treatment in this setting therefore is to prolong life, without adversely affecting the patient's quality of life. The average length of survival following diagnosis of MBC is 12 months for those receiving no treatment, compared with 18-24 months for those receiving chemotherapy. (39) At the point in therapy where eribulin will be used ie following at least one to two chemotherapeutic regimens for advanced disease, the length of survival is expected to be less.

Pre-treated breast cancer patients, such as those considered by this submission, have limited treatment options. 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 HER2-positive targeted therapies, the prognosis of HER2-positive MBC has reversed. (22) In a recent study of 798 patients with metastatic breast cancer, the 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) (23).

The chemotherapeutic agents with the best efficacy in breast cancer, the anthracyclines and taxanes, are typically used at earlier stages of the disease, leaving many LABC/MBC patients anthracycline and taxane-resistant, and thereby limiting the number of treatment options at this stage of disease (40). The proportion of patients responding to chemotherapy declines through successive lines of treatment (41), while no RCTs of the current NICE-approved monotherapies have demonstrated a survival advantage over any other single agent in the treatment of anthracycline and taxane-resistant metastatic disease (28).

As a result of this a great need exists for treatments that improve overall survival for women with MBC with a predictable and manageable tolerability profile.

Eribulin – Clinical effectiveness

Eribulin is a novel non-taxane inhibitor of microtubule dynamics. It is the first and only single chemotherapy agent to demonstrate a statistically significant overall survival benefit versus existing therapies in patients with late stage LABC/MBC in a phase III study.

Two phase III studies involving more than 1,800 patients form the basis of the current licensed indication for eribulin in breast cancer. In the landmark Phase III study 305 (EMBRACE) where the primary endpoint was overall survival, eribulin was the first cytotoxic agent to improve overall survival in heavily pre-treated patients with MBC versus treatment of physicians' choice (TPC). (6,7) This is acknowledged in current ESMO (30) and ASCO (31) metastatic breast cancer guidelines.

Overall survival is recognised as the most definitive cancer outcome (26) and is of most importance to patients and clinicians when making decisions regarding treatment options (27).

As mentioned above, there is no standard of care for these pre-treated patients in the advanced stages of breast cancer and there are few evidence-based treatment options available. The choice of treatment will depend on a number of factors including prior chemotherapy exposure and response, tolerability, patient preference, availability of drugs, the patient's quality of life and performance status.

In the absence of a single standard of care for women with anthracycline and taxane pre-treated breast cancer, Study 305 (EMBRACE) randomly allocated 762 women who had previously received at least two and a maximum of five chemotherapy regimens, in a 2:1 ratio either to eribulin (508) or treatment of the physician's choice (TPC; 254); TPC arm included any monotherapy currently available for the treatment of cancer, including capecitabine, gemcitabine and vinorelbine, used in MBC treatment. (6,7)

Median overall survival was significantly improved in women assigned to eribulin (13.1 months) compared with TPC (10.6 months), an increase in duration of survival of 23% (2.5 months) (p=0.041). (7) The updated analysis performed after 77% of patients had died and on request of the regulatory authorities, confirmed these results; median OS (eribulin 13.2 months vs. TPC 10.5 months) was improved by 2.7 months (p=0.014). (8) The magnitude of the OS should be considered in the context of the population enrolled in this study, which had been pre-treated in the advanced setting with at least 2 previous chemotherapies.

Eribulin also demonstrates consistent efficacy when compared with TPC in a number of secondary outcomes. (6,7) Median progression free survival (PFS) was 3.6 months for eribulin and 2.2 months for TPC, when assessed by investigator review (p = 0.002), and 3.7 months and 2.2 months, respectively, when assessed by independent review (p = 0.137). The objective response rate (ORR; a complete response or a partial response) was 12.2% for eribulin, compared with 4.7% for TPC, when assessed by independent review (p=0.002).

The clinical benefit rate (complete response and partial response and stable disease for at least 6 months) was 22.6% for eribulin vs 16.8% for TPC, when assessed by independent review.

In study 305, patients were pre-stratified by prior capecitabine treatment. The majority of patients in the trial (73.4%) had received prior capecitabine in the metastatic setting. This is in keeping with current UK practice. Recently published data from audits undertaken at three UK hospitals showed that more than 80% of patients had received prior capecitabine when prescribed eribulin under the CDF. (35,36,37)

A further updated OS analysis of study 305 (EMBRACE) was performed after 95% of patients had died and eribulin showed a consistent OS benefit over TPC (9).

- In those patients who had received prior capecitabine treatment (73.4% of the trial population), the OS was statistically significant with a HR of 0.78 (95% CI: 0.65, 0.94).
- Median OS was 13.0 months for eribulin (n=370) and 10.1 months for TPC (n=189), an extension in median survival of 2.9 months (p=0.008).

The second Phase III study in earlier line metastatic breast cancer, Study 301, was an open-label, randomised, study in patients with locally advanced or metastatic breast cancer to investigate the efficacy of eribulin monotherapy compared to capecitabine monotherapy. Patients had previously received up to three prior chemotherapy regimens, including both an anthracycline and a taxane and a maximum of two for advanced disease. The percentage of patients who had received 0, 1 or 2 prior chemotherapy treatments for metastatic breast cancer were 20.0%, 52.0% or 27.2% respectively, making this a predominantly second-line study. (10,11)

Study 301 provides further supporting evidence for the efficacy and safety of eribulin in MBC against the commonly used agent capecitabine. The duration of OS (in months) was similar to that seen in study 305.

The median OS among patients receiving eribulin (n=554) was 15.9 months versus 14.5 months in the capecitabine group (n=548), p=0.056. Eribulin demonstrated a trend favouring improved OS (co-primary endpoint) as compared with capecitabine but this improvement did not reach statistical significance. (10,11) It is thought that treatment earlier in the course of MBC is less likely to impact OS (20.0 % and 52% of patients having 0 or 1 prior chemotherapy). Even if therapeutically more active, a first or second line regimen may not impact on OS when multiple subsequent lines of effective treatment are administered. The influence of post-progression therapy on OS may also have had an impact as there was an imbalance with more patients in the eribulin arm receiving further anticancer treatment compared to capecitabine (70.4% and 62.0% respectively).

Importantly, the results of a HRQOL assessment conducted in study 301 show that eribulin does not adversely impact HRQOL (as assessed by EORTC QLQ-C30). The majority of patients (≥74%) in both treatment groups maintained or improved their global health status/HRQOL vs baseline. (83) In addition, separate sub-analyses in subgroup 1 and subgroup 2 show consistent results with those in the overall population.

Study 301 was designed to further evaluate the effect of eribulin on prespecified subgroups including human epidermal growth factor receptor 2 [HER2/*neu*] negative) status. Therefore, patients were pre-stratified according to geographical region and HER2 status. (11)

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[redacted]

Upon request from the European Medicines Agency (EMA), a pooled analysis of study 301 and Study 305 (EMBRACE) was undertaken to determine whether the observed benefit of eribulin was consistent. The objective of this pooled analysis was to assess OS in the overall intent-to-treat (ITT) population and in subgroups based on HER2 status. Treatment with eribulin was associated with an OS benefit over control in most patient subgroups, including HER2-negative (n=1320) (median OS: 15.2 vs 12.3 months; 2.9-month difference; HR: 0.82; $p = 0.002$). (46,47)

This study is included in the submission as supportive evidence only of eribulin's consistent overall survival benefit. The results are not used to inform the cost effectiveness analysis (see section 5.2 for further information).

Therefore, on the basis of current clinical practice and unmet clinical need, the submission considers two separate subgroups separately, namely: (see Table 1)

Subgroup 1

1. HER2-negative patients with locally advanced or metastatic breast cancer (LABC/MBC), whose disease has progressed after one prior chemotherapy regimen in the advanced setting.

Subgroup 2:

2. Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated).

End-of-life criteria

Eribulin is indicated for LABC/MBC patients who have a short life expectancy, normally less than 24 months:

- Although therapeutic advances have been made, the overall prognosis for patients with MBC remains poor, with an average length of survival of 12 months for those receiving no treatment, compared to 18-24 months for those receiving chemotherapy (39).
- Study 305 (EMBRACE) reported a median OS of 13.1 months in the eribulin arm and in study 301, the median OS in the eribulin arm was 15.9 months (10).

Eribulin offers an extension to life of an additional 3 to 4.6 months, compared with current NHS treatment:

- In subgroup 1, the results of the cost effectiveness analysis show a mean overall survival benefit for eribulin of 4.61 months. Considering the difference in the median values observed in the study 301 and the model, both of them are just below a 3 months OS benefit. (See section 5.3, 5.7)
- In subgroup 2, the results of the cost effectiveness analysis show a mean overall survival benefit for eribulin of 3.04 months. Considering the difference in the median values observed in the study 305 and the model, the median in the study 305 is just below a 3 months OS benefit whereas the median derived from the model is above a 3 months OS benefit. (See section 5.3, 5.7)

Therefore, eribulin is suitable for consideration as a 'life-extending treatment at the end of life' under the revised end-of-life criteria proposed in the "Consultation on proposals for a new cancer drugs fund (CDF) operating model from 1st April 2016".

Eribulin – Safety information

Eribulin was first approved on the 15th November 2010 in the US and has since been made available in more than 60 countries worldwide to approximately 85,000 women with MBC.

Eribulin's safety profile is well characterised in two global phase III studies in the MBC setting, which showed that eribulin had a manageable profile of adverse events which is similar to those of other chemotherapeutic agents used in this setting. Oncologists and associated healthcare professionals caring for patients with MBC are experienced in dealing with these adverse events.

When assessing the overall safety profile in Study 305 (EMBRACE), the majority of patients are able to continue treatment with eribulin. It is associated with less fatal AEs and fewer discontinuations and dose interruptions due to AEs than TPC. (7)

- Deaths due to serious AEs were lower in the eribulin arm than the TPC arm (4.0% vs. 7.7%, respectively).
- Discontinuations due to AEs were lower in the eribulin group than in the TPC group (13.3% vs. 15.4%, respectively).
- Dose interruptions were lower in the eribulin group than the TPC group (5.0% vs. 10.1%, respectively).

Development of Grade 3/4 AEs of neutropenia occurred in 21.1% and 24.1% of eribulin and TPC patients, respectively. However, neutropenia led to discontinuation in only 0.6% of patients, while febrile neutropenia (4.6%) was infrequent. (7)

Peripheral neuropathy, a common side effect seen with some chemotherapies, was generally mild/ moderate (Grade 1/2) with the occurrence of Grade 3/4 peripheral neuropathy being low (around 8%); 63% of those patients with peripheral neuropathy were able to continue treatment. (7)

The incidence of GI events such as constipation, diarrhoea, and vomiting with eribulin was low (< 25%); where these GI AEs occurred they were generally mild (CTCAE Grade 1). (7)

In an earlier line study (Study 301), the incidence of some of the most frequently reported AEs and SAEs for eribulin-treated patients was lower than in Study 305 eg febrile neutropenia (1.3% vs 4.6%) and asthenia/fatigue (32% vs 53.7%). (11)

Recently published "real world" data from independent audits undertaken in the UK (35,36,37), France (66) and Spain (67) have mirrored the efficacy and safety results of the phase III evidence and have shown that eribulin is well tolerated in a routine clinical practice setting, reflecting that patients are not impacted greatly by eribulin's side effect profile.

This is further supported by the fact that in England to date, eribulin is the 7th most prescribed treatment in the Cancer Drugs Fund (CDF) and has been given to more than 2300 patients since it was first made available through the regional CDF panels in April 2011. This reinforces the fact the UK clinicians have confidence in using eribulin as clinicians will not prescribe treatments that they do not consider are well tolerated.

A recent study assessed the trade offs that breast cancer patients are willing to make among the risk of severe adverse events and efficacy (specifically survival) when choosing a chemotherapy (65). The study showed that, despite the risk of adverse events, an incremental survival advantage is highly influential in patient preferences for chemotherapy.

The view of the patient group Breast Cancer Now is that “eribulin may give patients a few extra months at the end of their life and is well tolerated by many patients. For patients who have terminal breast cancer and their families, additional good quality time is priceless.”

Given this patient view, the outcome of the patient preference study and in combination with the available safety data presented in this submission for eribulin, it can be fairly argued that eribulin has a manageable safety profile without adversely affecting HRQOL and does not necessitate for patients making compromises between efficacy and safety.

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

In summary, eribulin offers patients a therapeutic option that has been shown to improve overall survival and has a manageable and predictable toxicity profile in the late-line treatment setting of LABC/MBC.

1.4 Summary of the cost-effectiveness analysis

In the absence of relevant economic evaluations found in the literature, a de novo cost effectiveness analysis was conducted for eribulin within the two subgroups identified. The economic evaluation was performed by developing a partition survival model similar to previous models developed in LABC/MBC as well as according to the NICE technical and clinical guidelines. In comparison to TA250, this economic evaluation of eribulin was based on patient-level data to model the survival functions and within-trial collected patient reported outcomes for the elicitation of the utilities. These two elements are very important in terms of reducing uncertainty around the outcomes. Finally, apart from probabilistic and deterministic sensitivity analyses, additional sensitivity analysis scenarios were performed assessing variations in comparators for both subgroups, primary and secondary treatment duration, prevalence of the AEs considered and variations in time horizon of the analysis.

In both subgroups, eribulin was associated with higher costs but provided additional quality-adjusted life years (QALYs) compared to capecitabine in subgroup 1 and TPC in subgroup 2. The basecase ICERs was found to be £36,244 per QALY for subgroup 1 and £35,624 for subgroup 2.

All the sensitivity analyses conducted strongly indicate that the evaluation is very robust with all the ICER derivatives being a very narrow range from the basecase ICERs. The basecase ICERs for subgroup 1 and 2 are fairly close to the willingness to pay thresholds used for other treatments which have been recently approved by NICE. Considering the increased willingness to pay thresholds for treatments meeting the “end of life criteria”, both the observed basecase ICERs and sensitivity analysis ICERs fall below these thresholds considering that eribulin meets the “end of life” criteria as mentioned in section 5.11.

Considering all of the above, the cost effectiveness analysis demonstrates that eribulin in the two specified subgroups has been robustly and conservatively demonstrated to meet all the accepted criteria for a cost-effective end of life treatment and could be considered good value for money for adoption by the NHS.

Table 3 Incremental cost-effectiveness results

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline	Incremental analysis
Subgroup 1								
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 36,244	£ 36,244
Capecitabine (comparator)	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A
Subgroup 2								
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 35,624	£ 35,624
TPC (comparator)	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A

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

2 The technology

2.1 Description of the technology

Brand name: HALAVEN®

Approved name: Eribulin mesilate; E7389.

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

Mechanism of Action

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

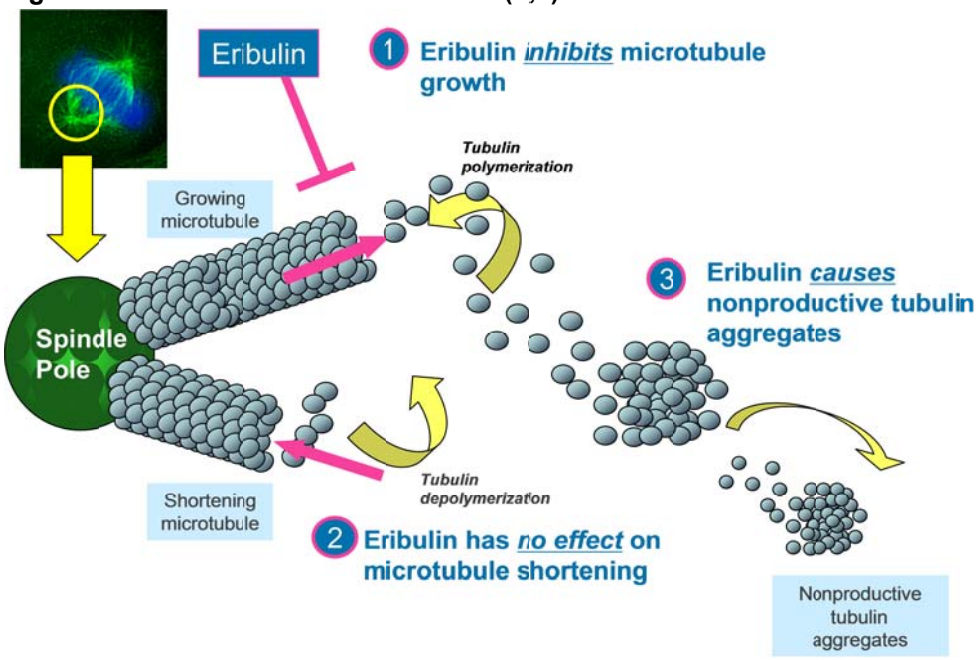
It is an innovative chemotherapy treatment which is a non-taxane inhibitor of microtubule dynamics, with a unique mechanism of action. Eribulin exerts its anticancer effects via a tubulin-based antimitotic mechanism leading to G2/M cell cycle arrest, disruption of mitotic spindles, and ultimately, apoptotic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

Taxanes which affect microtubule shortening show higher neuropathy characteristics, compared with eribulin which does not affect the microtubule shortening phase (3). Furthermore, the ability to sequester tubulin into non-productive aggregates, further distinguishes eribulin from other tubulin-targeting classes and, as a result, eribulin retains activity against drug-resistant cells that harbour β-tubulin mutations associated with taxane resistance. (4)

Preclinical studies in human breast cancer models have shown that eribulin also exerts profound effects on tumour biology and microenvironment that are unrelated to its classical antimitotic effects. These effects include (i) tumour vascular remodelling, resulting in enhanced tumour core perfusion and elimination of hypoxia, (ii) reversal of epithelial-mesenchymal transition (EMT) resulting in less aggressive tumour phenotypes, and (iii) profound decreases in tumour cell migration and invasion capacity, parameters that directly affect tumour metastatic potential. (5)

These pre-clinical studies suggest that the effects of eribulin on tumour cell biology and tumour host interactions could provide a likely basis for an increase in overall survival despite continued presence, or even growth, of tumours and metastasis. The findings propose that eribulin, in addition to having primary anticancer effects related to its antimitotic effect, also modifies residual tumour phenotype to be less aggressive and therefore less likely to metastasize by triggering a shift from mesenchymal to epithelial phenotypes. These results support the concept that after eribulin treatment, residual tumours become less life-threatening and “easier to live with” in contrast to the effects of some of the other treatment options, such as the taxanes.

Figure 1: Eribulin mechanism of action (1,2)



2.2 Marketing authorisation/CE marking and health technology assessment

European Marketing Authorisation

Eribulin was first approved by the European Commission in 2011 and it received an updated European Marketing Authorisation Approval (MAA) on the 27th June 2014 for the treatment of women with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.

The European Commission has recently approved a variation to the terms of the Marketing Authorisation of eribulin for the treatment of adult patients with unresectable liposarcomas who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease.

The initial European public assessment report (EPAR) (2011), the EPAR for the updated indication (2014) and the current Summary of Product Characteristics (SPC) are provided in Appendix 1.

Eribulin is contraindicated in breast-feeding and in those patients who have a hypersensitivity to the active substance or to any of the excipients.

Non-EU regulatory approval

Outside the EU, eribulin is currently approved for use for the treatment of women with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease in Australia, Canada, Hong Kong, India, Israel, Macau, Morocco, Philippines, Russia, South Korea, Thailand and the US.

It is approved for use in locally advanced or metastatic breast cancer that has progressed after at least two chemotherapeutic regimens in an additional 15 non-EU countries.

Health technology assessment

Eribulin is not currently the subject of any other health technology assessment in the UK.

AWMSG advice (Reference No. 1212)

Eribulin mesilate (Halaven®) is recommended as an option for restricted use within NHS Wales after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine.

http://www.awmsg.org/awmsgonline/app/appraisalinfo/1212

SMC advice (1065/15)

Eribulin is accepted for restricted use within NHS Scotland for use in patients with locally-advanced or metastatic breast cancer who have progressive disease after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine if indicated.

http://www.scottishmedicines.org.uk/SMC_Advice/Advice/1065_15_eribulin_Halaven/eribulin_Halaven_Resubmission

2.3 Administration and costs of the technology

Please see Table 4 overleaf.

Table 4 Costs of the technology being appraised

Pharmaceutical formulation	Halaven 0.44 mg/ml solution for injection. It is supplied as a clear, colourless aqueous solution, ready for injection in either a 2ml or 3ml vial In each vial, 1ml contains eribulin mesilate equivalent to 0.44 mg eribulin.
Acquisition cost (excluding VAT) *	The list price is £361 per 2 ml vial and £541.50 per 3ml vial. A patient access scheme has been submitted and approved as part of this STA, offering a straight discount off the list price.
Method of administration	Intravenous.
Doses	The recommended dose of the ready to use solution is 1.23 mg/m^2 (equivalent to 1.4 mg/m^2 of eribulin mesilate). If desired, the dose may be diluted in up to 100 ml of normal saline for injection (an aqueous solution of 0.9% w/v of sodium chloride).
Dosing frequency	Each dose should be administered intravenously over 2–5 minutes on Days 1 and 8 of a 21-day cycle.
Average length of a course of treatment	Each treatment cycle, comprising two doses (Days 1 and 8), every 21 days.
Average cost of a course of treatment	At the list price, based on the recommended dose and an average body surface area of 1.74m^2, this equates to using one 2ml vial and one 3ml vial per dose, which is £1,805 per cycle (excl. VAT). Based on 6 courses of treatment, this works out at an overall cost of £10,830 per patient (excl. VAT).
Anticipated average interval between courses of treatments	Patients will move from cycle to cycle immediately unless specific Grade 3/4 adverse events necessitate a dose delay.
Anticipated number of repeat courses of treatments	The anticipated number of repeat courses of treatments is 6. In Study 305 (EMBRACE) (6), the median number of cycles of eribulin was between 5 and 6. In Study 301 (10), the median number of cycles of eribulin was 6.
Dose adjustments	Patients should be clinically evaluated during treatment by physical examination and laboratory testing including complete blood counts. If Grade 3 or 4 adverse events are present, then treatment should be delayed to allow recovery. Patients should only be retreated when ANC is ≥1 x 10^9/L and platelets are ≥75 x 10^9/L and all other toxicity from a previous cycle has recovered to Grade 2 or less. A dose reduction to 0.97 mg/m^2 is recommended for the retreatment of patients with specific Grade 3/4 adverse events in the previous cycle (See Section 4.2 of SPC for details [Appendix 1]). If adverse events reoccur, an additional dose reduction to 0.62 mg/m^2 is recommended. Further reoccurrence may warrant treatment discontinuation. Impaired liver function due to metastases: The recommended dose in patients with mild hepatic impairment (Child-Pugh A) is 0.97 mg/m^2 and for patients with moderate hepatic impairment (Child-Pugh B) is 0.62 mg/m^2. Severe hepatic impairment has not been studied but it is expected that a more marked dose reduction is needed. Impaired liver function due to cirrhosis: This patient group has not been studied. The doses above may be used in mild and moderate impairment but close monitoring is advised as the doses may need readjustment. Patients with moderately or severely impaired renal function (creatinine clearance <50 ml/min) may have increased eribulin exposure and may need a reduction of the dose. For all patients with renal impairment, caution and close safety monitoring is advised.
Anticipated care setting	Eribulin should only be administered under the supervision of a qualified physician experienced in the appropriate use of cytotoxic medicinal products. It is anticipated that eribulin treatment will therefore be managed in a secondary care setting.

Abbreviations: ANC, absolute neutrophil count; EMBRACE, Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389
Source: Halaven SPC (Appendix 1), unless otherwise stated

Patient Access Scheme (PAS)

A simple patient access scheme offering a straight discount of the list price has been referred to NICE for inclusion in this technology appraisal. The PAS was formally agreed with the Department of Health on the 14th January 2016.

2.4 Changes in service provision and management

The infrastructure for the administration of chemotherapeutic agents for the treatment of breast cancer is already in place within the NHS.

LABC/MBC is generally managed by a multi-disciplinary healthcare team in tertiary, secondary and primary care. The location of care for eribulin, along with staff usage, and the cost of administration, monitoring and tests is similar to other IV chemotherapeutic agents currently used in clinical practice. In England to date, eribulin has been given to more than 2300 patients through the Cancer Drugs Fund and does not require additional resource over and above the provision of other IV chemotherapeutic agents within the NHS.

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

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

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

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

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

2.5 Innovation

Eisai do consider eribulin to be innovative as it is a non-taxane inhibitor of microtubule dynamics, with a unique mechanism of action and it is the first and only single chemotherapy agent to demonstrate a statistically significant overall survival benefit in patients with late stage LABC/MBC compared to other available therapies.

As described in Section 2.1, eribulin exerts its anticancer effects via a tubulin-based antimitotic mechanism leading to G2/M cell cycle arrest, disruption of mitotic spindles, and ultimately, apoptotic cell death following prolonged mitotic blockage (1,2). It does this by inhibiting the growth phase of microtubule dynamics, without affecting the shortening phase,

and sequesters tubulin into non-productive aggregates (1). This pattern is distinct from that of members of tubulin-targeting classes currently in clinical use, including taxanes (e.g. docetaxel) and vinca alkaloids (e.g. vinorelbine).

Preclinical studies in human breast cancer models have shown that eribulin also exerts profound effects on tumour biology and microenvironment that are unrelated to its classical antimitotic effects. These effects include (i) tumour vascular remodelling, resulting in enhanced tumour core perfusion and elimination of hypoxia, (ii) reversal of epithelial-mesenchymal transition (EMT) resulting in less aggressive tumour phenotypes, and (iii) profound decreases in tumour cell migration and invasion capacity, parameters that directly affect tumour metastatic potential. (5)

Importantly, as stated above, 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 having progressed after first line chemotherapy. These are patient populations with limited treatment options and an unmet medical need. Clinical data to support the overall survival benefit with eribulin is taken from the Phase III studies, Study 305 (EMBRACE) (6,7,8,9) and study 301 (10,11,12) and is described in detail in Section 4.

In both of these patient subgroups, none of the current NICE-approved treatments have demonstrated a survival benefit over any other.

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

3 Health condition and position of the technology in the treatment pathway

Disease overview

Disease incidence

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. The incidence has almost doubled over the last three decades, with over 47,000 women (> 99% of cases) and around 300 men (< 1%) newly diagnosed with breast cancer in England and Wales during 2013. 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. (13)

Breast cancer severity and prognosis

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

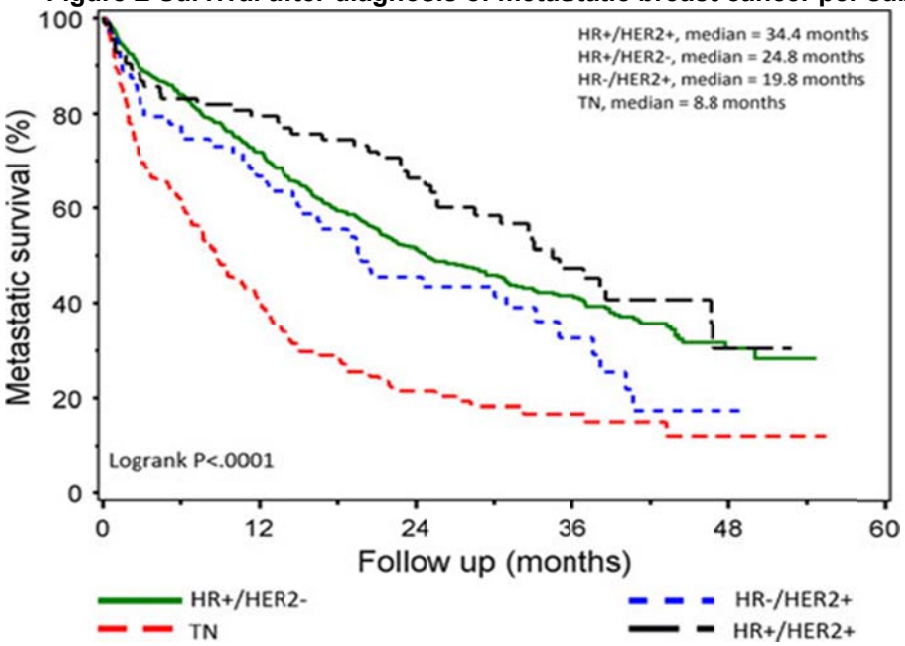
The extent or severity of the cancer can be determined by the Tumour, Nodes, Metastasis (TNM) staging system. The TNM staging system takes into account the size of the tumour, whether the lymph nodes are affected, and whether cancer has spread to other parts of the body (metastasised) (14,15).

LABC/MBC, is the most advanced form of breast cancer, where the cancer is no longer localised to the breast and has spread to other parts of the body, commonly the lungs, liver, brain and bone (15). Although few patients are diagnosed with MBC at the outset (around 5% (16)), the risk of recurrence persists for many years following remission of non-metastatic disease. It is estimated that 30%, 46%, and 71% of patients initially diagnosed with stages I, II, and III disease, respectively, will eventually progress to metastatic disease (16). 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 (17). LABC/MBC has a significant impact on quality of life (18,19,20), and patients commonly suffer psychological and psychiatric disturbances (21).

There is currently no cure for LABC/MBC and the long-term prognosis is poor.

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 HER2-positive targeted therapies, the prognosis of HER2-positive MBC has reversed. (22) In a recent study of 798 patients with metastatic breast cancer, the 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) (23). (Figure 2, overleaf)

Figure 2 Survival after diagnosis of metastatic breast cancer per subtype



Abbreviations: HR, Hormone receptor; HER2, Human epidermal growth factor receptor 2; TN, Triple negative

Effect on patients, carers and society

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

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

Systemic therapy, in the form of hormonal therapies, chemotherapeutic agents (HER2-negative patients), and targeted/biologic agents (HER2-positive patients), are current treatment options for LABC/MBC. There are a variety of single and combination therapies that can be used in a sequential regimen approach; therefore, when disease progression occurs during first-line treatment a second is tried, and so on.

Approximately 85% of patients with LABC/MBC are diagnosed with HER2-negative disease. 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.

Treatment for this advanced stage of the disease is focused on prolonging survival, while controlling the symptoms experienced and improving the patient's quality of life (18).

Overall, quality of life is poor in patients with MBC. MBC patients have lower scores than non MBC in all of the functioning subscales of the EORTC QLQ-C30 (20). Between 25% and 33% of women with MBC report difficulties in physical, role and social functioning. More than 25% of the women report poor global health status. Many patients report difficulties in at least one activity of daily living.

An important goal of MBC treatment is to improve or maintain HRQOL. Tumour response following treatment in MBC has been shown to be associated with improvement in HRQOL (24). HRQOL associated with appetite loss, fatigue and physical functioning have been shown to be prognostic factors for survival (25).

Overall survival is recognised as the most definitive cancer outcome (26) and is of most importance to patients when making decisions regarding treatment options (27).

Clinical pathways of care

Despite recent improvements in the treatment of MBC, there is still no consensus regarding the optimal standard of care for women requiring therapy after initial taxane and anthracycline treatment.

As described previously in the decision problem (Table 1), the populations considered suitable for eribulin treatment within this submission consist of two separate subgroups, namely:

Subgroup 1

1. HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.

Subgroup 2

2. Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated).

In line with the Phase III randomised, controlled trials (RCTs) – Study 305 (EMBRACE) (6,7,8,9) and Study 301 (10,11,12) – prior treatment included an anthracycline and a taxane.

These subgroups and the advanced stage of treatment at which these patients find themselves reflects the indication for eribulin, the population for which evidence is presented herein, and the two possible places for eribulin in the clinical management pathway.

As recognised by NICE guidelines, one of the key priorities for treating this advanced stage of breast cancer is to prolong survival, while controlling the symptoms experienced and improving the patient's quality of life (17). However, none of the available NICE-approved treatment options have demonstrated a survival benefit over any other (17,28).

Clinical Guidelines

The American Society of Clinical Oncology (ASCO) published a clinical practice guideline on chemotherapy and targeted therapy for women with HER2-negative advanced breast cancer in 2014 (31). For first-line chemotherapy at this stage of disease, the guidelines states that no single agent has demonstrated superiority, but that the evidence for efficacy is strongest for taxanes and anthracyclines.

The guidelines then state further that second and later-line therapy may be of clinical benefit and should be offered as determined by previous treatments, toxicity, coexisting medical conditions and patient choice. A qualifying statement reads:
"The most convincing data are for eribulin based on survival superiority against best standard treatment in a recent large RCT, but there is a lack of good comparative data between these various agents."

Based on the NICE clinical guideline for advanced breast cancer, Clinical Guideline 81 (29), it is recommended that chemotherapy treatment in the advanced setting commences with an anthracycline-based regimen. If disease progresses following anthracycline treatment or in cases where an anthracycline is unsuitable (if the person has previously received anthracycline-based adjuvant therapy or has a contraindication to anthracyclines), systemic chemotherapy should be offered in the following sequence:

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

Subgroup 1

1. **HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.**

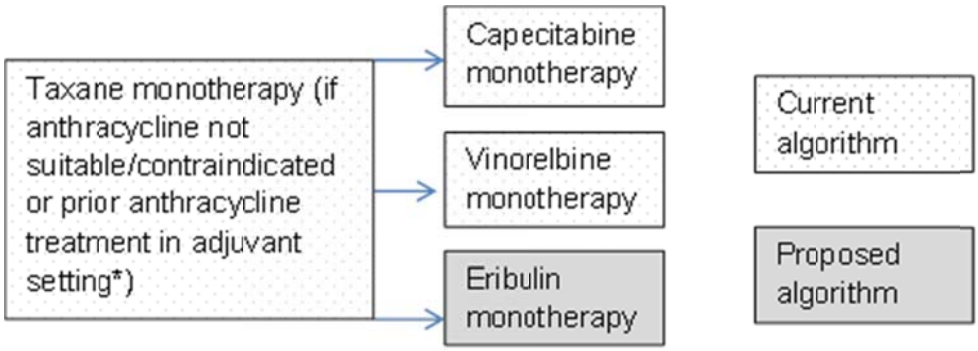
As described above, whereas historically, HER2+ tumour status has been associated with more aggressive disease and poorer patient outcomes; nowadays, those patient with a HER2+ status will receive targeted/biological agents. Therefore the prognosis for HER2-positive patients has reversed (22) and a recent study showed that 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) (23)

Accordingly, the HER2-negative LABC/MBC patient population is considered a particularly difficult group to manage effectively. By this stage patients will have progressed despite initial treatment with anthracyclines and taxanes, and further treatment options will be of limited effectiveness.

As mentioned above, patients with HER2-positive tumour status will nowadays receive targeted/biological agents. It is therefore proposed that in this HER2-negative patient population, eribulin be used as a second-line chemotherapy (as an alternative to capecitabine and vinorelbine).

The current pathway overleaf is based on NICE Clinical Guideline 81 (29) and the proposed position of eribulin in this pathway is depicted in Figure 3.

Figure 3 Current and Proposed Clinical Pathway for Treatment of LABC/MBC



* In the unlikely scenario where patients were able to receive anthracycline treatment, this would be an option prior to taxane monotherapy and the algorithm would then follow as above.

Subgroup 2

2. **Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated).**

In the landmark Phase III study, Study 305 (EMBRACE) where the primary endpoint was overall survival, eribulin was the first cytotoxic agent to improve overall survival in heavily pre-treated patients with MBC versus treatment of physicians' choice (TPC). (6) This is acknowledged in current ESMO (30) and ASCO metastatic breast cancer guidelines (31).

Study 305 randomly allocated women to eribulin or to treatment of the physician's choice (TPC) – in an approach agreed with the European Medicines Agency (EMA).

As highlighted above, both the relevant ASCO clinical guidelines (31) and NICE clinical guidelines (29) reflect that there is no clear standard of care in MBC. The Food and Drug Administration have concluded that TPC is an appropriate comparator in this case (32) and in fact many more recent and ongoing trials have adopted TPC as the control arm. These not only include two studies in breast cancer, the Th3RESA (Trastuzumab Emtansine Versus Treatment of Physician's Choice for Pretreated HER2-Positive Advanced Breast Cancer) trial (33) and the BEACON study (Breast Cancer Outcomes With NKTR-102: A Phase III Open-Label, Randomized, Multicenter Study of Etirinotecan Pegol [NKTR-102] Versus Treatment of Physician's Choice) (34), but also trials in lung cancer and melanoma (32).

In study 305 (EMBRACE), the TPC arm included single agents currently used in LABC/MBC treatment, such as capecitabine, vinorelbine, gemcitabine, anthracyclines and taxanes. This represents "a real-life situation" because it reflects the choices available to oncologists and their patients in the absence of a clear standard of care. Offering patients a choice of treatment and taking their preferences into account is crucial to this approach.

The agents that make up the TPC arm of the study have been validated by a small number of UK clinical experts who indicated that as patients with breast cancer are nowadays living much longer, many patients with MBC would have received anthracyclines and/or taxanes in the adjuvant setting a number of years previously and that it may therefore be appropriate to consider using anthracyclines and/or taxanes again, depending on the individual patient.

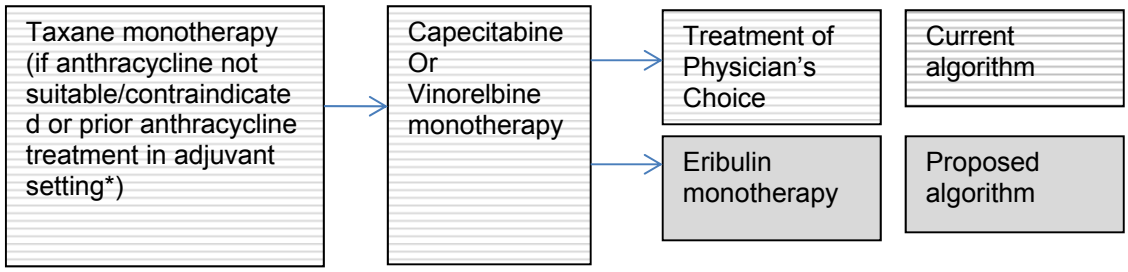
In study 305 (EMBRACE), the majority of patients received capecitabine as a second-line agent for advanced breast cancer. (7)

This mirrors treatment in the UK. Recently published data from independent audits undertaken at the Royal Marsden Hospital (35), Christie Hospital NHS Foundation Trust (36) and Imperial College Healthcare NHS Trust (37) showed that more than 80% of patients had received prior capecitabine when prescribed eribulin under the CDF.

Therefore by using TPC as a comparator in clinical trials and by positioning eribulin for use after capecitabine in this submission, a pragmatic approach is employed to compare eribulin to the current treatment landscape, consisting of a variety of therapeutic options instituted by practicing physicians on a day-to-day basis. Agents making up the TPC group after capecitabine include those which were used by >10% of patients ie vinorelbine and gemcitabine and, as stated above, patients may also be re-challenged with anthracycline and taxane treatment.

It is therefore proposed that eribulin be used as a third-line chemotherapy after capecitabine. The current pathway below is based on NICE Clinical Guideline 81 and the proposed position of eribulin in this pathway is depicted in Figure 4 below.

Figure 4 Clinical Management Pathway for LABC/MBC



* In the unlikely scenario where patients were able to receive anthracycline treatment, this would be an option prior to taxane monotherapy and the algorithm would then follow as above.

Current clinical practice

Whilst the NICE clinical guidelines clearly defines vinorelbine monotherapy and capecitabine monotherapy as options for second-line treatment and beyond, in clinical practice, as indicated above, it is apparent that for patients with LABC/MBC, particularly at this advanced point in their treatment, numerous types of treatment may be used. The choice of treatment will depend on factors including HER2-status, prior chemotherapy exposure and response, tolerability, patient preference, availability of drugs, the patient's quality of life and performance status (17,29).

Therefore, there may be more interventions used in clinical practice at second-line or later than those outlined in the NICE clinical guideline and this is reflected in the agents making up the TPC arm of study 305 (6). However, as acknowledged by NICE (17), there is minimal high-quality evidence about the relative clinical effectiveness of treatments used in this setting.

It is clear that eribulin provides a much needed evidence-based treatment option for patients whose disease has progressed after at least one prior chemotherapy regimen in the advanced setting (second-line and later). Eribulin is the first monotherapy to demonstrate statistically significant improvements in OS in LABC/MBC patients previously treated with an anthracycline and a taxane, while offering a safety and tolerability profile that is acceptable for a follow-on chemotherapeutic agent.

Life expectancy of people with LABC/MBC

As mentioned above, there is currently no cure for LABC/MBC and the long-term prognosis is poor.

Whereas 5-year survival rates of 99% have been reported for tumours diagnosed at the earliest stage, 5-year survival in those diagnosed with metastatic disease is low, around 15% (38). As reported in the NICE assessment report for lapatinib and trastuzumab, the average length of survival following diagnosis of MBC is 12 months for those receiving no treatment, compared with 18-24 months for those receiving chemotherapy. (39)

Number of patients in England & Wales with LABC/MBC

The number of patients in England and Wales who have LABC/MBC and are eligible to receive eribulin ie have progressed after at least one chemotherapeutic regimen for advanced disease are estimated below and detailed in Section 8.

Country	Input	Output	Source
Population of England & Wales		57,408,700	https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates#timeseries
PREVALENCE + INCIDENCE:			
Prevalence of Breast Cancer (BC)	0.14%	80,372	Cancer Mpact database, Kantar Health (97)
Prevalence of Metastatic Breast Cancer (MBC)	7.39%	5,940	Cancer Mpact database, Kantar Health (97)
Patients receiving Chemo	100.00%	5,940	Assumption
Patients on Second Line Chemo	65.37%	3,883	Cancer Mpact database, Kantar Health (97)

Issues relating to current clinical practice

Pre-treated breast cancer patients, such as those considered by this submission, have limited treatment options. The chemotherapeutic agents with the best efficacy in breast cancer, the anthracyclines and taxanes, are typically used at earlier stages of the disease, leaving many LABC/MBC patients anthracycline and taxane-resistant, and thereby limiting the number of treatment options at this stage of disease (40).

The proportion of patients responding to chemotherapy declines through successive lines of treatment (41), while no RCTs of the current NICE-approved monotherapies have demonstrated a survival advantage over any other single agent in the treatment of anthracycline and taxane-resistant metastatic disease (28). This is a weakness in the clinical evidence acknowledged by NICE (17), particularly as the majority of patients believe that the primary goal of treatment is to prolong their life (27).

The tolerability of current LABC/MBC treatment varies; chemotherapy agents can be particularly toxic and are recognised to be the most burdensome aspect of cancer management for patients (42). Side effects commonly include peripheral neuropathy, alopecia, mucositis, nausea, vomiting, increased infection, and fatigue. These can adversely affect a patients' quality of life (42), be costly to manage (43), and lead to early discontinuation of a particular therapy (44) in a significant number of patients, thereby impacting on overall treatment outcomes.

As such, management of patients with LABC/MBC is a trade-off between the risk of unpleasant side effects (toxicity) and the potential benefits (clinical efficacy, e.g. OS) (17). Treatment choices are thus strongly influenced by physician and patient preference in terms of side effect profiles and outcomes such as OS.

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

- The majority of chemotherapy regimens require IV administration and vary in their infusion times (e.g. paclitaxel is administered over 3 hours). Patients may experience difficulties with venous access as a result of multiple prior therapies, while long infusion times can be inconvenient and increase the burden to the patients' lives.
- Variability exists in frequency of dosing schedules (e.g. vinorelbine requires weekly administration). The lack of consistency and the impact that missing doses may have on clinical outcomes mean that patient outcomes may also be inconsistent.
- Many IV chemotherapy regimens require reconstitution or dilution before administration (e.g. gemcitabine, vinorelbine), increasing the burden on healthcare resources, and potentially leading to dosing errors. Vinorelbine is also a vesicant (45).
- Premedication with steroids and/or antihistamines to prevent hypersensitivity reactions during administration is necessary with many chemotherapeutic agents (e.g. docetaxel, paclitaxel). This increases the time required for treatment administration as well as the overall cost of treatment and adds to the potential drug-related adverse effects that the patient may experience.

It is clear through its usage on the Cancer Drugs Fund that eribulin provides a much needed treatment option in the UK. It extends overall survival in LABC/MBC patients without an intolerable side effect profile, and thus maintains patients' quality of life and reduces the need for dose reductions, delays, or discontinuations.

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

Eribulin is the first monotherapy to demonstrate statistically significant improvements in overall survival in LABC/MBC patients previously treated with an anthracycline and a taxane, while offering a safety and tolerability profile that is comparable to other chemotherapeutic agents commonly used in clinical practice. Eribulin is generally well tolerated, with few discontinuations and dose interruptions due to adverse events.

There is also no evidence that eribulin is a vesicant or irritant (Halaven SPC - Appendix 1). Furthermore, eribulin is provided as a ready to use solution, avoiding the need for time consuming reconstitution or dilution associated with many IV chemotherapeutic agents. It is

administered as a quick and convenient 2-5 minute IV infusion with no special handling or tubing required.

As such, the use of eribulin may be associated with healthcare resource savings. Each cycle of treatment with eribulin consists of only two doses, administered on Days 1 and 8 of the 21-day cycle. Pre-medication (antihistamine or steroids) to prevent hypersensitivity reactions is not routinely required prior to injection.

Identification of equality issues

There are no specific equality issues.

4 Clinical effectiveness

Summary of efficacy

In the absence of a single standard of care for women with pre-treated breast cancer, study 305 (EMBRACE) randomly allocated 762 women who had previously received at least two and a maximum of five chemotherapy regimens, in a 2:1 ratio either to eribulin (n=508) or treatment of the physician's choice (TPC; n=254); TPC arm included currently available monotherapies, including capecitabine, gemcitabine and vinorelbine, used in MBC treatment. (6,7) This represents "a real-life situation" because there are no guidelines on which chemotherapy to use at this stage of the disease and reflects choices made by the oncologist and their patients.

In this landmark study where the primary endpoint was overall survival, eribulin was the first cytotoxic agent to improve overall survival in heavily pre-treated patients with MBC versus treatment of physicians' choice (TPC).

- Median overall survival was significantly improved in women assigned to eribulin (13.1 months) compared with TPC (10.6 months), an increase in duration of survival of 23% (2.5 months) (p= 0.041). (7)
- The updated analysis performed after 77% of patients had died and on request of the regulatory authorities, confirmed these results; median OS (eribulin 13.2 months vs. TPC 10.5 months) was improved by 2.7 months (p=0.014). (8)
- The magnitude of the OS should be considered in the context of the population enrolled in this study, which had been pre-treated in the advanced setting with at least 2 previous chemotherapies.

Eribulin also demonstrates consistent efficacy when compared with TPC in a number of secondary outcomes (6,7):

- Median progression free survival (PFS) was 3.6 months for eribulin and 2.2 months for TPC, when assessed by investigator review (p = 0.002), and 3.7 months and 2.2 months, respectively, when assessed by independent review (p = 0.137).
- The objective response rate (ORR; a complete response or a partial response) was 12.2% for eribulin, compared with 4.7% for TPC, when assessed by independent review (p=0.002).
- The clinical benefit rate (complete response and partial response and stable disease for at least 6 months) was 22.6% for eribulin vs 16.8% for TPC, when assessed by independent review

In study 305, patients were pre-stratified by prior capecitabine treatment. The majority of patients in the trial (73.4%) had received prior capecitabine in the metastatic setting. This is in keeping with current UK practice. Recently published data from audits undertaken at three UK hospitals showed that more than 80% of patients had received prior capecitabine when prescribed eribulin under the CDF. (35,36,37)

A further updated OS analysis of study 305 (EMBRACE) was performed after 95% of patients had died and eribulin showed a consistent OS benefit over TPC (9).

- In those patients who had received prior capecitabine treatment (73.4% of the trial population), the OS was statistically significant with a HR of 0.78 (95% CI: 0.65, 0.94).
- Median OS was 13.0 months for eribulin (n=370) and 10.1 months for TPC (n=189), an extension in median survival of 2.9 months (p=0.008).

A second Phase III study in earlier line metastatic breast cancer, Study 301, was an open-label, randomised, study in patients with locally advanced or metastatic breast cancer to investigate the efficacy of eribulin monotherapy compared to capecitabine monotherapy. Patients had previously received up to three prior chemotherapy regimens, including both an anthracycline and a taxane and a maximum of two for advanced disease. The percentage of patients who had received 0, 1 or 2 prior chemotherapy treatments for metastatic breast cancer were 20.0%, 52.0% or 27.2% respectively, making this a predominantly second-line study. (10,11)

Study 301 provides further supporting evidence for the efficacy and safety of eribulin in MBC, against the commonly used agent capecitabine. The duration of OS (in months) was similar to that seen in study 305:

- The median OS among patients receiving eribulin (n=554) was 15.9 months versus 14.5 months in the capecitabine group (n=548), p=0.056
- Eribulin demonstrated a trend favouring improved OS (co-primary endpoint) as compared with capecitabine but this improvement did not reach statistical significance. (10,11)

Importantly, the results of a HRQOL assessment conducted in study 301 show that eribulin does not adversely impact HRQOL (as assessed by EORTC QLQ-C30). The majority of patients (≥74%) in both treatment groups maintained or improved their global health status/HRQOL vs baseline. (83) In addition, separate sub-analyses in subgroup 1 and subgroup 2 show consistent results with those in the overall population.

Study 301 was designed to further evaluate the effect of eribulin on prespecified subgroups including human epidermal growth factor receptor 2 [HER2/*neu*] negative) status. Therefore, patients were pre-stratified according to geographical region and HER2 status. (11)

Upon request from the European Medicines Agency (EMA), a pooled analysis of study 301 and Study 305 (EMBRACE) was undertaken to determine whether the observed benefit of eribulin was consistent:

- The objective of this pooled analysis was to assess OS in the overall intent-to-treat (ITT) population and in subgroups based on HER2 status.
- Treatment with eribulin was associated with an OS benefit over control in most patient subgroups, including HER2-negative (n=1320) (median OS: 15.2 vs 12.3 months; 2.9-month difference; HR: 0.82; p = 0.002). (46,47)
- This study is included in the submission as supportive evidence only of eribulin's consistent overall survival benefit. The results are not used to inform the cost effectiveness analysis (see section 5.2 for further information).

4.1 Identification and selection of relevant studies

Search Strategies

As stated previously, populations considered suitable for eribulin treatment within this submission consist of two separate subgroups, namely:

Subgroup 1:
1. HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.

Subgroup 2:
2. Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated).

Therefore, two systematic reviews were conducted to retrieve relevant clinical data from the published literature regarding the efficacy and safety of eribulin in each of the above patient populations. In both systematic reviews, 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 and restricted to English language only. This was supplemented by additional searching of clinicaltrials.gov and conference proceedings from ASCO, ESMO, AACR and ISPOR. The manufacturer's clinical trial database was also searched for all completed studies from the eribulin clinical trial programme and these were also assessed for inclusion, including unpublished studies.

Using Boolean operators and specific syntax, the searches used terms (including MeSH headings as appropriate) for eribulin, including any alternative names (e.g. Halaven, E7389).

Full details of the search strategies used in both systematic reviews are provided in Appendix 2.

Study Selection

Eligibility criteria

Studies identified were initially assessed based on title and abstract (Step 1). Publications not meeting inclusion criteria in in Step 1 were excluded and listed alongside the reason of study exclusion (Step 2). Full text publications were retrieved from those abstracts meeting inclusion criteria in Step1 and assessed based on the full text. (Step 3) After the full text review, all papers meeting inclusion were retained for data extraction, and those papers not meeting inclusion criteria were excluded and listed alongside the reason for the exclusion.

Inclusion and exclusion criteria for each of the two systematic reviews are shown in Table 5 and Table 6 overleaf.

Table 5 Eligibility criteria used in search strategy: HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.

	Inclusion	Exclusion
Population	Adult patients AND [MBC OR Advanced breast cancer (ABC)] AND HER2-negative AND Following one prior chemotherapy	Non-human OR Children OR Adolescents OR Males OR First line Not distinguished HER2 status OR Neoadjuvant OR Studies with a unique focus on patients from outside Europe/USA were excluded
Intervention	Eribulin (monotherapy)	All other treatments or combinations
Comparator	Any	
Outcomes	PFS, OS (median and percent survival at 1 year), ORR, TTR, duration response, TTP, adverse events	All others
Study design	RCT (Phase II, III or IV) regardless of design (parallel, crossover, open label, single or double blinded) OR Meta-analysis OR Systematic Reviews	Editorials OR Notes OR Comments OR Letters OR Reviews OR Abstracts without full paper available OR Phase I studies
Language	English	Non-English studies

Abbreviations: ABC, Advanced breast cancer; HER2, Human epidermal growth factor receptor 2; MBC, Metastatic breast cancer; ORR, Objective response rate; OS, Overall survival; PFS, Progression free survival, RCT, randomised, controlled trial; TTP, Time to progression; TTR, Time to response

Table 6 Eligibility criteria used in search strategy: Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated)

	Inclusion	Exclusion
Population	Adult patients AND [MBC OR Advanced breast cancer (ABC)] AND AND 3L+	Non-human OR Children OR Adolescents OR Males OR Studies with a unique focus on patients from outside Europe/USA were excluded
Intervention	Eribulin (monotherapy)	All other treatments or combinations
Comparator	Any	
Outcomes	PFS, OS (median and percent survival at 1 year), ORR, TTR, duration response, TTP, adverse events	All others
Study design	RCT (Phase II, III or IV) regardless of design (parallel, crossover, open label, single or double blinded) OR Meta-analysis OR Systematic Reviews	Editorials OR Notes OR Comments OR RWE OR Letters OR Other Reviews OR Abstracts without full paper available OR Phase I studies
Language	English	Non-English studies

Abbreviations: ABC, Advanced breast cancer; HER2, Human epidermal growth factor receptor 2; MBC, Metastatic breast cancer; ORR, Objective response rate; OS, Overall survival; PFS, Progression free survival, RCT, randomised, controlled trial; RWE, Real world evidence; TTP, Time to progression; TTR, Time to response

Flow Diagrams of included and excluded studies

Subgroup 1

1. *HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.*

Following assessment and exclusion of studies based on title, abstract and full text, 8 records from the systematic review, including a clinical study report (CSR), were identified in total covering one eribulin study and a pooled analysis:

- Study 301 (10,11,12)
- Pooled analysis of Study 301 and Study 305 (EMBRACE) (46,47)

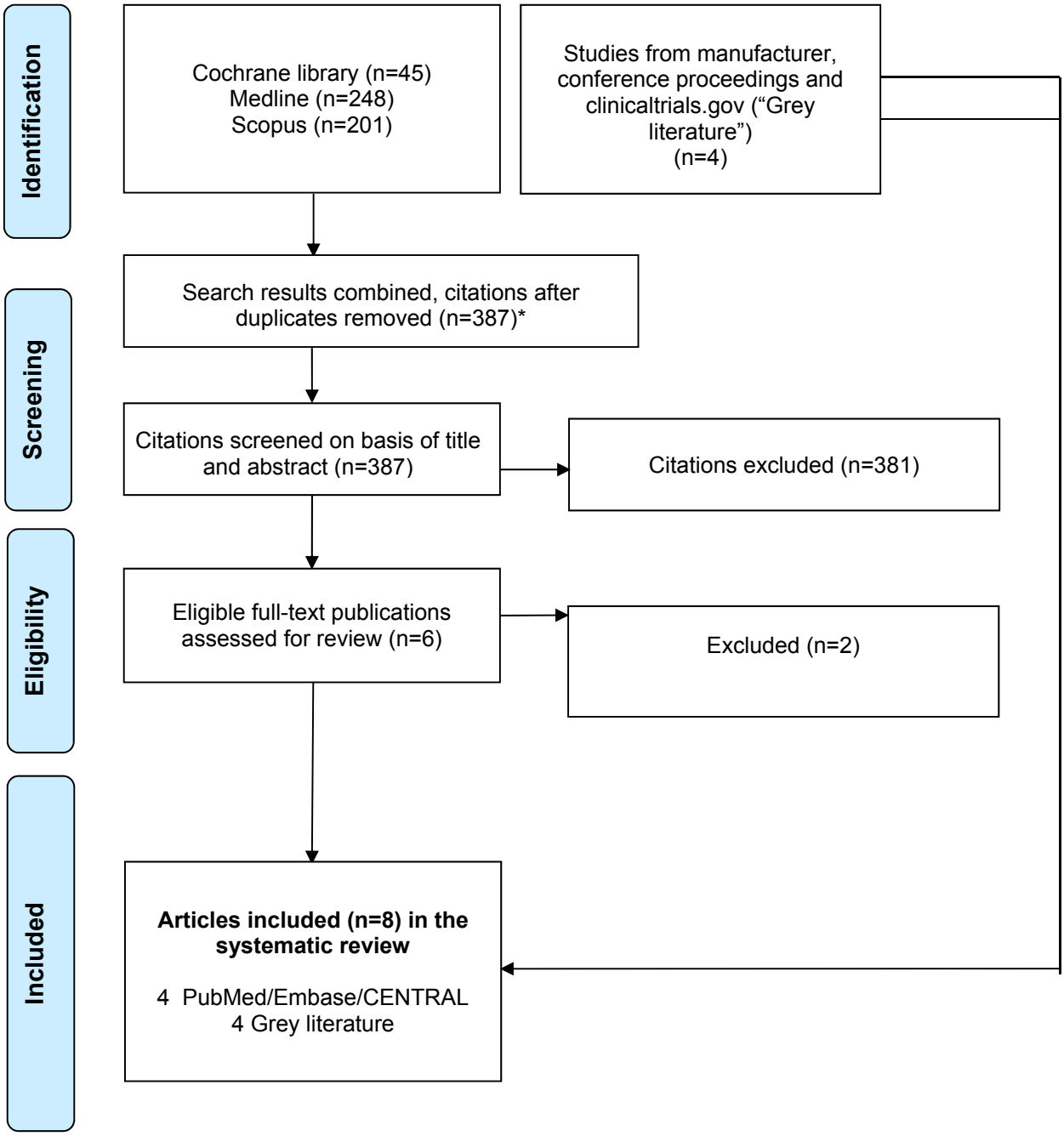
Two records, Twelves et al (48) and Twelves et al (49) were conference abstracts for the pooled analysis that has been subsequently published as a full manuscript by Twelves et al (46).

One record Vahdat et al (49) was designed primarily to assess safety and is discussed further in section 4.

A list of excluded studies is provided in Appendix 2.

The flow diagram for the systematic review is shown in Figure 5 overleaf.

Figure 5 PRISMA Study Attrition Diagram used in search strategy: HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.



*if the information in an poster abstract is overlapped with the content of an article, this poster was considered as a duplicate

Subgroup 2:

2. *Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated)*

Following assessment and exclusion of studies based on title, abstract and full text, 9 records from the systematic review, including a clinical study report (CSR), were identified in total covering one eribulin study:

1. Study 305 (EMBRACE) (6,7,8,9)

Two records were conference abstracts for the EMBRACE study that has been subsequently published in full:

2. Twelves et al (51) and Vahdat et al (52)

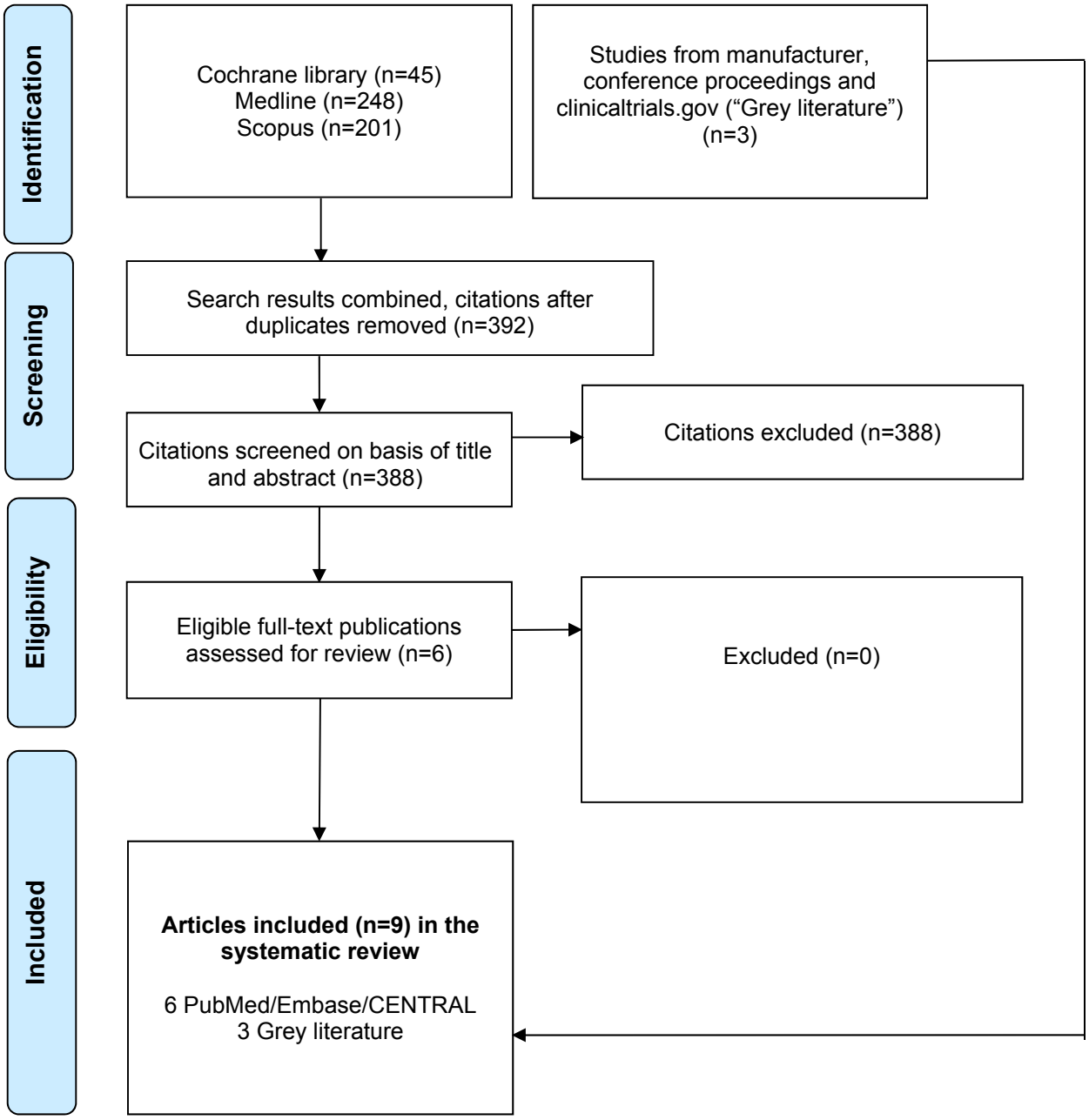
Three records were conference abstracts providing retrospective subgroup analyses of the EMBRACE study. These were all unplanned, exploratory, post-hoc analyses which did not provide additional information relevant to the subgroups described in the decision problem (Table 1) and are therefore not considered further in the submission.

3. Blum et al (53), Cardoso et al (54) and Cortes et al (55)

A list of excluded studies is provided in Appendix 2.

The flow diagram for the systematic review is shown in Figure 6 overleaf.

Figure 6 PRISMA Study Attrition Diagram used in search strategy: Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated)



Data sources of identified studies

Two RCTs for eribulin were identified in the searches and are described further in this submission. The main sources of information for these trials are listed overleaf.

Phase III Study 305 (EMBRACE)

- Cortes et al (6)
- Additional information was drawn from the CSR for the study 305 (E7389-G000-305) (7), as well an additional study report (E7389-G000-305 – update analysis) (8) and a further analysis at 95% of events in those patients who had received capecitabine (9), detailing additional analyses of overall survival from study 305.

Phase III Study 301

- Kaufman et al (10)
- Additional information was drawn from the CSR for Study 301 (E7389-G000-301) (11) and an analysis from study 301 of HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting. (12)

In addition, a pooled analysis of the above Phase III RCTs was identified in the searches and is described further in this submission as supportive evidence only. The results are not used to inform the cost effectiveness analysis (see section 5.2 for further information).

The main source of information for this pooled analysis is listed below.

- Twelves et al (46,47)

4.2 List of relevant randomised controlled trials

The systematic reviews of clinical evidence identified two RCTs of eribulin in the population of interest to this submission and a pooled analysis of these studies. (Table 7)

Study 305 (EMBRACE) compared eribulin with treatment in the form of Treatment of Physician's Choice (TPC), comprising any monotherapy for the treatment of cancer available to the study investigators. TPC is described in more detail in Section 4.3. However, TPC did include the three chemotherapy agents identified in the NICE scope – capecitabine, gemcitabine and vinorelbine (Table 1).

Study 305 (EMBRACE) included patients who had received at least two chemotherapy regimens for metastatic disease (Table 8) and the majority of patients (73.4%) had received prior capecitabine. Therefore this study provides the evidence for subgroup 2 in the decision problem (Table 1).

Study 301 compared eribulin with capecitabine in patients with locally advanced or metastatic breast cancer who had received a maximum of two chemotherapy regimens for advanced disease. This study therefore provides the evidence for subgroup 1 in the decision problem (Table 1).

Table 7 List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
Study 305 (EMBRACE); Phase III, global, randomised, open-label, parallel two-arm, multi-centre study	Eribulin mesilate 1.4 mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle (licensed dosing regimen). (Equivalent to 1.23 mg/m^2 of eribulin, as stated in the SPC)	TPC which could consist of any monotherapy (chemotherapy, hormonal, biologic) or supportive care only.	Patients with LABC/MBC† that had **received two to five prior chemotherapy regimens (≥ two for advanced disease)**, including an anthracycline and a taxane, unless contraindicated	CSR (7) Supporting references: Cortes et al (6) Additional study report of overall survival (8) Further analysis at 95% of events in post-capecitabine patients (9)
Study 301; Phase III, global, randomised, open-label, parallel two-arm, multi-centre study	Eribulin 1.23mg/m^2 2–5 min IV infusion on Days 1 and 8 of a 21-day cycle (licensed dosing regimen).	Capecitabine	Patients with LABC/MBC† that had **received up to three prior chemotherapy regimens (≤ two for advanced disease**), including an anthracycline and a taxane,	CSR (11) Supporting references: Kaufman et al (10) Analysis in HER2-negative 2nd line patients (12)

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

Studies excluded from further discussion

There are no studies which have been excluded from further discussion.

4.3 Summary of methodology of the relevant randomised controlled trials

Two phase III studies involving more than 1,800 patients form the basis of the current licensed indication for eribulin (Halaven SPC – Appendix 1)

Study 305 (EMBRACE)

Study 305 (EMBRACE), the pivotal Phase III eribulin RCT, compared the efficacy and safety of eribulin with Treatment of Physician's Choice (TPC). The selection of TPC as a comparator reflects the real life choices for MBC patients who have already been treated with an anthracycline and a taxane. The patients in this study had locally recurrent or metastatic breast cancer, and had **previously received at least two and a maximum of five chemotherapy regimens**, including an anthracycline and a taxane (unless contraindicated). (6,7)

In study 305, TPC was defined as any available single agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer, radiotherapy or best supportive care. For all patients enrolled in the EMBRACE study a TPC agent was first defined by the physician and this choice could be discussed with the patient to ensure the most appropriate treatment was selected for them. The selection of the TPC agent took place prior to randomisation.

Study 301

The second Phase III study in earlier line metastatic breast cancer, Study 301, was an open-label, randomised, study in patients with locally advanced or metastatic breast cancer to investigate the efficacy of eribulin monotherapy compared to capecitabine monotherapy. Patients had **previously received up to three prior chemotherapy regimens**, including both an anthracycline and a taxane and a maximum of two for advanced disease. (10,11)

Study 301 included some patients who did not receive any prior chemotherapy for advanced disease and therefore not within the current licensed indication. However, the percentage of patients who had received 0, 1 or 2 prior chemotherapy treatments for metastatic breast cancer were 20.0%, 52.0% or 27.2% respectively, making this a predominantly second-line study. (Halaven SPC – Appendix 1)

Pooled analysis

Upon request from the European Medicines Agency (EMA), a pooled analysis of study 301 and Study 305 (EMBRACE) was undertaken to determine whether the observed benefit of eribulin was consistent. (46,47)

The objective of this pooled analysis was to assess OS in the overall intent-to-treat (ITT) population and in subgroups based on HER2 status. Progression-free survival (PFS) was also evaluated.

Trial designs

Study 305 (EMBRACE)

Study 305 was a multi-national, Phase III, open-label, randomised parallel two-arm study, conducted in 762 patients (508 eribulin, 254 TPC) with LABC/MBC (6,7)

Patients were pre-stratified according to geographical region, HER2 status, and prior treatment with capecitabine, and then randomised in a 2:1 ratio to receive either eribulin or TPC. For all patients in the study a TPC agent was first defined; physicians could discuss the TPC option with the patient to ensure the most appropriate treatment was selected for them. The agent of the patient's and physician's choice was then confirmed by the investigator using an interactive voice response system. Patients were then stratified and randomised to one of the two treatment arms according to a randomisation schedule. Centres were required to enter patient identification and information on stratification factors. Treatment allocation and a randomisation number were given for each patient. This process ensured that each agent of the physician's choice was independently randomised against eribulin to support subgroup analyses.

Investigators and patients were not blinded to study treatment as this was an open-label study. However, the Eisai study team was blinded to data for the primary outcome (OS) until database lock to avoid potential bias. Independent statisticians conducted an interim analysis and assisted with queries surrounding all death events.

Study 301

Like Study 305 (EMBRACE), Study 301 was also a multi-centre, Phase III, open-label, randomised parallel two-arm study. It was conducted in 1,102 patients (554 eribulin, 548 capecitabine) with LABC/MBC. (10,11)

Patients were pre-stratified according to geographical region and HER2 status and then randomised in a 1:1 ratio to receive either eribulin or capecitabine. The Eisai study statistical team was blinded to dosing data and treatment group assignment until database lock to avoid potential bias. Independent statisticians conducted the interim analyses and assisted with queries.

Pooled analysis

This was a pooled analysis of study 305 (EMBRACE) and study 301. Adjustment for the study designs and control arms were necessary because of the 2:1 randomisation in EMBRACE, the number of lines of prior therapy and the differing control arms between the studies. (46,47)

Data were stratified by geographical region, previous capecitabine use and study (and by HER2 status in the overall population). For patients with HER2-negative disease, data were also stratified by triple-negative status.

Eligibility criteria

The inclusion and exclusion criteria for the relevant RCTs are summarised in Table 8 overleaf. The pooled analysis included all patients from study 305 (EMBRACE) and Study 301 and therefore the inclusion and exclusion criteria are as per the individual studies.

Both studies 301 and 305 included adult female patients with LABC/MBC who had progressed despite chemotherapy treatment and had an ECOG performance status of two or less. Patients must have previously received an anthracycline and a taxane.

The main difference between the studies relates to the number of prior chemotherapeutic regimens. In Study 305 (EMBRACE), patients had to have received between two and five prior regimens, whereas in study 301, patients were eligible for the study if they had received up to three prior chemotherapeutic regimens and no more than two prior regimens in the advanced or metastatic setting.

Table 8 Eligibility criteria of Study 305 (EMBRACE) and Study 301

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
Study 305 (EMBRACE)	Patients eligible for the study had to meet the following criteria: • Female patients aged ≥ 18 years with confirmed carcinoma of the breast. • Patients with LABC/MBC† who had **received between two and five prior chemotherapeutic regimens**: o Regimens had to include an anthracycline and a taxane in any combination or order. o One or two of these regimens could have been administered as adjuvant and/or neoadjuvant therapy, but at least two had to be given for relapsed or metastatic disease. o Patients had proved refractory to the most recent chemotherapy, documented by progression on or within 6 months of therapy. o Patients with HER2 positive tumours could have additionally been treated with trastuzumab. o Patient could additionally have been treated with hormone therapy. • 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 performance status of zero to two. • Life expectancy of ≥ 3 months. • Adequate renal, bone marrow and liver function, as determined by laboratory tests, based on pre-specified values. • Patients willing and able to comply with the study protocol and gave written consent.	Patients were excluded from the study for any of the following: • Patients who had received chemotherapy, trastuzumab or hormonal therapy within 3 weeks, or any investigational drug within 4 weeks of commencing treatment. • Radiation therapy encompassing > 30% of marrow. • Prior treatment with mitomycin C or nitrosourea. • Pulmonary lymphangitic involvement that resulted in pulmonary dysfunction requiring active treatment. • Patients with brain or subdural metastases, unless they had completed local therapy and had discontinued use of corticosteroids for this indication for ≥ 4 weeks before starting study treatment. • Patients with meningeal carcinomatosis. • Patients who were receiving anti-coagulant therapy (warfarin or related compounds), other than for line patency, and could not have been changed to heparin-based therapy if randomised to eribulin. If a patient was to continue on mini-dose warfarin, then they were to be closely monitored. • Severe/uncontrolled intercurrent illness/infection, significant cardiovascular impairment or known positive HIV status. • Patients with organ allografts requiring immunosuppression. • Patients with pre-existing neuropathy > Grade 2 (≤ Grade 2 neuropathy did not preclude a patient from being enrolled). • Patients with a hypersensitivity to Halichondrin B and/or a chemical derivative. • Patients with a prior malignancy (other than previous breast cancer, carcinoma in situ of the cervix, or non-melanoma skin cancer), unless diagnosed and definitively treated ≥ 5 years previously with no evidence of recurrence. • Women who were pregnant/ breast-feeding; women of childbearing potential with a positive pregnancy test at screening/ no pregnancy test/ surgically sterile/ using adequate contraception measures.
Study 301	Patients eligible for the study had to meet the following criteria: • Female patients aged ≥ 18 years with confirmed carcinoma of the breast. • Patients with LABC/MBC† who **had received up to three prior chemotherapeutic regimens and no more than two prior regimens for advanced and/or metastatic disease***:	Patients were excluded from the study for any of the following: • Patients who had received > three prior chemotherapy regimens for their disease, including adjuvant therapies, or who received more than two prior chemotherapy regimens for advanced disease • Patients who had received capecitabine as a

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	o Regimens had to include an anthracycline and a taxane either in combination or in separate regimens. o Patients must have progressed during or after their last anticancer therapy, and this was to be documented. o Patients with HER2 positive tumours could have additionally been treated with trastuzumab in centres where this was available. o Patients with known ER positive tumours could additionally have been treated with hormone therapy. • Resolution of all chemotherapy or radiation-related adverse events to Grade 1 severity or lower, except for stable sensory neuropathy > Grade 2 and alopecia. • ECOG performance status of zero to two. • Life expectancy of ≥ 3 months. • Adequate renal, bone marrow and liver function, as determined by laboratory tests, based on pre-specified values. • Patients willing and able to complete the EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) with breast cancer module QLQ-BR23 and Pain VAS • Patients willing and able to comply with the study protocol and gave written consent.	prior therapy for their disease • Patients who had received chemotherapy, radiation or biological therapy within 2 weeks, or hormonal therapy within 1 week before study treatment start, or any investigational drug within 4 weeks before study treatment start. • Radiation therapy encompassing > 30% of marrow. • Prior treatment with mitomycin C or nitrosourea. • Pulmonary lymphangitic involvement that resulted in pulmonary dysfunction requiring active treatment, including the use of oxygen. • Patients with brain or subdural metastases, unless they had completed local therapy and had discontinued use of corticosteroids for this indication for ≥ 4 weeks before starting study treatment. • Patients with meningeal carcinomatosis. • Patients who were receiving anti-coagulant therapy (warfarin or related compounds), other than for line patency, and could not have been changed to heparin-based therapy. If a patient was to continue on mini-dose warfarin, then they were to be closely monitored. • Severe/uncontrolled intercurrent illness/infection, significant cardiovascular impairment or known positive HIV status. • Patients with organ allografts requiring immunosuppression. • Patients with pre-existing neuropathy > Grade 2 (≤ Grade 2 neuropathy did not preclude a patient from being enrolled). • Patients with a hypersensitivity to Halichondrin B and/or a chemical derivative. • Patients with a prior malignancy (other than previous carcinoma in situ of the cervix, or non-melanoma skin cancer), unless diagnosed and definitively treated ≥ 5 years previously with no evidence of recurrence. • Women who were pregnant/ breast-feeding; women of childbearing potential with a positive pregnancy test at screening/ no pregnancy test/ surgically sterile/ using adequate contraception measures.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EMBRACE, Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389; EORTC, European Organization for Research on the Treatment of Cancer; ER, oestrogen receptor; HER2, Human epidermal growth factor receptor 2; HIV, Human Immunodeficiency Virus; LABC, Locally advanced breast cancer; MBC, Metastatic breast cancer; VAS, Visual Analogue Scale †Defined in study 305 and study 301as locally recurrent or MBC.
* Any single-agent therapy, and any combination of cytotoxic, hormonal, biological targeted agents, and/or humanized antibodies, scheduled to be administered as a preplanned treatment, given concomitantly, sequentially, or both, was considered one regimen. Planned neoadjuvant chemotherapy (to debulk the tumour prior to surgical intervention) plus postoperative adjuvant chemotherapy was also considered one regimen.
Source: 7,11

Settings and Locations where data were collected

Study 305 (EMBRACE) was conducted in 135 secondary care centres in 19 countries (Argentina, Australia, Belgium, Brazil, Canada, Croatia, Czech Republic, France, Germany, Hungary, Italy, Poland, Russia, South Africa, Spain, Switzerland, Turkey, United Kingdom, and the United States). Fifty-one patients at 10 centres in the United Kingdom were treated.

Study 301 was conducted in 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). There were no UK centres.

Trial drugs and concomitant medications

Study 305 (EMBRACE)

Eribulin (n=508, randomised)

- Eribulin administered as an IV infusion of 1.23 mg/m^2 over 2–5 minutes on Days 1 and 8 of a 21 day cycle.
- Patients moved from cycle to cycle immediately unless specific grade 3/4 adverse events necessitated a dose delay

TPC (n=254, randomised)

- Defined as any available single-agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer; radiotherapy; or best supportive care, administered according to local practice. The use of other investigational drugs, or products not registered for cancer treatment was not permitted.
- Combination therapies were not allowed, reflecting the higher toxicity generally associated with these treatments (17), and their relatively low use in clinical practice in later lines of therapy.

Medications allowed during the study included: any medication considered necessary for the patient's welfare that was not expected to interfere with the evaluation of the study, at the discretion of the investigator.

Primary prophylaxis with G-CSF for the prevention of neutropenia was not a requirement of the study (unless defined by local practice protocols).

Medications disallowed in the eribulin group during the study included: other investigational drugs; anti-tumour therapies including chemotherapy, hormone therapy, radiation therapy, gene therapy, biologics, or immunotherapy.

Medications disallowed in the TPC group included: any other anti-tumour therapy not identified as the TPC; any drugs not allowed concomitantly with the selected TPC, according to the relevant package insert.

Study 301

Eribulin (n=554, randomised)

- Eribulin administered as an IV infusion of 1.23mg/m^2 over 2–5 minutes on Days 1 and 8 of a 21 day cycle.

Capecitabine (n=548, randomised)

- Capecitabine 1250mg/m2 administered orally twice daily in two equal doses on days 1 to 14, every 21 days

Medications allowed during the study included: any medication considered necessary for the patient's welfare that was not expected to interfere with the evaluation of the study.

As per Study 305 (EMBRACE), primary prophylaxis with G-CSF for the prevention of neutropenia was not a requirement (unless defined by local practice protocols).

Medications disallowed in the eribulin and capecitabine groups during the study included: other investigational drugs; anti-tumour therapies including chemotherapy, hormone therapy, radiation therapy, gene therapy, biologics, or immunotherapy.

Outcome measures and assessments

As recognised by NICE guidelines, one of the key priorities for treating this advanced stage of breast cancer is to prolong survival, while controlling the symptoms experienced and improving the patient's quality of life (17). Both Study 305 (EMBRACE) and Study 301 employed primary and secondary efficacy outcomes, including OS, PFS, ORR and duration of response, that are all commonly used measures of efficacy for breast cancer drugs and clinically relevant.

The primary outcome of OS is considered the most reliable cancer outcome, particularly in the pre-treated population considered here (i.e. short life expectancy, where results are expected in a reasonable timeframe and there are limited effective next line therapies) (26). It is precise and easy to measure, documented by the date of death and thus is not subject to assessment bias. However, no RCTs of the currently NICE-approved monotherapies have demonstrated a survival advantage over any other single agent in the treatment of anthracycline and taxane-resistant MBC (28).

In both Study 305 (EMBRACE) and study 301, OS was the primary outcome measure.

Progression Free Survival (PFS) was a co-primary endpoint in Study 301 and a secondary outcome measure in Study 305 (EMBRACE.) Other secondary outcome measures in both studies included objective response rate. Study 301 assessed Health Related Quality of life as a secondary outcome measure.

The pooled analysis of studies 305 and 301 assessed OS in the overall ITT population and in subgroups based on HER2 status. PFS was also evaluated.

Further details of the outcomes investigated in both Phase III trials and the pooled analysis, together with the measures used to assess these outcomes are provided in Table 9 overleaf.

Table 9 Primary and secondary outcomes of Study 305 (EMBRACE), Study 301 and Pooled Analysis

Trial no. (acronym)	Primary outcome(s)	Assessment Measures	Secondary outcome(s)	Assessment Measures
Study 305 EMBRACE	OS	Defined as the time from the date of randomisation until death from any cause. Survival was recorded during the study and following treatment discontinuation for any reasons other than consent withdrawal. Follow-up for survival was assessed at three-monthly intervals until death.	PFS	Defined as the time from randomisation until disease progression or death due to any cause in the absence of disease progression. Tumour assessment was performed according to the RECIST methodology (56). Baseline tumour assessments were performed within 4 weeks of the start of treatment, consisting of: CT or MRI scans of the chest, abdomen, pelvis, and any other areas of suspected disease; photographs of skin lesions (if present); and bone scans. Tumour assessments were performed in all patients at eight-weekly intervals (± 1 week), or sooner if there was suspicion of disease progression. Scans and photography were performed in those areas where disease was found at baseline, and in any new areas of suspected disease. Bone scans were only repeated during the study if clinically indicated. Tumour responses were confirmed by a second assessment ≥ 4 weeks later. Patients with CR/PaR or SD, 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 both the investigator's assessment of disease (imaging data and clinical examination) and an independent blinded review of imaging data.
			ORR	Defined as the number of patients with a confirmed complete response (CR) or confirmed partial response (PaR) divided by the number of patients in the analysis population. 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. Tumour response was evaluated according to RECIST criteria (56) Target and non-target lesions were assigned to response assessment categories (Table 10), and the overall tumour response determined for all possible combinations of target and non-target lesions, with or without the occurrence of new lesions (Table 11)

Trial no. (acronym)	Primary outcome(s)	Assessment Measures	Secondary outcome(s)	Assessment Measures
Study 301	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.	ORR	Defined as the number of patients with a confirmed complete response (CR) or confirmed partial response (PaR) divided by the number of patients in the analysis population. Tumour assessment was performed according to the RECIST methodology (56). 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 patients 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. Tumour responses were confirmed by a second assessment ≥ 4 weeks later. Patients with CR/PaR or SD, (Table 10, Table 11) who withdrew from treatment before disease progression, continued to have tumour assessments every 3 months until progressive disease or the start of a new anticancer treatment. Tumour assessments were made by investigators via imaging data and clinical examinations. Imaging data was independently reviewed (CT, MRI, bone scans, x-rays, and photographs) in a blinded fashion at a central facility. Efficacy outcomes of tumour response were presented for both investigator and independent reviews.
	PFS	Defined as the time from the date of randomisation to the date of recorded progression of the disease (see tumour assessment details) or the death of the subject from any cause, whichever occurred first. Analyses were conducted based on the investigator's assessment of disease (imaging data and clinical examination) and an independent blinded review of imaging data.	HRQOL	HRQOL was assessed using the using EORTC QLQ-C30 (version 3.0) (77,80) and the breast module QLQ-BR23 (version 1.0) (56) questionnaires at baseline, 6 weeks and 3, 6, 12, 18 and 24 months (or disease progression/treatment change), and at unscheduled visits (10). Baseline EORTC questionnaires were completed in clinic before randomisation. Subsequent questionnaires were completed in the clinic before any study-related procedures for that visit and before tumour assessment results were communicated to the patient. Patients were asked to complete questionnaires at each clinic visit, even if they had declined previously. Compliance was assessed by counting completed questionnaires. The QLQ-C30 consists of 30 questions addressing 5 functional scales (cognitive, emotional, physical, social, and role), 9 symptom scales (appetite loss, constipation, diarrhoea, dyspnoea, fatigue, financial difficulties, insomnia, nausea and vomiting, and pain), and 1 GHS/QoL scale.

Trial no. (acronym)	Primary outcome(s)	Assessment Measures	Secondary outcome(s)	Assessment Measures
				The EORTC QLQ-BR23 focuses on breast-cancer-specific issues and includes 23 questions addressing 4 functional (body image, future perspective, sexual enjoyment, and sexual functioning) and symptom scales (arm symptoms, breast symptoms, systemic therapy side-effects, and upset by hair loss). (58) All scores for the EORTC QLQ-C30 and EORTC QLQ-BR23 were transformed to a scale from 0 to 100 (58). Higher scores in the functional scales and GHS/QoL represent an improvement in functioning and HRQoL, whereas higher scores in the symptom scales or items represent deterioration of HRQoL.
Pooled Analysis	OS ITT Population	As per studies 305 and 301	PFS ITT Population	As per studies 305 and 301. Investigator review data were used for this analysis to account for the possible underestimation od the independent review data due to informative censoring.
	OS HER2-negative	As per studies 305 and 301	PFS HER2-negative	As per studies 305 and 301. Investigator review data were used for this analysis to account for the possible underestimation od the independent review data due to informative censoring.

Abbreviations: CR, Complete response; DOR, Duration of Response; EORTC, European Organisation for Research on the Treatment of Cancer; HER2, Human epidermal growth factor receptor 2; HRQoL, Health Related Quality of Life; OS, Overall Survival; ORR, Objective Response Rate, PD, Progressive disease; PaR, Partial response; PFS, Progression Free Survival; QLQ-C30, Quality of Life Questionnaire-Core 30; RECIST, Response evaluation criteria in solid tumours; SD, Stable disease.
Source: 7,11,46

Table 10 Tumour response assessment categories

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

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

Table 11 Objective response criteria

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

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

The methodology of Study 305 (EMBRACE), study 301 and the pooled analysis is summarised in Table 12 overleaf.

Table 12 Comparative summary of methodology of the RCTs and Pooled Analysis

Trial no. (acronym)	Study 305 (EMBRACE)	Study 301	Pooled Analysis
Objective	Primary objective: To evaluate the overall survival of patients treated with eribulin versus TPC in patients with LABC/MBC†, who had received two to five prior chemotherapy regimens. Secondary objectives: To evaluate PFS, ORR, DOR and safety.	Primary objective: To compare the efficacy of eribulin versus capecitabine monotherapy in terms of OS and PFS in subjects with LABC/MBC†. Secondary objectives: To assess QoL, ORR, one, two and three year survival, DOR, tumour related symptoms and safety	Upon request from the EMA, a pooled analysis of study 301 and Study 305 (EMBRACE) study was undertaken to determine whether the observed benefit of eribulin was consistent. The objective of this pooled analysis was to assess OS in the overall ITT population and in important subgroups of breast cancer patients including those based on HER2 status. PFS was also evaluated.
Location	135 secondary care centres in 19 countries, including 10 centres in the UK, treating 51 patients	210 secondary care centres in 24 countries. There were no UK centres.	As per locations of Study 301 and Study 305 (EMBRACE)
Trial design	A multi-centre, Phase III, open-label, randomised parallel two-arm study, conducted in 762 patients (508 eribulin, 254 TPC) with LABC/MBC†. Patients were pre-stratified according to geographical region, HER2 status, and prior treatment with capecitabine, and then randomised in a 2:1 ratio to receive either eribulin or TPC.	A multi-centre, Phase III, open-label, randomised parallel two-parallel-arm study, conducted in 1,102 patients (554 eribulin, 548 capecitabine) with LABC/MBC†. Patients were pre-stratified according to geographical region and HER2 status and then randomised in a 1:1 ratio to receive either eribulin or capecitabine.	A pooled analysis of studies 305 and 301. Adjustment for study was necessary because of the 2:1 randomisation in EMBRACE. Data were stratified by geographical region, previous capecitabine use and study (and by HER2 status in the overall population). For patients with HER2-negative disease, data were also stratified by triple-negative status.
Eligibility criteria for participants	• Patients previously treated with 2-5 chemotherapy regimens, including a taxane and an anthracycline; **at least 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 performance status of zero to two. • Life expectancy of ≥ 3 months. • Adequate renal, bone marrow and liver function, as determined by laboratory tests, based on pre-specified values.	• Patients 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 > Grade 2 and alopecia. • ECOG performance status of zero to two. • Life expectancy of ≥ 3 months. • Adequate renal, bone marrow and liver function • Patients willing and able to complete the EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) with breast cancer module QLQ-BR23 and Pain VAS	As per eligibility criteria for Study 305 (EMBRACE) and study 301

Trial no. (acronym)	Study 305 (EMBRACE)	Study 301	Pooled Analysis
Intervention(s) (n =) and comparator(s) (n =)	Eribulin (n=508, randomised) Eribulin administered as an IV infusion of 1.23mg/m^2 (equivalent to 1.4mg/m^2 eribulin mesilate) over 2–5 minutes on Days 1 and 8 of a 21 day cycle. TPC (n=254, randomised)	Eribulin (n=554, randomised) Eribulin administered as an IV infusion of 1.23mg/m^2 (equivalent to 1.4mg/m^2 eribulin mesilate) over 2–5 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	Eribulin (n=1062, randomised) Control (TPC or capecitabine, n=802, randomised)
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, any drugs not allowed concomitantly with the selected TPC, according to the relevant package insert.	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 (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.	As per Study 305 (EMBRACE) and study 301
Primary outcomes	OS Further detail on scoring methods and timings of assessments is provided in Table 9.	OS PFS Further detail on scoring methods and timings of assessments is provided in Table 9.	OS in ITT population OS in subgroups based on HER2 and hormone-receptor status Scoring methods and timings of assessments as per Study 301 and Study 305 (EMBRACE)
Secondary outcomes	• PFS • ORR • Safety Further detail on scoring methods and timings of assessments is provided in Table 9.	• ORR • HRQoL • Safety Further detail on scoring methods and timings of assessments is provided in Table 9.	PFS in ITT population PFS in subgroups based on HER2 status Scoring methods and timings of assessments as per Study 301 and Study 305 (EMBRACE)

Trial no. (acronym)	Study 305 (EMBRACE)	Study 301	Pooled Analysis
Pre-planned subgroups	As described above, patients were pre-stratified according to geographical region, HER2 status, and prior treatment with capecitabine Further detail on those patients who received prior treatment with capecitabine in provided in Section 4.8.	As described above, patients were pre-stratified according to geographical region and HER2 status. Further detail on HER2-negative patients who received one prior chemotherapy regimen is provided in Section 4.8.	As described above, the objective of this pooled analysis was to assess OS in the overall ITT population and in important subgroups of breast cancer patients including those based on HER2 status.

Abbreviations: DOR, duration of response; EORTC QLQ-C30; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30; EMA, European Medicines Agency; HER2, Human epidermal growth factor receptor 2; ITT, Intent-to-treat; LD, Longest diameter; MBC, Metastatic breast cancer; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; HRQoL, Health Related Quality of Life; RECIST, Response evaluation criteria in solid tumours; TPC, Treatment of Physician's Choice. †Defined in both studies as locally recurrent or MBC.
Source: 7,11,46

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

Table 13 overleaf provides a summary of the statistical analyses for Study 305 (EMBRACE), Study 301 and the pooled analysis. The table includes information on the hypotheses for the studies, the relevant statistical analysis, sample size and power calculations, as well as the population groups analysed in each study.

Table 13 Summary of statistical analyses in Study 305 (EMBRACE), Study 301 and Pooled Analysis

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Study 305 (EMBRACE)	Study designed to provide evidence to either: • support the null hypothesis, that the survival distributions in the eribulin and TPC groups were equal, or; • to reject this hypothesis in favour of the alternative hypothesis, that the survival distributions between groups are not equal.	**Primary outcome (OS):** • Compared between the randomised treatment groups in the ITT population, • using a two-sided stratified log-rank test at a significance level of 0.049. • test was stratified by HER2 status, prior capecitabine treatment, and geographical region. • Kaplan-Meier survival curves were used to summarise the OS, using 95% limits at selected time points. • Kaplan-Meier estimate of the median survival time, and first and third quartiles was presented with 95% CIs. • HR was presented based on fitting a Cox regression model and was stratified according to the type of treatment received, HER2 status, prior capecitabine treatment and geographical region. • An additional Cox regression model was fitted in which the HR was also adjusted for the number of prior chemotherapy regimens and ER status (covariates).	• Primary analysis was planned to occur when 411 deaths had been recorded; it was estimated that 630 patients in total (420 in eribulin and 210 in TPC) needed to be enrolled, leading to an initial estimated maximum study duration of 26.5 months. As pre-specified in the protocol, the overall event rate was evaluated 15 months after the first patient was recruited. Since the number of deaths was smaller than expected at this point, the sample size was increased to allow up to a maximum of 1,000 patients. Sample size re-assessment was done on an ongoing basis in a blinded fashion. As soon as it became apparent that 411 deaths would be reached within a reasonable timeframe, study recruitment was stopped at 762 randomised patients. The primary analysis was actually performed when 422 (55%) patients had died. • A further updated analysis of OS was conducted at the request of the regulatory authorities, when 77% of deaths had occurred, representing a more mature dataset with longer follow up. Results for this updated analysis are presented.	**Population datasets analysed:** ***ITT population:*** all patients who were randomised, irrespective of whether or not they actually received study treatment or whether they received the medication they were randomised to. ***PP population:*** all patients in the ITT population who met the major inclusion criteria for the study, and who did not have any other major protocol violation. Major violations included patients who were treated on the opposite treatment group than the one to which they were randomised. ***Response evaluable population:*** all patients with measurable disease, defined as the presence of at least one measurable lesion, using RECIST criteria (56). This was identified by independent review. ***Safety population:*** all patients who were randomised and who received at least a partial dose of study treatment. The population was based on the actual treatment received. **Primary outcome measure (OS):** • Primary analysis of the primary outcome (OS) was compared between the eribulin and TPC groups in the ITT population. • These analyses were also performed on the PP population. • For patients for whom a date of death was not recorded, i.e., those who were lost to follow-up or who were alive at the date of data cut-off, time to death was censored at the time of last contact.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		Secondary outcomes: • 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. • Kaplan-Meier plots and the Kaplan-Meier estimates of the medians, and first and third quartiles were presented with the 95% CI for PFS and duration of response. • PFS was compared between the treatment groups using a two-sided stratified log-rank test at the 5% significance level. • ORR was analysed using exact Pearson Clopper 2-sided 95% confidence limits for the tumour response rates in each treatment group, and was statistically compared between the two treatment groups using a Fisher's Exact Test.		**Secondary outcomes:** • PFS was assessed in both the ITT and PP populations, • The response evaluable population was considered the primary population for the analysis of ORR. • For the analysis of PFS, patients who had not progressed on the data cut-off date or who were lost to follow-up, were censored at that date.
Study 301	Study designed to provide evidence to either: • support the null hypothesis, that the survival distributions in the eribulin and capecitabine groups were equal, or; • to reject this hypothesis in favour of the alternative hypothesis, that the survival distributions	**Primary outcome (OS):** • Compared between the randomised treatment groups in the ITT population, • using a two-sided stratified log-rank test at a significance level of 0.04 • test was stratified by HER2 status and geographical region. • Kaplan-Meier survival curves were used to summarise the OS, using 95% limits at selected time points. • Kaplan-Meier estimate of the median survival time, and first and	• The sample size calculation was based on a superiority test for comparing overall survival between the two groups treated with E7389 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 hazard ratio was 0.80 (a 3-month increase	**Population datasets analysed:** ***ITT population:*** all patients who were randomised. ***PP population:*** all patients in the ITT population who received study drug for at least one full cycle and had no major protocol violations. ***Safety population:*** all patients who were randomised and who received at least one dose of study treatment. Analyses of the primary and secondary efficacy endpoints were performed on the ITT

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	between groups are not equal.	third quartiles was 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 **Primary outcome (PFS):** • 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. • Kaplan-Meier plots and the Kaplan-Meier estimates of the medians, and first and third quartiles were presented with the 95% CI for PFS. • PFS was compared between the treatment groups 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.	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.	and PP populations. Safety analyses were performed only on the Safety population. **Primary Outcome Measure (OS):** • Primary analysis of the primary outcome (OS) was compared between the eribulin and capecitabine groups in the ITT population. • For patients for whom a date of death was not recorded, i.e., those who were lost to follow-up or who were alive at the date of data cut-off, time to death was censored at the time of last contact. **Primary Outcome Measure (PFS):** • For the analysis of PFS, patients who had not progressed on the data cut-off date or who were lost to follow-up, were censored at that date.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		Secondary Outcomes (ORR): • Response rate was based on the independent review of disease assessments and investigator's assessments. • Response rate was compared between the two groups using the Cochran-Mantel-Haenszel test with adjustment of stratification factors geographic region and HER2/*neu* status. • If test was not feasible or unreliable due to large number of strata relative to number of responders, Fisher's exact test was used. • Response rate was summarised by treatment group with the 95% CI using Clopper−Pearson method **Secondary Outcomes (HRQoL):** • HRQoL population was defined as patients with QoL assessments at each time point within ITT population. • Data were also analysed separately for patients with HER2-negative or triple-negative disease. • Compliance for completing EORTC questionnaires was evaluated descriptively for each treatment group. • Pattern-mixture models were used to account for data missing-not-at-random (59). No imputation for missing data was conducted. • Mixed models on a set of covariates were performed to estimate effect		**Secondary Outcomes (ORR):** • Subjects with unknown or missing response were treated as nonresponders, i.e., they were included in the denominator when calculating percentages.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		difference on repeated responses over a selected period of time and between treatment arms. • Longitudinal analysis outcomes were expressed as least squares mean and standard error. • To test the difference in least squares mean change from baseline between treatment arms, a 2-sided test with P≤0.05 (unadjusted for multiplicity) was considered to be nominally statistically significant. • MID was defined as smallest difference in scores between groups in the scales of interest, which patients perceived as beneficial. Literature-based threshold values for MID were used for scales in the EORTC QLQ-C30 (60) • Because there are no published MIDs on the QLQ-BR23, a 10-point change was considered consistent with previous estimates (61) • For functional scales, an increase in change score from baseline of ≥1 MID was defined as "improved," a decrease of ≥1 MID was defined as "worsened," and a change in either direction of <1 MID was defined as "stable." • For symptom scales, the same criteria were applied with reverse direction. • Proportions of patients classified as "improved," "stable," or "worsened" were calculated for each scale and		

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		cycle. • Tests of proportions were done using Chi-squared or Fisher's exact tests, as appropriate. • Cox analysis was used to compare the MID changes for eribulin versus capecitabine (using a reference HR of 1). Adjusted values are stated for the HR. • TSW was defined as time until clinically meaningful deterioration by a specified threshold for each patient-reported endpoint. • TSW was calculated for each HRQoL scale using Kaplan-Meier curves. • A proportional hazards model (censoring on death, study drop-out, or study discontinuation) was used to estimate adjusted HR values of TSW plus each respective 95% CI. • For patients with >1 TSW event or who deteriorated without improvement, a generalized estimating equation was used to estimate the relative probabilities of observing TSW between treatment arms.		

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Pooled Analysis	The objective of this pooled analysis was to assess OS in the overall intent-to-treat (ITT) population and in subgroups based on HER2 and hormone-receptor status. Progression-free survival (PFS) was also evaluated.	• Adjustment for study was necessary because of the 2:1 randomisation in EMBRACE. • Median OS and PFS were derived from survival curves adjusted by study. • Cox regression was used to calculate HRs for OS and PFS. • Data were stratified by geographical region, previous capecitabine use and study (and by HER2 status in the overall population). • For patients with HER2-negative disease, data were also stratified by triple-negative status. • *p* values were based on two-sided, stratified, log-rank tests.	As per studies 305 and 301	As per studies 305 and 301

Abbreviations: CI, Confidence Interval; CR, Complete response; DOR, Duration of Response; EORTC, European Organisation for Research on the Treatment of Cancer; HR, Hazard Ratio; ITT, intent-to-treat; HRQoL, Health Related Quality of Life; MID, minimum important differences; ORR, Objective Response Rate; OS, Overall Survival; PD, Progressive disease; PaR, Partial response; PFS, Progression Free Survival; PP, Per Protocol; QLQ-BR23, EORTC breast cancer-specific quality of life questionnaire; QLQ-C30, Quality of Life Questionnaire-Core 30; RECIST, Response evaluation criteria in solid tumours; SD, Stable disease; TPC, Treatment of Physician's Choice; TSW, Time to symptom worsening
Source: 7,11,46,83

4.5 Participant flow in the relevant randomised controlled trials

Participant flow

Study 305 (EMBRACE)

A total of 762 patients were randomised in this study (Table 14 and Figure 7; 508 to eribulin and 254 to TPC (2:1 randomisation; ITT population). Twelve patients were discontinued before the start of treatment (six in each arm), and one patient received a different treatment (eribulin) to the one allocated (TPC). In total, 503 patients received eribulin and 247 patients received TPC (safety population).

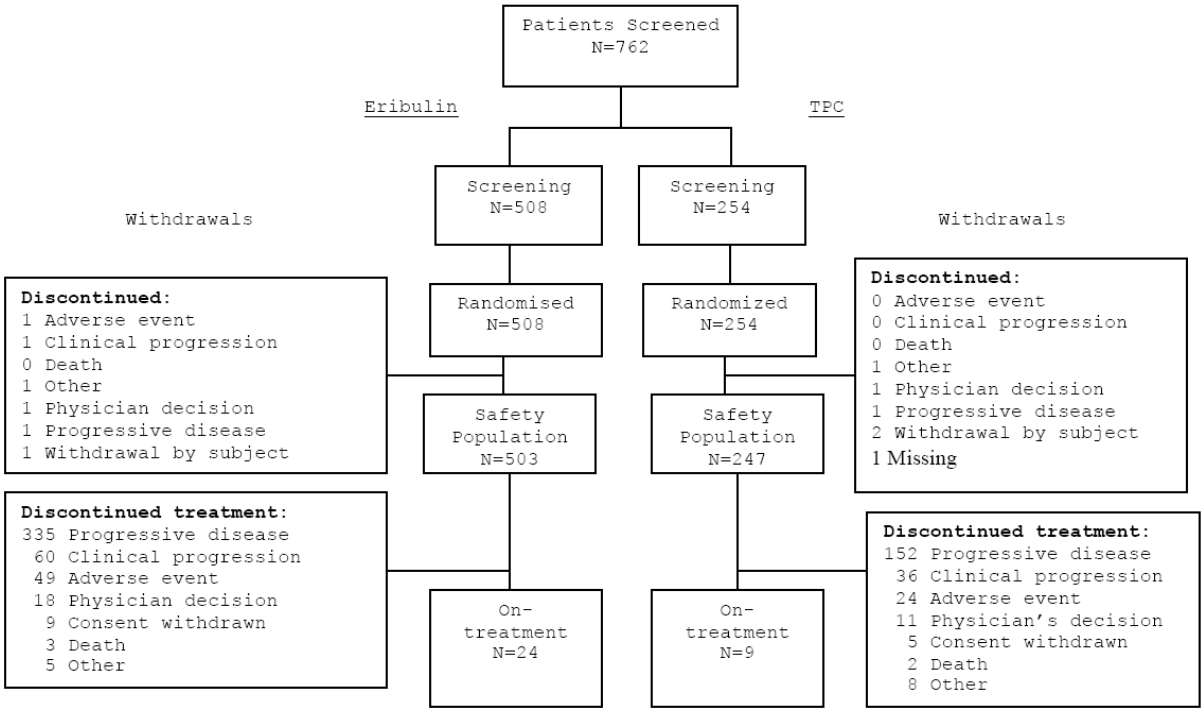
A total of 484 (95.3%) patients in the eribulin group and 244 (96.1%) patients in the TPC group had discontinued study treatment at the time of data cut-off for the primary analysis (when 55% of patients had died; See Section 4.7). The main reason for discontinuation in both treatment groups was progressive disease (assessed by RECIST, Table 14).

Table 14 Patient disposition: Study 305 (EMBRACE)

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

Abbreviations: ITT, Intent-to-treat; PP, Per protocol; RECIST, Response evaluation criteria in solid tumours; TPC, Treatment of Physician's Choice. †Percentages are based on all randomised patients; ‡ITT Population: All patients who were randomised irrespective of whether or not they actually received medication; §Safety Population: All patients who were randomised and who received at least a partial dose of study treatment; ¶Response Evaluable Population: All patients with measurable disease, defined as the presence of at least one measurable lesion, as per RECIST by independent review; ††PP Population: All patients in the ITT Population who met the major inclusion criteria for the study, and who did not have any other major protocol violation; ‡‡Reasons for discontinuation are based on the planned treatment in the ITT Population; §§performed when 55% of people had died.
Source: 7

Figure 7: Study 305 (EMBRACE) study flow chart



Abbreviations: TPC, Treatment of Physician's Choice.
Source: 7

Although best supportive care only and radiotherapy were treatment options in the TPC arm, all treated patients in the TPC group received pharmacotherapy, and are summarised in Table 15 overleaf. Chemotherapy was the most common treatment in the TPC group (n=238, 93.7%, ITT population) followed by hormonal treatment (n=9, 3.5%, ITT population). Although patients could have been treated with biologic therapy (trastuzumab) in centres where this treatment was available, no patients actually received this therapy. The remaining seven patients in the TPC arm (ITT population) were discontinued prior to treatment initiation (n=6) or received eribulin instead of the planned TPC (n=1).

Table 15 Treatment of Physician's Choice: Study 305 (EMBRACE) (ITT population)

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

Abbreviations: ITT, Intent-to-treat; TPC, Treatment of Physician's Choice. †Taxanes included paclitaxel (21 patients), docetaxel (10 patients), nab-paclitaxel (five patients) and ixabepilone (three patients) (one patient received paclitaxel in combination with gemcitabine and was included in the gemcitabine group); ‡Anthracyclines included doxorubicin (19 patients), liposomal doxorubicin (four patients) and mitoxantrone (one patient); §Other chemotherapeutic agents were cisplatin, carboplatin, cyclophosphamide, etoposide, mitomycin, fluorouracil and methotrexate (one patient received cyclophosphamide and methotrexate). ¶The remaining seven patients in the ITT population were discontinued prior to treatment initiation or received eribulin instead of the planned TPC.
Source: 7

Overall exposure to study treatment was longer in the eribulin group compared with the TPC group (118 days vs. 64 days [chemotherapy] and 30 days [hormonal], respectively; Table 16). More than half of patients (58.6%) received five or more cycles of eribulin treatment, with 22.7% (n=114) and 2.4% (n=12) of patients on treatment for > 6 months and > 1 year, respectively. The longer duration of therapy with eribulin demonstrates the superior efficacy and tolerability of eribulin compared with TPC, since therapy was discontinued on disease progression and PFS was longer with eribulin treatment than TPC.

Furthermore, there is a positive safety and tolerability profile demonstrated by eribulin within this trial; specifically, the percentage of patients with dose discontinuation or dose interruption due to AEs experienced was lower in the eribulin group compared with the TPC group (The safety and tolerability of eribulin is discussed further in Section 4.12).

Table 16 Exposure to eribulin: Study 305 (EMBRACE) (Safety population)

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

Abbreviations: NA, Not applicable; TPC; treatment of Physician's Choice.
Source: 7

Study 301

A total of 1,102 patients were randomised in this study (Table 17, Figure 8); 554 to eribulin and 548 to capecitabine. Twelve patients were discontinued before the start of treatment (ten in the eribulin arm and two in the capecitabine arm). In total, 544 patients received eribulin and 546 patients received capecitabine (safety population).

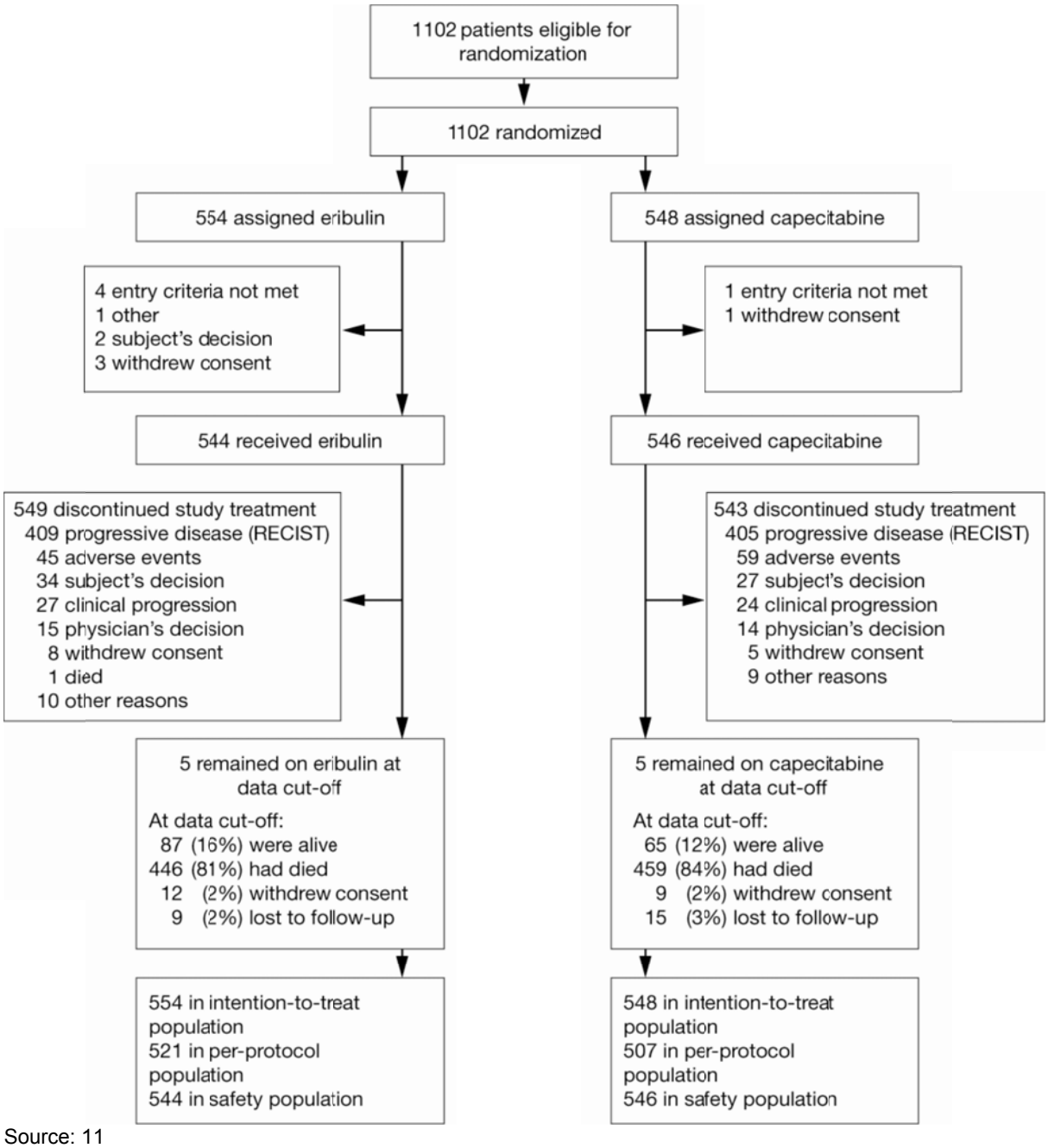
A total of 549 (99.1%) patients in the eribulin group and 543 (99.1%) patients in the capecitabine group had discontinued study treatment at the time of data cut-off; See Section 4.7). The main reason for discontinuation in both treatment groups was progressive disease (assessed by RECIST, Table 17).

Table 17 Patient disposition: Study 301

	Treatment Group		Total
	Eribulin (N = 554) n (%)[†]	Capecitabine (N = 548) n (%)[†]	(N = 1,102) n (%)[†]
Randomised	554	548	1102
ITT Population[‡]	554 (100.0%)	548 (100.0%)	1102 (100.0%)
Safety Population[§]	544 (98.2%)	546 (99.6%)	1090 (98.9%)
PP Population[††]	521 (94.0%)	507 (92.5%)	1028 (93.3%)
Discontinued from study treatment	549 (99.1%)	543 (99.1%)	1092 (99.1%)
Reason for discontinuation from study treatment[‡‡]			
Adverse Events (including toxicity)	45 (8.1%)	59 (10.8%)	104 (9.4%)
Withdrew Consent	8 (1.4%)	5 (0.9%)	13 (1.2%)
Progressive Disease according to RECIST criteria	409 (73.8%)	405 (73.9%)	814 (73.9%)
Clinical progression	27 (4.9%)	24 (4.4%)	51 (4.6%)
Physician's decision	15 (2.7%)	14 (2.6%)	29 (2.6%)
Lost to Follow-up	1 (0.2%)	2 (0.4%)	3 (0.3%)
Death	1 (0.2%)	0 (0%)	1 (0.1%)
Other	5 (0.9%)	6 (1.1%)	11 (1.0%)
Survival Status at data cut-off			
Alive	87 (15.7%)	65 (11.9%)	152 (13.8%)
Died	446 (80.5%)	459 (83.8%)	905 (82.1%)
Lost to Follow-up	9 (1.6%)	15 (2.7%)	24 (2.2%)

Abbreviations: ITT, Intent-to-treat; PP, Per protocol; RECIST, Response evaluation criteria in solid tumours; TPC, Treatment of Physician's Choice. †Percentages are based on all randomised patients; ‡ITT Population: All patients who were randomised; §Safety Population: All patients who were randomised and who received at least one dose of study treatment; ††PP Population: All patients in the ITT Population who received study drug for at least one full cycle and had no major protocol violations; ‡‡Reasons for discontinuation are based on the planned treatment in the ITT Population;
Source: 11

Figure 8: Study 301 study flow chart



Source: 11

Overall exposure to study treatment was similar in the eribulin group compared with the capecitabine group (125 days vs. 119 days, respectively; Table 18). As seen in study 305 (EMBRACE), more than half of patients (56.3%) received five or more cycles of eribulin treatment.

Table 18 Exposure to eribulin: Study 301 (Safety population)

	Eribulin (N=544)	Capecitabine (N=546)
Duration of exposure, median days (min, max)[a]	125 (21–1372)	119 (21-1442)
Number of cycles received, n (%)		
1–2	118 (21.7%)	151 (27.7%)
3–4	120 (22.1%)	107 (19.6%)
5–6	107 (19.7%)	73 (13.4%)
> 6	199 (36.6%)	215 (39.4%)
Range	1–65 cycles	1-61 cycles
Dose intensity, median mg/m^2/week (min, max)[b]	0.86 (0.4, 1.0)	10524.40 (1694.3, 12455.7)
Relative dose intensity, % (min, max)[c]	92% (40, 110)	90% (10, 110)
Patients with dose interruption, n (%)	7 (1.3%)	NA

Abbreviations: 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/m2/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: 11

Baseline characteristics

Demographic data

Demographic data for all patients included in Study 305, study 301 and the pooled analysis are shown in Table 19, overleaf. The two treatment groups were well balanced in terms of demographic characteristics.

The pooled analysis indicates that the median age of patients across both Phase III studies was 54 years and 90.9% of patients were white.

Table 19 Patient demographics: Study 305 (EMBRACE), Study 301 and Pooled Analysis (ITT Population)

Trial no. (acronym) Characteristic	Eribulin	Control	Total
Study 305 (EMBRACE) (n = 762)	**(n = 508)**	**TPC (n = 254)**	**(n = 762)**
Median Age (range)	55.0 years (28–85)	55.0 years (27–81)	55.0 years (27–85)
Age distribution, n (%) < 40 yrs ≥ 40 – < 65 yrs ≥ 65 yrs	 34 (6.7%) 380 (74.8%) 94 (18.5%)	 17 (6.7%) 180 (70.9%) 57 (22.4%)	 51 (6.7%) 560 (73.5%) 151 (19.8%)
Race, n (%) Caucasian Black Asian/Pacific Islander Other	 470 (92.5%) 20 (3.9%) 3 (0.6%) 15 (3.0%)	 233 (91.7%) 14 (5.5%) 2 (0.8%) 5 (2.0%)	 703 (92.3%) 34 (4.5%) 5 (0.7%) 20 (2.6%)
Geographic region, n (%) North America, Western Europe, Australia Eastern Europe Latin America, South Africa	 325 (64.0%) 129 (25.4%) 54 (10.6%)	 163 (64.2%) 64 (25.2%) 27 (10.6%)	 488 (64.0%) 193 (25.3%) 81 (10.6%)
Reproductive status, n (%) Fertile Post-menopausal Surgically sterile Infertile	 46 (9.1%) 379 (74.6%) 78 (15.4%) 5 (1.0%)	 20 (7.9%) 199 (78.3%) 35 (13.8%) 0	 66 (8.7%) 578 (75.9%) 113 (14.8%) 5 (0.7%)
Study 301 (n = 1102)	**(n = 554)**	**Capecitabine (n = 548)**	**(n = 1102)**
Median Age (range)	54.0 years (24–80)	53.0 years (26–80)	54.0 years (24–80)
Age distribution, n (%) ≤ 40 yrs 40 to < 55 yrs ≥ 55 to < 65 yrs ≥ 65 – < 75 yrs ≥ 75 yrs	 59 (10.6%) 220 (39.7%) 179 (32.3%) 89 (16.1%) 7 (1.3%)	 73 (13.3%) 234 (42.7%) 179 (32.7%) 53 (9.7%) 9 (1.6%)	 132 (12.0%) 454 (41.2%) 358 (32.5%) 142 (12.9%) 16 (1.5%)
Race, n (%) White Black or African American Asian/Pacific Islander Other	 496 (89.5%) 15 (2.7%) 18 (3.2%) 25 (4.5%)	 495 (90.3%) 16 (2.9%) 18 (3.3%) 19 (3.5%)	 991 (89.9%) 31 (2.8%) 36 (3.3%) 44 (4.0%)
Geographic region, n (%) North America, Western Europe, Asia Eastern Europe Latin America, South Africa	 137 (24.7%) 307 (55.4%) 110 (19.9%)	 132 (24.1%) 305 (55.7%) 111 (20.3%)	 269 (24.4%) 612 (55.5%) 221 (20.1%)
Reproductive status, n (%) Fertile Post-menopausal Surgically sterile Infertile	 86 (15.5%) 387 (69.9%) 77 (13.9%) 4 (0.7%)	 80 (14.6%) 389 (71.0%) 73 (13.3%) 6 (1.1%)	 166 (15.1%) 776 (70.4%) 150 (13.6%) 10 (0.9%)
Pooled Analysis (n = 1864)	**(n = 1062)**	**(n = 802)**	**(n = 1864)**
Median Age (range)	55 years (24–85)	53.0 years (26–80)	54.0 years (24–80)
Race, n (%) White Black Asian/Pacific Islander Other	 966 (91.0%) 35 (3.3%) 21 (2.0%) 40 (3.8%)	 728 (90.8%) 30 (3.7%) 20 (2.5%) 24 (3.0%)	 1694 (90.9%) 65 (3.5%) 41 (2.2%) 64 (3.4%)

Abbreviations: ITT, Intent-to-treat; TPC, Treatment of Physician's Choice.
Source: 7,11,46

Baseline Disease and Tumour Characteristics

The eribulin and control groups were also generally well-matched in terms of baseline disease and tumour characteristics (e.g. HER2 status, ER/PR status, and site of disease) (Table 20, overleaf).

In the pooled analysis, 47.4% of patients had an ECOG performance status of 0; 51.7% and 4.7% of patients had an ECOG performance status of 1 and 2, respectively. 70.8% of patients in studies 305 and 301 were HER2-negative.

The median duration of disease differed between studies 305 and 301 ie 5.2 years vs 2.8 years respectively. This reflects the fact that in Study 305 (EMBRACE), patients were heavily pre-treated, whereas Study 301 was predominantly a second-line study.

Table 20 Baseline Disease and Tumour Characteristics: Study 305 (EMBRACE), Study 301 and Pooled Analysis (ITT Population)

Trial no. (acronym) Characteristic	Eribulin	Control	Total
Study 305 (EMBRACE) (n = 762)	**(n = 508)**	**TPC (n = 254)**	**(n = 762)**
Median time since original diagnosis (range)	5.4 years (0.1, 37.4)	5.1 years (0.6, 22.9)	5.2 years (0.1, 37.4)
ER Status, n (%)[†]			
+	336 (70.0%)	171 (70.4%)	507 (70.1%)
–	143 (29.8%)	72 (29.6%)	215 (29.7%)
Unknown	1 (0.2%)	0	1 (0.1%)
PR Status, n (%)[†]			
+	254 (56.2%)	123 (54.7%)	377 (55.7%)
–	197 (43.6%)	102 (45.3%)	299 (44.2%)
Unknown	1 (0.2%)	0	1 (0.1%)
HER2 status, n (%)[†]			
+	83 (18.0%)	40 (17.2%)	123 (17.8%)
–	373 (81.1%)	192 (82.8%)	565 (81.6%)
Unknown	4 (0.9%)	0	4 (0.6%)
Triple negative (ER/PR/HER2-negative), n (%)[†]	93 (18.3%)	51 (20.9%)	144 (19.8%)
No. of organs involved[‡], n (%)			
1	85 (16.7%)	35 (13.8%)	120 (15.7%)
2	172 (33.9%)	82 (32.3%)	254 (33.3%)
3	145 (28.5%)	77 (30.3%)	222 (29.1%)
4	71 (14.0%)	37 (14.6%)	108 (14.2%)
5	24 (4.7%)	16 (6.3%)	40 (5.2%)
≥ 6	9 (1.8%)	7 (2.8%)	16 (2.1%)
Tumour sites in > 10% patients overall, n (%)			
Bone	306 (60.2%)	158 (62.2%)	464 (60.9%)
Liver	296 (58.3%)	159 (62.6%)	455 (59.7%)
Lymph nodes	220 (43.3%)	118 (46.5%)	338 (44.4%)
Lung	197 (38.8%)	95 (37.4%)	292 (38.3%)
Pleura	87 (17.1%)	42 (16.5%)	129 (16.9)
Breast	54 (10.6%)	24 (9.4%)	78 (10.2%)
ECOG performance status, n (%)			
0	217 (42.7%)	103 (40.6%)	320 (42.0%)
1	244 (48.0%)	126 (49.6%)	370 (48.6%)
2	39 (7.7%)	22 (8.7%)	61 (8.0%)
Study 301 (n = 1102)	**(n = 554)**	**Capecitabine (n = 548)**	**(n = 1102)**
Median time since original diagnosis (range)	3.0 years (0.2, 28.3)	2.6 years (0.2, 21.6)	2.8 years (0.2, 28.3)
ER Status, n (%)			
+	259 (46.8%)	278 (50.7%)	537 (48.7%)
–	233 (42.1%)	216 (39.4%)	449 (40.7%)
Not done	62 (11.2%)	54 (9.9%)	116 (10.5%)
PR Status, n (%)			
+	227 (41.0%)	234 (42.7%)	461 (41.8%)
–	262 (47.3%)	248 (45.3%)	510 (46.3%)
Not done	65 (11.7%)	66 (12.0%)	131 (11.9%)
HER2 status, n (%)			
+	86 (15.5%)	83 (15.1%)	169 (15.3%)
–	375 (67.7%)	380 (69.3%)	755 (68.5%)
Not done	93 (16.8%)	85 (15.5%)	178 (16.2%)
Triple negative (ER/PR/HER2-negative), n (%)	150 (27.1%)	134 (24.5%)	284 (25.8%)

Trial no. (acronym) Characteristic	Eribulin	Control	Total
No. of organs involved, n (%)			
1	113 (20.4%)	92 (16.8%)	205 (18.6%)
2	174 (31.4%)	177 (32.3%)	351 (31.9%)
3	153 (27.6%)	149 (27.2%)	302 (27.4%)
4	80 (14.4%)	80 (14.6%)	160 (14.5%)
5	25 (4.5%)	31 (5.7%)	56 (5.1%)
≥ 6	9 (1.6%)	18 (3.3%)	27 (2.5%)
Missing	0	1 (0.2%)	1 (0.1%)
Tumour sites in > 10% patients overall, n (%)			
Bone	299 (54.0%)	308 (56.2%)	607 (55.1%)
Liver	247 (44.6%)	271 (49.5%)	518 (47.0%)
Lymph nodes	268 (48.4%)	274 (50.0%)	542 (49.2%)
Lung	279 (50.4%)	280 (51.1%)	559 (50.7%)
Pleura	57 (10.3%)	57 (10.4%)	114 (10.3%)
Breast	113 (20.4%)	104 (19.0%)	217 (19.7%)
Skin	56 (10.1%)	65 (11.9%)	121 (11.0%)
ECOG performance status, n (%)			
0	250 (45.1%)	230 (42.0%)	480 (43.6%)
1	293 (52.9%)	301 (54.9%)	594 (53.9%)
2	11 (2.0%)	16 (2.9%)	27 (2.5%)
3	0	1 (0.2%)	1 (0.1%)
Pooled Analysis (n = 1864)	**(n = 1062)**	**(n = 802)**	**(n = 1864)**
Median time since original diagnosis	4.2 years	3.3 years	3.8 years
ER Status, n (%)			
+	595 (56.0%)	449 (56.0%)	1044 (56.0%)
–	376 (35.4%)	288 (35.9%)	664 (35.6%)
Unknown	91 (8.6%)	65 (8.1%)	156 (8.4%)
PR Status, n (%)			
+	481 (45.3%)	357 (44.5%)	838 (45.0%)
–	459 (43.2%)	350 (43.6%)	809 (43.4%)
Not Done	122 (11.5%)	95 (11.8%)	217 (11.6%)
HER2 status, n (%)			
+	169 (15.9%)	123 (15.3%)	292 (15.6%)
–	748 (70.4%)	572 (71.3%)	1320 (70.8%)
Unknown	145 (13.7%)	107 (13.3%)	252 (13.5%)
Triple negative (ER/PR/HER2-negative), n (%)	243 (22.9%)	185 (23.1%)	428 (23.0%)
No. of organs involved, n (%)			
1	198 (18.6%)	127 (15.8%)	325 (17.4%)
2	346 (32.6%)	259 (32.3%)	605 (32.5%)
3	298 (28.1%)	226 (28.2%)	524 (28.1%)
≥4	218 (20.5%)	189 (23.6%)	416 (22.3%)
ECOG performance status, n (%)			
0	467 (44.0%)	333 (41.5%)	883 (47.4%)
1	537 (50.6%)	427 (53.2%)	964 (51.7%)
2	50 (4.7%)	38 (4.7%)	88 (4.7%)
3	0	1 (0.1%)	1 (0.1%)

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

Source: 7,11,46,62

Prior Chemotherapy Regimens

In both studies 301 and 305, most patients had received at least prior chemotherapy regimen in the adjuvant and/or LABC/MBC setting, with a median duration of the last chemotherapy of 3.53 months and a range of 0 to 32.0 months. In Study 305 (EMBRACE), ninety-nine percent of patients had previously received a taxane, 98.7% had received an anthracycline, and 73.4% had received capecitabine (Table 21).

The figures from the pooled analysis of both studies in Table 21 show that in the eribulin group, patients had most commonly received two prior chemotherapy regimens for advanced disease (35.1% compared with 29.4% in the control group.), whereas patients had most commonly received one regimen for advanced disease in the control group (37.4% compared with 27.1% in the eribulin group). This reflects that as discussed previously, patients with different levels of pre-treatment were eligible for the individual studies. Accordingly, more than half the patients in Study 301 had received only one prior regimen for advanced disease, whereas in Study 305 (EMBRACE), patients had most commonly received two regimens for LABC/MBC.

Table 21 Prior Chemotherapy Regimens: Study 305 (EMBRACE), Study 301 and Pooled Analysis (ITT Population)

Trial no. (acronym) Characteristic	Eribulin	Control	Total
Study 305 (EMBRACE) (n = 762)	**(n = 508)**	**TPC (n = 254)**	**(n = 762)**
No. of prior chemotherapy regimens (adjuvant and LABC/MBC setting), n (%)			
1	1 (0.2%)	0	1 (0.1%)
2	65 (12.8%)	31 (12.2%)	96 (12.6%)
3	176 (34.6%)	83 (32.7%)	259 (34.0%)
4	166 (32.7%)	79 (31.1%)	245 (32.2%)
5	85 (16.7%)	51 (20.1%)	136 (17.8%)
≥ 6	13 (2.6%)	9 (3.5%)	22 (2.9%)
Duration of last chemotherapy (months)			
Median (min, max)†	3.57 (0.0, 32.0)	3.50 (0.1, 25.3)	3.53 (0.0, 32.0)
No. of patients who previously (adjuvant and LABC/MBC setting) received: n (%)			
Taxanes	503 (99.0%)	251 (98.8%)	754 (99.0%)
Anthracyclines	502 (98.8%)	250 (98.4%)	752 (98.7%)
Capecitabine	370 (72.8%)	189 (74.4%)	559 (73.4%)
Study 301 (n = 1102)	**(n = 554)**	**Capecitabine (n = 548)**	**(n = 1102)**
No. of prior chemotherapy regimens (adjuvant and LABC/MBC setting), n (%)			
0	1 (0.2%)	0	1 (0.1%)
1	147 (26.5%)	153 (27.9%)	300 (27.2%)
2	319 (57.6%)	314 (57.3%)	633 (57.4%)
3	84 (15.2%)	78 (14.2%)	162 (14.7%)
4	3 (0.5%)	2 (0.4%)	5 (0.5%)
5	0	1 (0.2%)	1 (0.1%)
Duration of last chemotherapy (months)			
Median (min, max)†	3.1 (0.0, 27.6)	3.1 (0.0, 30.0)	3.1 (0.0, 30.0)
No. of prior regimens in LABC/MBC setting, n (%)			
0	116 (20.9%)	104 (19.0%)	220 (20.0%)
1	280 (50.5%)	293 (53.5%)	573 (52.0%)
2	154 (27.8%)	146 (26.6%)	300 (27.2%)
> 2	4 (0.7%)	5 (0.9%)	9 (0.8%)
Pooled Analysis (n = 1864)	**(n = 1062)**	**(n = 802)**	**(n = 1864)**
No. of prior chemotherapy regimens (adjuvant and LABC/MBC setting), n (%)			
0	1 (0.1%	0	1 (0.1%)
1	148 (13.9%)	153 (19.1%)	301 (16.1%)
2	384 (36.2%)	345 (43.0%)	729 (39.1%)
3	260 (24.5%)	161 (20.1%)	421 (22.6%)
≥ 4	267 (25.1%)	142 (17.7%)	409 (21.9%)
No. of prior regimens in LABC/MBC setting, n (%)			
0	117 (11.0%)	104 (13.0%)	221 (11.9%)
1	288 (27.1%)	300 (37.4%)	588 (31.5%)
2	373 (35.1%)	236 (29.4%)	609 (32.7%)
> 2	284 (26.7%)	161 (20.1%)	445 (23.9%)

Abbreviations: ITT, Intent-to-treat; TPC, Treatment of Physician's Choice. †patients with zero duration of last chemotherapy were patients who received only a single dose of the last chemotherapy agent that they were receiving prior to starting on study; Source: 7,11,46

4.6 Quality assessment of the relevant randomised controlled trials

A quality assessment of studies 305 (EMBRACE) and 301 are presented in Appendix 3.

A summary of the responses applied to each of the quality assessment criteria for both of the RCTs is shown below in Table 22.

Table 22 Quality assessment results for Study 305 (EMBRACE) and Study 301

Trial no. (acronym)	Study 305 (EMBRACE)	Study 301
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	NA	NA
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	NA	NA
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

Abbreviations: NA, Not applicable

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Primary efficacy outcome: Overall survival

Study 305 (EMBRACE) primary analysis (ITT Population) (6,7)

Study 305 met its primary endpoint based: in the primary analysis of OS in the ITT population performed when 55% (422) of patients had died, median OS was significantly longer with eribulin versus TPC (13.1 months/399 days vs. 10.6 months/324 days,

p = 0.041), representing a 23% increase (2.5 months/75 days) in the duration of survival. The use of eribulin reduced the hazard or risk of death by 19% compared with TPC (HR 0.809, 95% CI: 0.660, 0.991). This increase in OS is clinically relevant for patients at this stage of disease and makes eribulin the first and only monotherapy to provide statistically significant improvements in OS in pre-treated patients with MBC.

Study 305 (EMBRACE) updated analysis (ITT Population) (6,8)

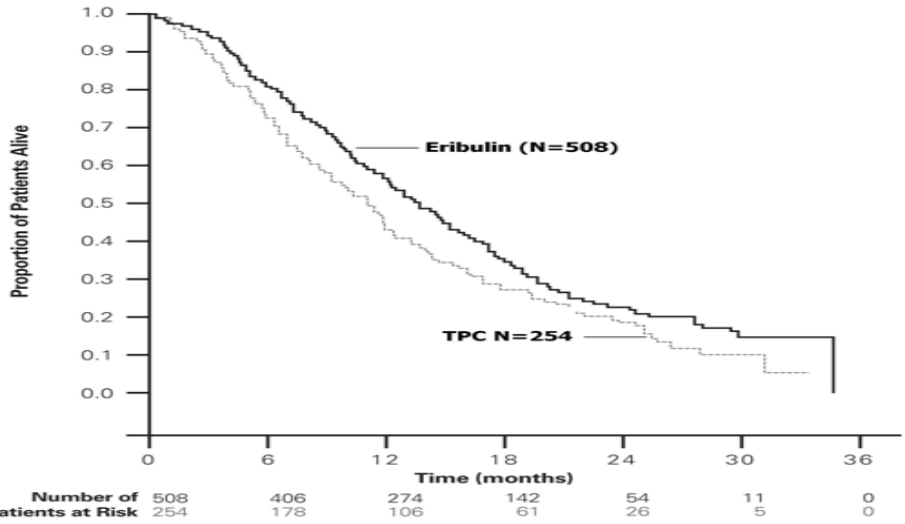
This result was confirmed with an updated OS analysis carried out when 77% of patients had died, with the median OS of the eribulin group (13.2 months/403 days) compared with the TPC group (10.5 months/321 days) improved by 2.7 months (82 days; HR 0.805, 95% CI: 0.667, 0.958, p=0.014) (Table 23 and Figure 9). The updated analysis demonstrates that the survival curves separated early and remained separated for the duration of the analysis (See also SPC [Appendix 1] for results of the updated analysis).

Table 23 Kaplan-Meier analysis of overall survival (updated analysis): Study 305 (EMBRACE) (ITT population)

Parameter	Treatment Group	
	Eribulin (N = 508)	TPC (N = 254)
Number of patients who died†, n (%)‡	386 (76.0%)	203 (79.9%)
Overall Survival, months		
Median (95% CI)	13.2 (12.1, 14.4)	10.5 (9.2, 12.0)
Diff in Medians (95% CI)	2.7 (2.9, 2.4)	
Stratified log-rank test:	p = 0.014	
One-year survival rate, proportion (95% CI)	0.545 (0.501, 0.588)	0.428 (0.367, 0.490)
Two-year survival rate, proportion (95% CI)	0.219 (0.179, 0.260)	0.192 (0.138, 0.246)
HR, (eribulin/TPC): main analysis§		
Estimate (95% CI)	0.805 (0.667, 0.958)	

Abbreviations: CI, Confidence interval; ER, Oestrogen receptor; HER2, Human epidermal growth factor receptor 2; HR, Hazard ratio; ITT, Intent-to-treat; NE, Not estimable due to insufficient events; TPC, Treatment of Physician's Choice. †Updated analysis for study 305 was carried out when 77% of total study patients had died. ‡The remaining patients were censored; §HR based on a Cox model including HER2 status, prior capecitabine treatment, and geographical region as strata.
Source: SPC (Appendix 1) and References 6 and 8

Figure 9: Kaplan-Meier analysis of overall survival (updated analysis): Study 305 (EMBRACE) (ITT population)



Abbreviations: ITT, Intent-to-treat; TPC, Treatment of Physician's Choice.
Source: SPC (Appendix 1) and References 6 and 8

Study 301 primary analysis (ITT Population) (10,11)

In Study 301, the primary analysis for OS was based on 905 (82%) events or deaths in the trial. The median OS among patients receiving eribulin was 15.9 months and 14.5 months in the capecitabine group (Table 24). The hazard ratio (HR) for OS (eribulin vs capecitabine) was 0.879 (95% CI, 0.770 to 1.003), and a p-value of 0.056.

Eribulin demonstrated a trend favouring improved OS as compared with capecitabine but this improvement did not reach statistical significance. It is thought that treatment earlier in the course of MBC is less likely to impact OS (20.0 % and 52% of patients having 0 or 1 prior chemotherapy). Even if therapeutically more active, a first or second line regimen may not impact on OS when multiple subsequent lines of effective treatment are administered. The influence of post-progression therapy on OS may also have had an impact as there was an imbalance with more patients in the eribulin arm receiving further anticancer treatment compared to capecitabine (70.4% and 62.0% respectively).

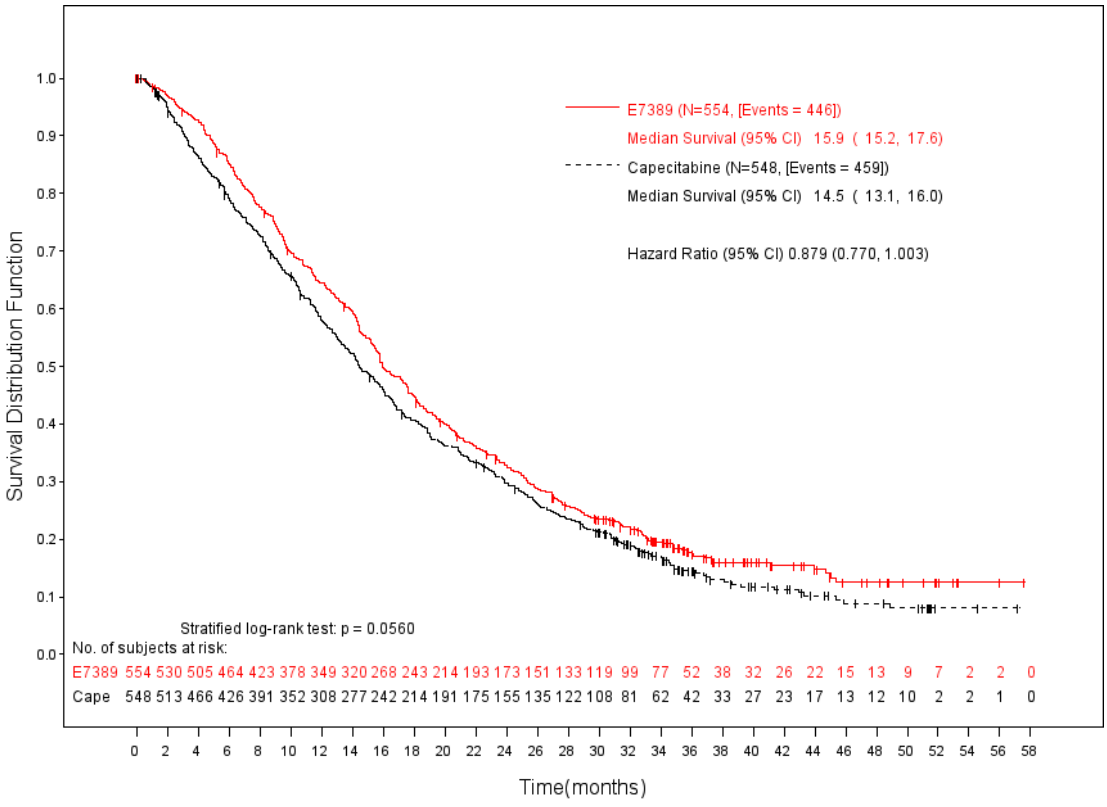
The benefit for OS emerged early and was maintained over the course of the study. Kaplan-Meier analysis of OS in the ITT population is shown in Figure 10, overleaf.

Table 24 Kaplan-Meier analysis of overall survival (primary analysis): Study 301 (ITT population)

Parameter	Treatment Group	
	Eribulin (N = 554)	Capecitabine (N = 548)
Number of patients who died†, n (%)‡	446 (80.5%)	459 (83.8%)
Overall Survival, months Median (95% CI) Diff in Medians (95% CI) Stratified log-rank test:	 15.9 (15.2, 17.6) 1.4 (2.1, 1.6) p = 0.056	 14.5 (13.1, 16.0)
One-year survival rate, proportion (95% CI)	0.644 (0.604, 0.684)	0.580 (0.538, 0.622)
Two-year survival rate, proportion (95% CI)	0.328 (0.289, 0.368)	0.298 (0.259, 0.337)
HR, (eribulin/capecitabine): main analysis§ Estimate (95% CI)	 0.879 (0.770, 1.003)	

Abbreviations: CI, Confidence interval; HR, Hazard ratio; ITT, Intent-to-treat; †Primary analysis for study 301 was carried out when 82% of total study patients had died; ‡The remaining patients were censored; §HR based on a Cox model including HER2 status and geographical region as strata.
Source: SPC (Appendix 1) and References 10 and 11

Figure 10: Kaplan-Meier analysis of overall survival: Study 301 (ITT population)



Source: SPC (Appendix 1) and References 10 and 11

Pooled Analysis: ITT population (46,47)

As described in Section 4.3, upon request from the European Medicines Agency (EMA), a pooled analysis of study 301 and Study 305 (EMBRACE) was undertaken to determine

whether the observed benefit of eribulin was consistent and this data is included in this submission as supportive evidence.

The OS curve in the overall ITT population showed early separation in favour of eribulin that was maintained. Median OS was 15.2 months in patients who received eribulin, compared with 12.8 months in the control group (HR 0.85; 95% CI: 0.77-0.95, *p* = 0.003). (46,47)

Progression-free survival

Study 305 (EMBRACE) (6,7)

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

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

The PFS results were consistent with the OS results, with a longer duration of PFS observed in the eribulin group compared with the TPC group. Overall, treatment with eribulin reduces the risk of progression by 24% (investigator review) and 14% (independent review), compared with TPC (Table 25, overleaf). In the ITT population, median PFS was 3.6 months/110 days for eribulin and 2.2 months/66 days for TPC, when assessed by investigator review (p = 0.002), and 3.7 months/113 days and 2.2 months/68 days, respectively, when assessed by independent review (p = 0.137).

This apparent difference arose from the censoring of almost twice as many patients in the independent review than in the investigator review. Study scans stopped once the investigator had declared disease progression, leading to many censored patients in the independent review, who could only assess nonmeasurable disease for progression if non-target lesions progressed or new lesions appeared. For the PP population, the difference was statistically significant for both investigator and independent analyses (p < 0.05). The maximum effect was observed within the first 6 months; however the difference was apparent from the first radiographic assessment, performed as per protocol at Week 8 (Figure 11).

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

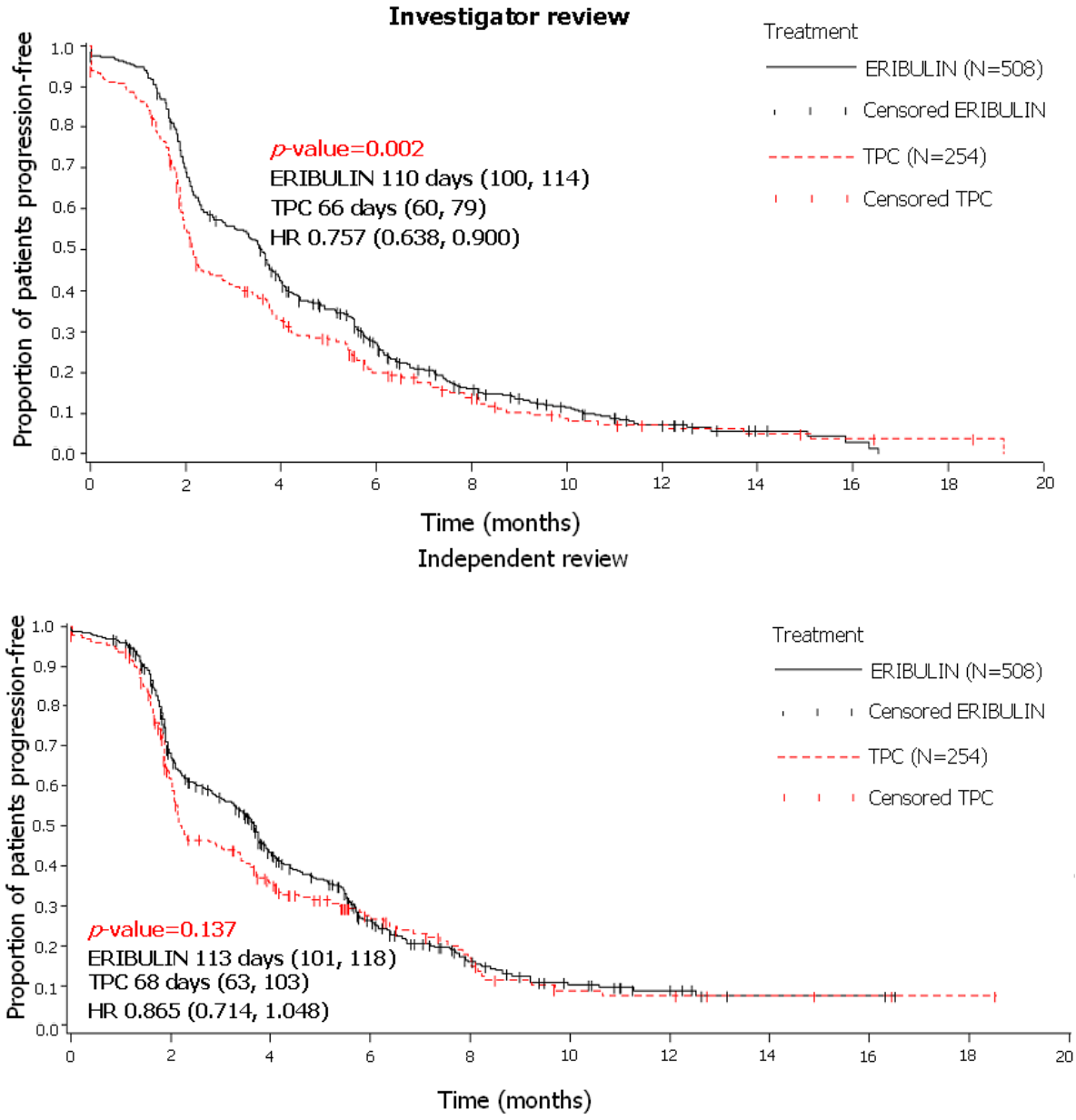
Table 25 Kaplan-Meier analysis of progression-free survival; Study 305 (EMBRACE) (ITT Population)

Parameter	Treatment Group: Study 305 (EMBRACE)			
	Independent review		Investigator review	
	Eribulin	TPC	Eribulin	TPC
ITT Population	**N=508**	**N=254**	**N=508**	**N=254**
Number of patients who progressed or died, n (%)†	357 (70.3%)	164 (64.6%)	429 (84.4%)	206 (81.1%)
Progression-free survival, months				
Median (95% CI)	3.7 (3.3, 3.9)	2.2 (2.1, 3.4)	3.6 (3.3, 3.7)	2.2 (2.0, 2.6)
Diff in Medians (95% CI)	1.5 (1.2, 0.5)		1.4 (1.3, 1.1)	
p-value	0.137		0.002	
HR (eribulin/TPC)‡ Estimate (95% CI)	0.865 (0.714, 1.048)		0.757 (0.638, 0.900)	

Abbreviations: CI, Confidence interval; HR, Hazard ratio; TPC, Treatment of Physician's Choice. †The remaining patients were censored; ‡HR based on a Cox model including HER2 status, prior capecitabine treatment and geographical region as strata
Source: 6 and 7

Figure 11: Kaplan-Meier analysis of progression-free survival: Study 305 (EMBRACE) (ITT population)

Investigator review (top) and independent review (bottom)



Abbreviations: HR, Hazard ratio; TPC, Treatment of Physician's Choice.
Source: 6 and 7

Study 301 (10,11)

Progression-free survival was measured from the date of randomization to the date of recorded progression of disease or the death of the subject from any cause, whichever occurred first. Data used for the primary analysis of PFS were obtained from an independent review of the imaging scans.

The analyses of PFS as assessed by the Independent Review Committee (IRC) and by investigator review are summarised in Table 26 and are presented as Kaplan–Meier plots in Figure 12, respectively. No difference in median PFS as assessed by the IRC was observed between the eribulin and capecitabine treatment groups; PFS was 4.1 and 4.2 months (HR=1.079; 95% CI=0.932, 1.250; *P*=0.3045) for the eribulin and capecitabine groups,

respectively. Progression-free survival using data from the investigator review was similar.

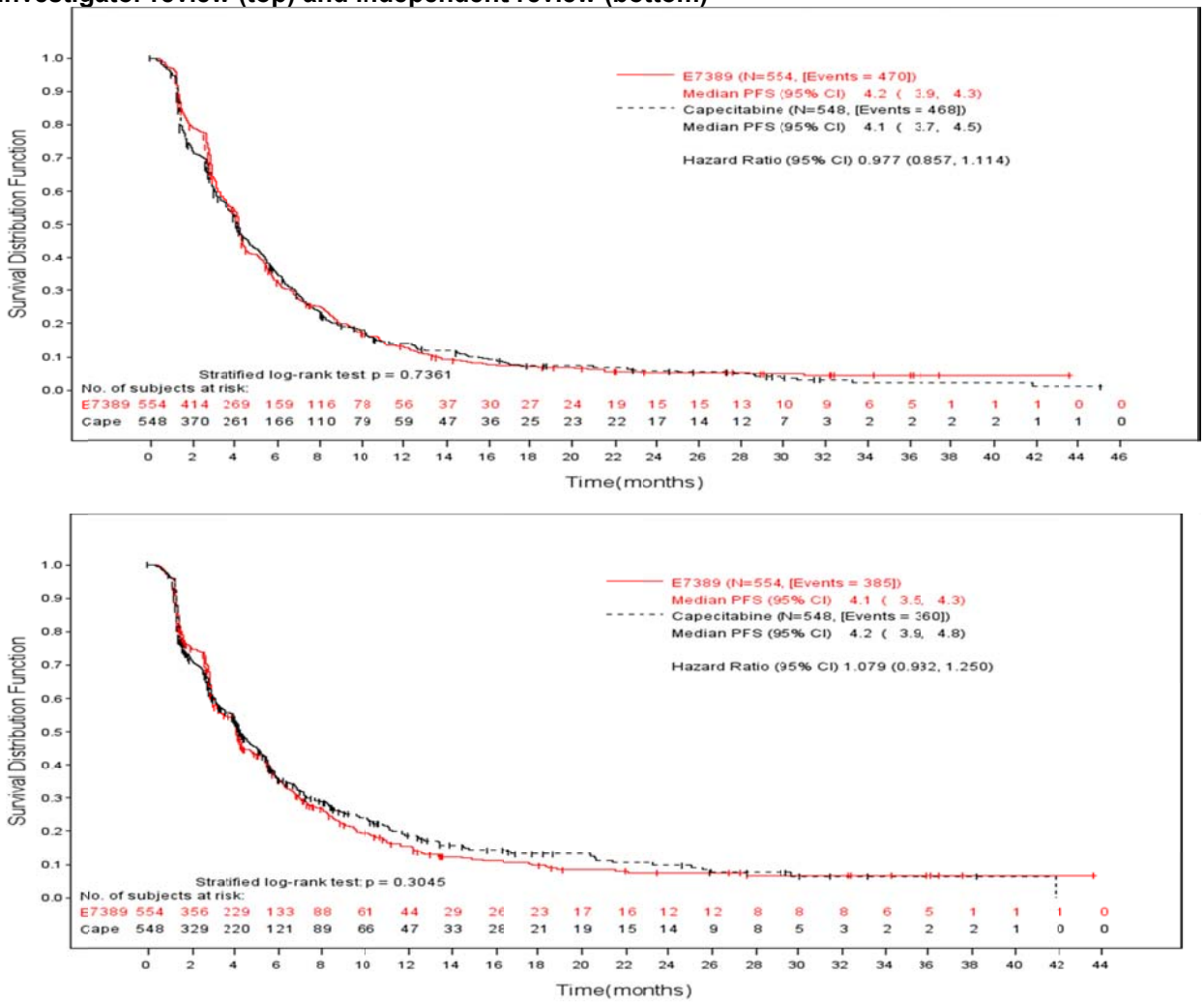
Table 26 Kaplan-Meier analysis of progression-free survival; Study 301 (ITT Population)

Parameter	Treatment Group: Study 301			
	Independent review		Investigator review	
	Eribulin	Capecitabine	Eribulin	Capecitabine
ITT Population	**N=554**	**N=548**	**N=554**	**N=558**
Number of patients who progressed or died, n (%)†	385 (69.0%)	360 (66.0%)	470 (84.8%)	468 (85.4%)
Progression-free survival, months Median (95% CI) p-value	4.1 (3.5, 4.3)	4.2 (3.9, 4.8) 0.3045	4.2 (3.9, 4.3)	4.1 (3.7, 4.5) 0.7361
HR (eribulin/TPC)‡ Estimate (95% CI)	1.079 (0.932, 1.250)		0.977 (0.857, 1.114)	

Abbreviations: CI, Confidence interval; HR, Hazard ratio; †The remaining patients were censored; ‡HR based on a Cox model including HER2 status and geographical region as strata
Source: 10 and 11

Figure 12: Kaplan-Meier analysis of progression-free survival: Study 301 (ITT population)

Investigator review (top) and independent review (bottom)



Abbreviations: Cape, Capecitabine; CI, Confidence Interval; E7389, eribulin; PFS, progression-free survival
Source: 10 and 11

Pooled Analysis (46,47)

As described in Section 4.3, upon request from the European Medicines Agency (EMA), a pooled analysis of study 301 and Study 305 (EMBRACE) was undertaken to determine whether the observed benefit of eribulin was consistent and this data is included in this submission as supportive evidence.

Median PFS in the ITT population was 3.9 months in patients who received eribulin, compared with 3.2 months in the control group (HR 0.88; 95% CI: 0.78-0.98, *p* = 0.020). (46,47)

Objective response rate

Study 305 (EMBRACE) (6,7)

Based on the independent review of patients with measurable disease at baseline (Response evaluable population; n=682), the ORR (patients with a CR or a PaR) was statistically significantly greater for eribulin compared with TPC (12.2% [95% CI: 9.4, 15.5] vs. 4.7% [95% CI: 2.3, 8.4], p = 0.002) (Table 27). Results from the investigator review were similar, with 13.2% (95% CI: 10.3%, 16.7%) of patients receiving eribulin achieving an objective response compared to 7.5% (4.3%, 11.9%) of patients in the TPC group (p = 0.028). The magnitude of the ORR should be considered in the context of the population enrolled in this study, which had been pre-treated in the advanced setting with at least 2 previous chemotherapies.

Study 301 (10,11)

The objective response rate (ORR) based on independent review was 11.0% (95% CI=8.5, 13.9) and 11.5% (95% CI=8.9, 14.5) for subjects in the eribulin and capecitabine groups, respectively (*P*=0.849; (Table 27) The ORR based on investigator review were slightly higher than the rates based on independent review, but neither were statistically significantly different between treatment groups.

Table 27 Objective response rate; Study 305 (EMBRACE) (Response evaluable population) and Study 301 (ITT Population)

Response Category	Treatment Group: Study 305 (EMBRACE)				Treatment Group: Study 301			
	Independent review		Investigator review		Independent review		Investigator review	
	Eribulin (N=468) n (%)	TPC (N=214) n (%)	Eribulin (N=468) n (%)	TPC (N=214) n (%)	Eribulin (N=554) n (%)	Capecitabine (N=548) n (%)	Eribulin (N=554) n (%)	Capecitabine (N=548) n (%)
CR	3 (0.6)	0	1 (0.2)	0	1 (0.2)	0	4 (0.7)	10 (1.8)
PaR	54 (11.5)	10 (4.7%)	61 (13.0)	16 (7.5)	60 (10.8)	63 (11.5)	85 (15.3)	99 (18.1)
SD	208 (44.4)	96 (44.9%)	219 (46.8)	96 (44.9)	313 (56.5)	303 (55.3)	332 (59.9)	278 (50.7)
PD	190 (40.6)	105 (49.1%)	176 (37.6)	97 (45.3)	125 (22.6)	133 (24.3)	99 (17.9)	126 (23.0)
Not Evaluable	12 (2.6)	3 (1.4%)	11 (2.4)	5 (2.3)	11 (2.0)	6 (1.1)	34 (6.1)	35 (6.4)
Unknown[a]	1 (0.2)	0	0	0	44 (7.9)	43 (7.8)	0	0
ORR (CR or PaR)	57 (12.2)	10 (4.7)	62 (13.2)	16 (7.5)	61 (11.0)	63 (11.5)	89 (16.1)	109 (19.9)
95% CI†	(9.4, 15.5)	(2.3, 8.4)	(10.3, 16.7)	(4.3, 11.9)	(8.5, 13.9)	(8.9, 14.5)	(13.1, 19.4)	(16.6, 23.5)
p-value‡	0.002		0.028		0.849		0.100	
CBR (CR+PaR+SD≥6 months)	106 (22.6)	36 (16.8)	130 (27.8)	43 (20.1)	145 (26.2)	147 (26.8)	182 (32.9)	188 (34.3
95% CI†	(18.9, 26.7)	(12.1, 22.5)	(23.8, 32.1)	(14.9, 26.1)	(22.6, 30.0)	(23.2, 30.7)	(29.0, 36.9)	(30.3, 38.4)
p-value	NR		NR		0.838		0.611	

Abbreviations: CBR, Clinical benefit rate; CI, Confidence interval; CR, Complete response; NR, Not reported; PD, Progressive disease; ORR, Objective response rate; PaR, Partial response; SD, Stable disease; TPC, Treatment of Physician's Choice. †Exact Pearson-Clopper 2-sided CI; ‡Fisher's Exact Test; [a] In Study 301, "Unknown" per IRC review included subjects who had no Baseline scans or who had only Baseline scans

Source: 6, 7, 10 and 11

Quality of life

Study 301 (10,11,83)

As described in section 4.3 (Table 9) and section 4.4 (Table 13), HRQoL was assessed in study 301 using the EORTC QLQ-C30 (version 3.0) (77,80) and the breast module QLQ-BR23 (version 1.0) (56) instruments. Based on this data, a post-hoc analysis was conducted to:

- compare physical symptoms, functional scores, and GHS/QoL in patients treated with eribulin versus capecitabine over time;
- estimate the proportion of patients experiencing clinically meaningful changes in HRQoL scales;
- compare the time to meaningful deterioration of HRQoL in both treatment arms, and
- conduct a 'mapping exercise' using a published mapping algorithm in order to estimate EQ-5D utilities from the patient reported outcomes captured in study 301. (Further information on the mapping is provided in section 5.4)

The full results for these patient reported outcomes are presented in a reference by Cortes et al (83) which was identified in the HRQoL literature search conducted for this submission (see Section 5.4) and some results are also presented in the published manuscript for the study (10) and the CSR (11).

Of 1102 patients randomized in study 301, 1062 (96.4%) completed the EORTC questionnaire at baseline and thus formed the HRQoL population.

The baseline scores for both questionnaires were similar (Table 28, overleaf). Across the symptom scales of QLQ-C30 questionnaire, patients had worse scores on fatigue, pain, insomnia, and financial difficulties (means >30).

The scores on QLQ-C30 functional scales were generally good (mean values around and above 70) with the exception of GHS/QoL scale where mean scores around 50 suggest significant impact of disease (63). However, the breast-cancer-specific functional scales of the QLQ-BR23 questionnaire showed impact on all domains for eribulin (mean scores 32–65), in particular, on sexual functioning (mean score 14.0; Table 28).

Table 28 Baseline QLQ-C30 & QLQ-BR23 results

Domain	Eribulin (n = 554)	Capecitabine (n = 548)
EORTC QLQ-C30 questionnaire (mean [SD])		
GHS/QoL	56.3 (22.21)	54.7 (21.67)
Physical functioning	72.9 (21.00)	71.9 (20.68)
Role functioning	73.4 (27.68)	70.0 (29.27)
Emotional functioning	68.8 (23.00)	68.4 (24.15)
Cognitive functioning	81.5 (20.36)	81.4 (21.18)
Social functioning	75.4 (26.28)	73.4 (28.19)
Fatigue	37.4 (23.70)	38.0 (24.72)
Nausea and vomiting	10.0 (18.04)	10.1 (19.33)
Pain	31.8 (28.41)	32.9 (29.45)
Dyspnea	23.3 (27.56)	25.1 (29.45)
Insomnia	31.3 (29.34)	31.1 (30.98)
Appetite loss	20.8 (28.13)	23.2 (29.76)
Constipation	13.2 (23.43)	14.5 (26.23)
Diarrhoea	8.1 (16.73)	8.2 (17.20)
Financial difficulties	32.6 (33.83)	30.1 (32.62)
EORTC QLQ-BR23 questionnaire (mean [SD])		
Body image	64.7 (28.73)	64.3 (30.23)
Sexual functioning	14.0 (20.34)	16.5 (22.51)
Sexual enjoyment	47.0 (25.27)	53.6 (26.13)
Future perspective	32.1 (31.29)	31.0 (30.84)
Systemic therapy side-effects	21.4 (16.16)	22.9 (17.17)
Breast symptoms	19.2 (22.74)	20.3 (24.86)
Arm symptoms	25.1 (26.28)	26.4 (26.25)
Upset by hair loss	51.6 (38.01)	49.5 (38.31)

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; GHS, Global health score; QoL, Quality of life; SD, Standard deviation;
Data shown are mean (SD). The shaded rows represent symptom scales
Source: 83

Compliance for completing the EORTC questionnaires during the study was ≥85% until 12 months, but was lower at 18 and 24 months (73–83%), and sample sizes decreased due to study attrition (Table 29 below, 83). Due to smaller sample sizes, analyses after 6 months should be interpreted with caution.

Table 29 Proportion of patients completing questionnaires at scheduled visits

Visit	Eribulin (n = 554)	Capecitabine (n = 548)
Baseline	96.8% (536/554)	96.0% (526/548)
6 weeks	91.1% (450/494)	86.6% (419/484)
3 months	89.2% (329/369)	87.7% (299/341)
6 months	87.4% (167/191)	87.6% (170/194)
12 months	86.2% (56/65)	87.5% (63/72)
18 months	73.3% (22/30)	82.8% (24/29)
24 months	76.5% (13/17)	75.0% (15/20)

Treatment effects on symptoms (83)

During the course of the study, patients receiving capecitabine had comparatively more severe symptoms (that is, higher symptom scores) for nausea and vomiting ($p<0.001$) and diarrhoea ($p<0.001$) compared with those treated with eribulin. The differences were clinically significant, as a higher proportion of patients who received capecitabine versus eribulin experienced clinically meaningful worsening of nausea and vomiting (MID 8; HR=1.177 [95% CI=1.013, 1.367]; $p<0.05$) and diarrhoea (MID 7; HR=1.189 [95% CI=1.020, 1.385]; $p<0.05$).

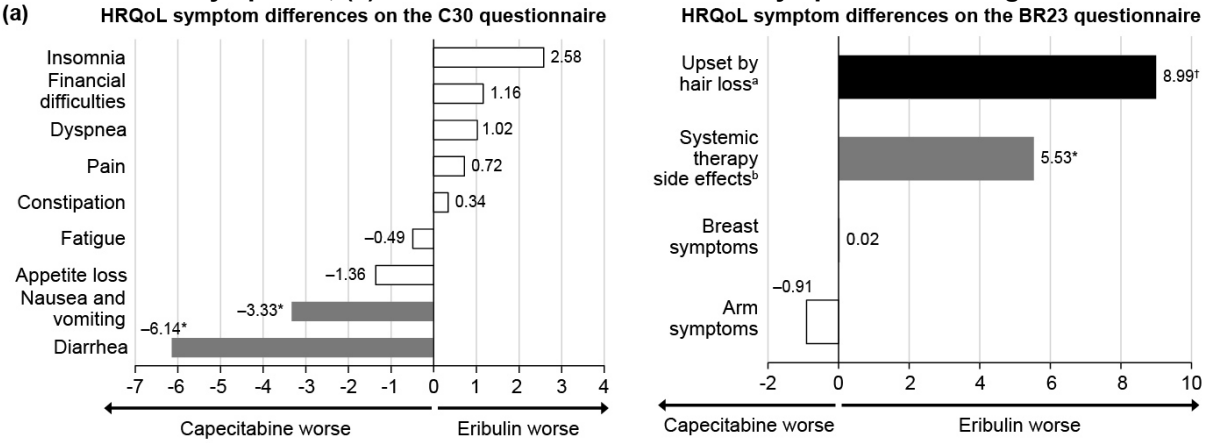
In comparison, patients receiving eribulin had worse mean scores for other systemic therapy side-effects including dry mouth, different tastes, irritated eyes, feeling ill, hot flushes, headaches, and hair loss ($p<0.001$), and upset by hair loss ($p<0.05$). A higher proportion of patients treated with eribulin experienced clinically meaningful worsening of systemic therapy side-effects than those treated with capecitabine (MID 10; HR=0.821 [95% CI=0.707, 0.953]; $p<0.01$).

The analysis of time to symptom worsening (TSW) supported the interpretation of the minimally important difference (MID) thresholds. Patients receiving capecitabine had significantly shorter TSW for nausea and vomiting (MID 8; 7.6 months vs 10.2 months; $p<0.05$), and diarrhoea (MID 7; 8.4 months vs 11.5 months; $p<0.05$) than those treated with eribulin. Similarly, patients treated with eribulin had significantly shorter TSW for systemic therapy side-effects (MID 10; 7.6 months vs 9.7 months; $p<0.05$) compared with those treated with capecitabine.

Results are shown in Figure 13 overleaf.

Figure 13 Effects of eribulin and capecitabine on physical symptom scales of the EORTC QLQ-C30 and QLQ-BR23 questionnaires (a) differences in mean scores; (b) proportion of patients with worsened symptoms; (c) differences in median time to symptom worsening

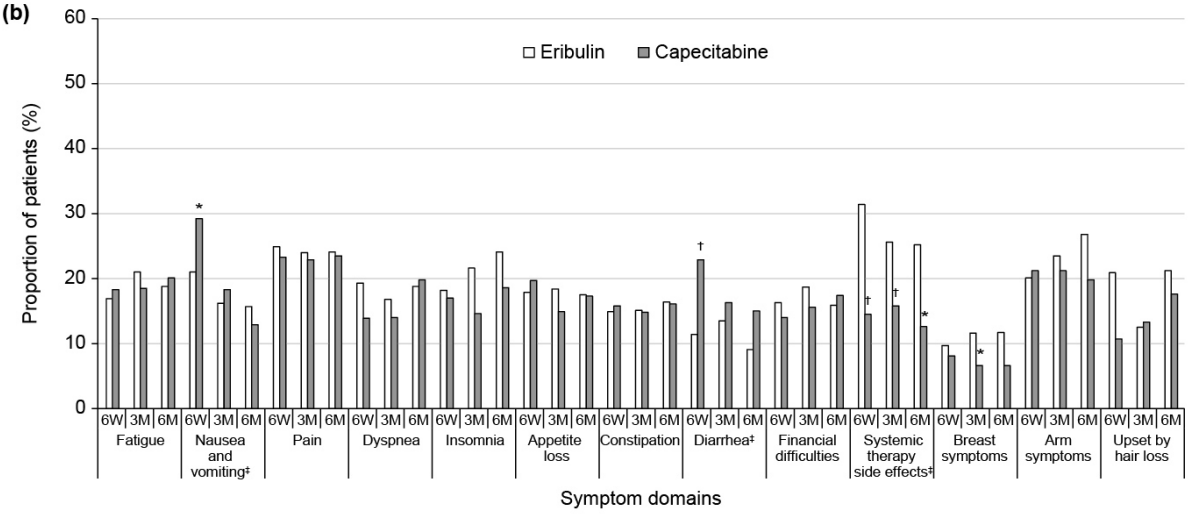
(a)



*P<0.001; †P<0.05

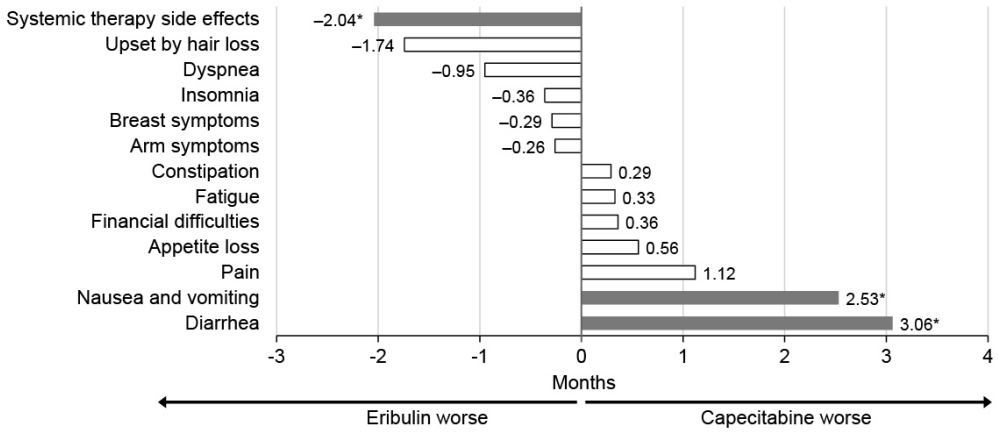
[a]Upset by hair loss is only answered by patients who experience hair loss. [b]Systemic therapy side effects include dry mouth, different tastes, irritated eyes, feel ill, hot flushes, headaches, hair loss. The linear mixed model estimated the change from baseline through month 24. Model adjusted with the following covariates: baseline patient-reported outcomes, age, human endocrine receptor 2 status, triple-negative status, European Cooperative Oncology Group score, number of prior chemotherapy regimens, hormone status, number of organs involved, and visceral involvement. EORTC, European Organisation for Research and Treatment of Cancer.

(b)



*P<0.05; †P<0.001; ‡indicates domains that were associated with significant differences in treatment arms during the entire course of the study.
Minimum important differences used in the analyses: fatigue = 13, nausea and vomiting = 8, pain = 13, dyspnea = 9, insomnia = 13, appetite loss = 14, constipation = 13, diarrhea = 7, financial difficulties = 10, systemic therapy side effects = 10, breast symptoms = 10, arm symptoms = 10, upset by hair loss = 10. W, weeks; M, months.

(c)



*P<0.05
The adjusted covariates include age group, race group, and categorical Eastern Cooperative Oncology Group score.

Source: 83

Treatment effects on patient functioning (83)

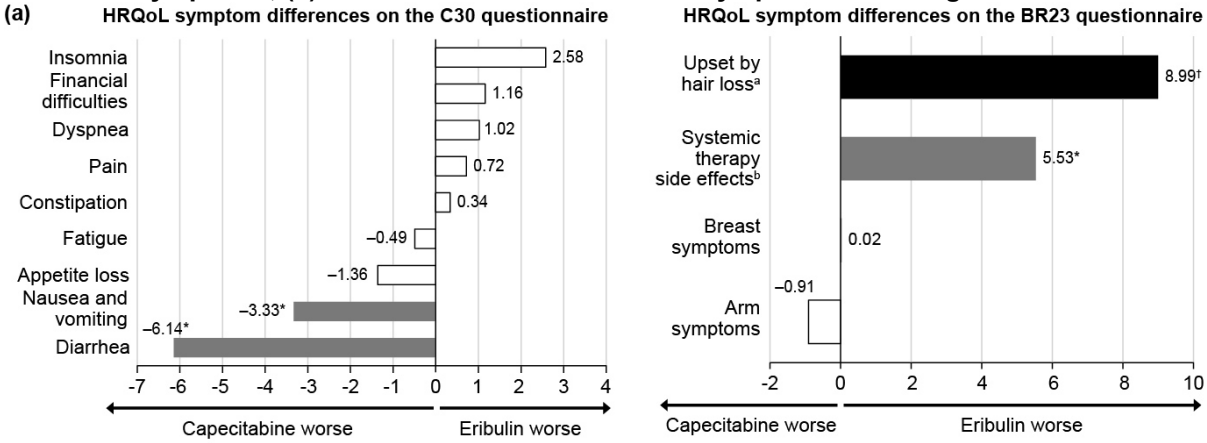
In the longitudinal analyses, baseline HRQoL scores were significantly associated with the change in HRQoL across all EORTC scales ($p<0.001$); that is, worse baseline scores were predictive of worse scores while on treatment. There were no differences between the 2 treatment arms in terms of impact on patients' functioning over time, as measured by changes in EORTC QLQ-C30 scores for functional scales. However, patients receiving eribulin had comparatively worse scores on the body image ($p<0.001$) and sexual functioning scales ($p<0.05$), measured by QLQ-BR23, than those receiving capecitabine.

As indicated by the MID analysis, 10% to 35% of patients in both treatment arms experienced a clinically significant worsening of their functioning, suggesting that the majority of patients experienced stable or improved functioning. No statistically significant differences over the course of the study were observed between the treatment groups, except that a higher proportion of patients receiving capecitabine reported a meaningful worsening on the future perspective scale than those receiving eribulin (MID 10; HR=1.173 [95% CI=1.015, 1.356]; $p<0.05$).

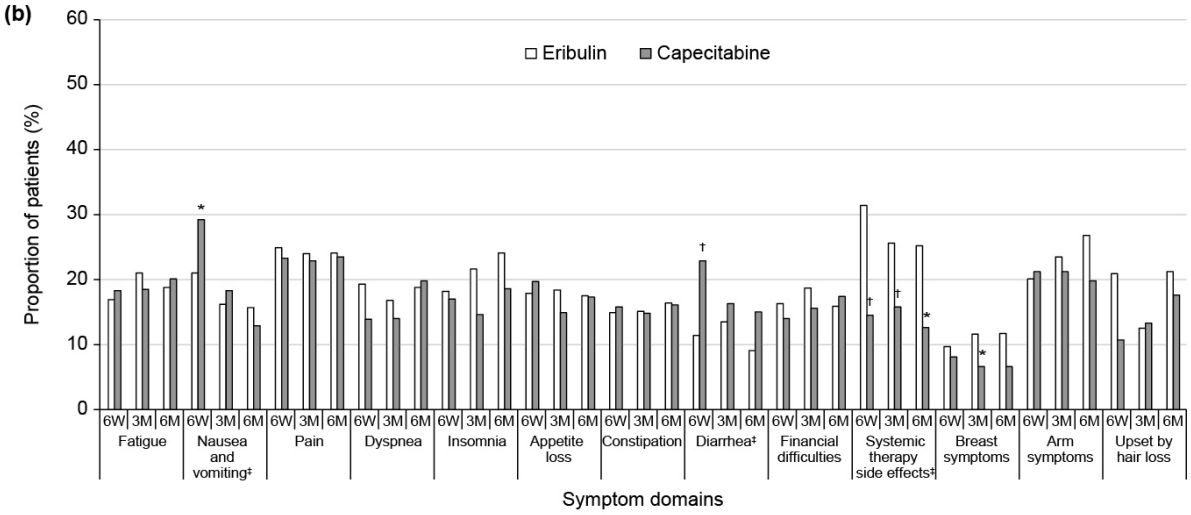
In the ITT population, median TSW was similar for the majority of the EORTC functional scales and the GHS/QoL scale, with only 1–2 months' difference between the treatment arms. Patients receiving eribulin had significantly longer TSW for body image (MID 10; 8.9 vs 6.0 months; $p<0.05$) and future perspective (MID 10; 6.1 months vs 4.7 months; $p<0.05$) than those treated with capecitabine.

Results are shown in Figure 14 overleaf.

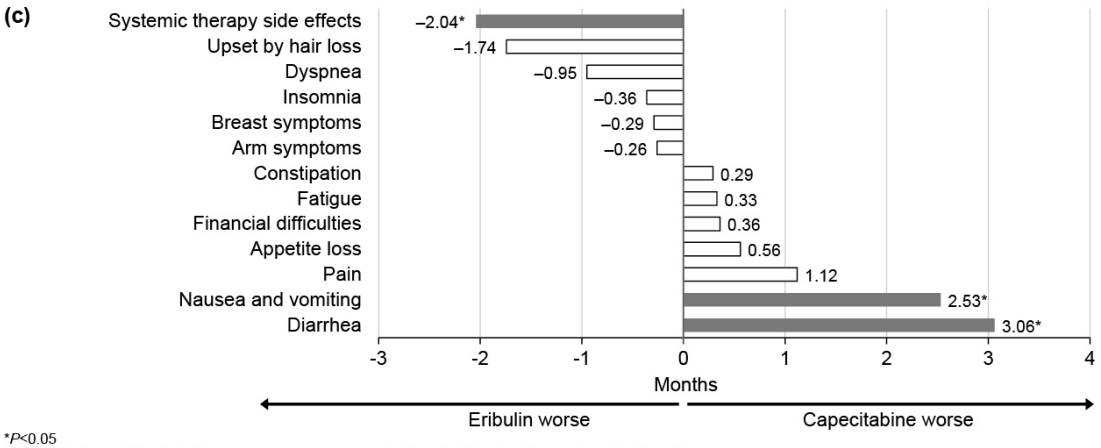
Figure 14 Effects of eribulin and capecitabine on function scales of the EORTC QLQ-C30 and QLQ-BR23 questionnaires (a) differences in mean scores; (b) proportion of patients with worsened symptoms; (c) differences in median time to symptom worsening



*P<0.001; †P<0.05
[a]Upset by hair loss is only answered by patients who experience hair loss. [b]Systemic therapy side effects include dry mouth, different tastes, irritated eyes, feel ill, hot flushes, headaches, hair loss. The linear mixed model estimated the change from baseline through month 24. Model adjusted with the following covariates: baseline patient-reported outcomes, age, human endocrine receptor 2 status, triple-negative status, European Cooperative Oncology Group score, number of prior chemotherapy regimens, hormone status, number of organs involved, and visceral involvement. EORTC, European Organisation for Research and Treatment of Cancer.



*P<0.05; †P<0.001; ‡indicates domains that were associated with significant differences in treatment arms during the entire course of the study.
Minimum important differences used in the analyses: fatigue = 13, nausea and vomiting = 8, pain = 13, dyspnea = 9, insomnia = 13, appetite loss = 14, constipation = 13, diarrhea = 7, financial difficulties = 10, systemic therapy side effects = 10, breast symptoms = 10, arm symptoms = 10, upset by hair loss = 10. W, weeks; M, months.

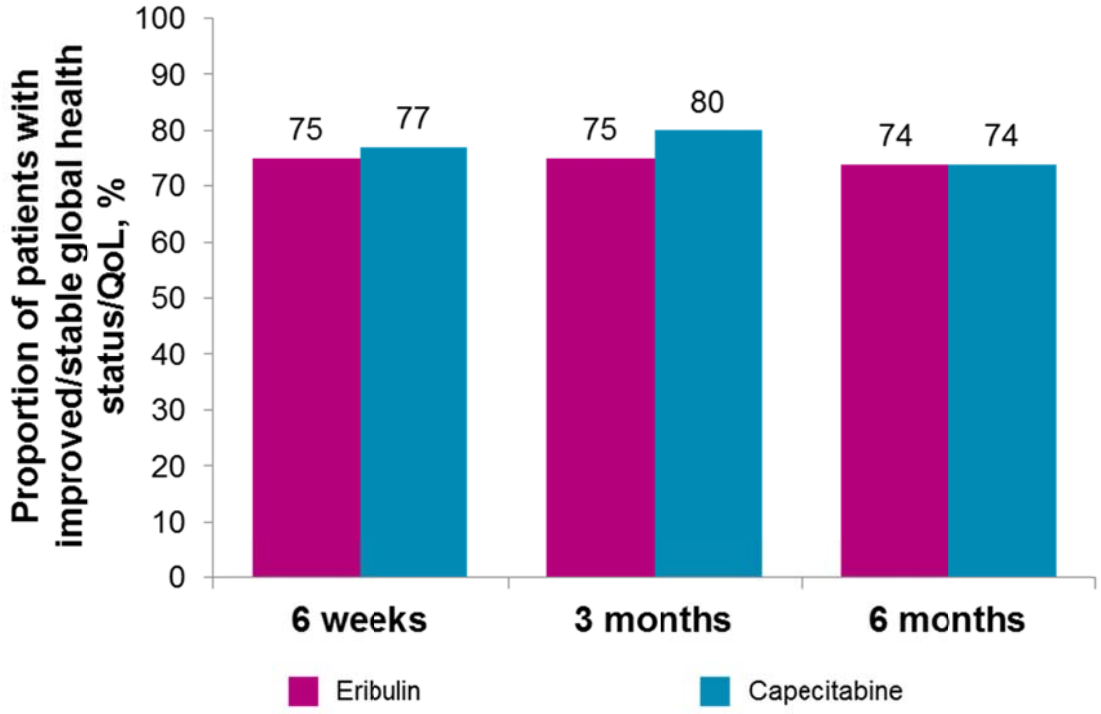


*P<0.05
The adjusted covariates include age group, race group, and categorical Eastern Cooperative Oncology Group score.
Source: 83

Conclusion

Overall, the median global health/QoL scores were similar between the eribulin and capecitabine groups. The majority of patients (≥74%) in both treatment groups maintained or improved their global health status/QoL vs baseline using MID analysis (see Figure 15 below)

Figure 15 Patients with improved/stable Global Health Status/QoL Score: Study 301



Source: 63

Patients treated with capecitabine had worse scores, and more rapid TSW for gastrointestinal symptoms (nausea and vomiting, diarrhoea), whereas patients treated with eribulin had worse scores for systemic therapy side-effects (dry mouth, food and drink taste, eyes painful, hair loss, feeling ill/unwell, hot flushes, headaches). However, only the differences for nausea and vomiting and diarrhoea were found to be statistically significant.

The importance of these results is substantial considering that in a cross-sectional study evaluating preferences associated with chemotherapy side effects (65), a reduced incidence of Grade 3/4 nausea and vomiting made the most difference to breast cancer patients.

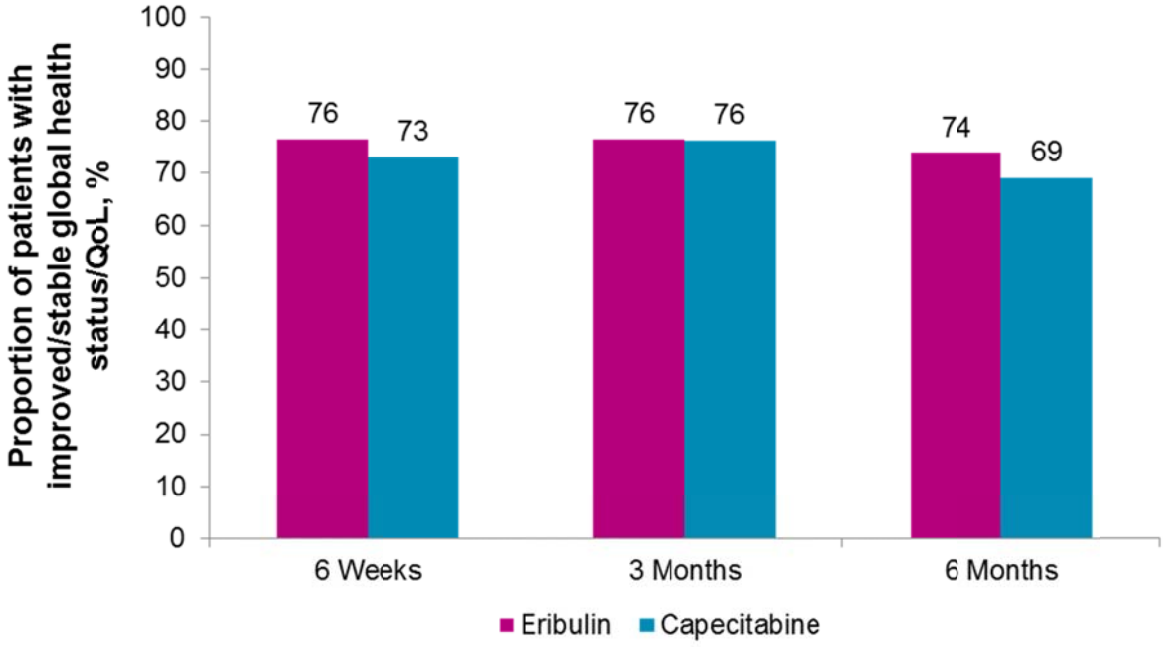
HRQoL in Subgroups 1 & 2

Subgroup 1

Apart from the overall analysis, specific sub-analysis of the aforementioned patient reported outcomes were also conducted to assess the treatment effect within patient populations that reflect as much as possible the identified subgroups of this submission (see section 4.8 for results of efficacy outcomes for the identified subgroups).

With regards to subgroup 1, the results in the HER2-negative subgroup of study 301 were similar to those in the overall population in all analyses.

Figure 16 Patients with improved/stable Global Health Status/QoL Score: Study 301 HER2 negative



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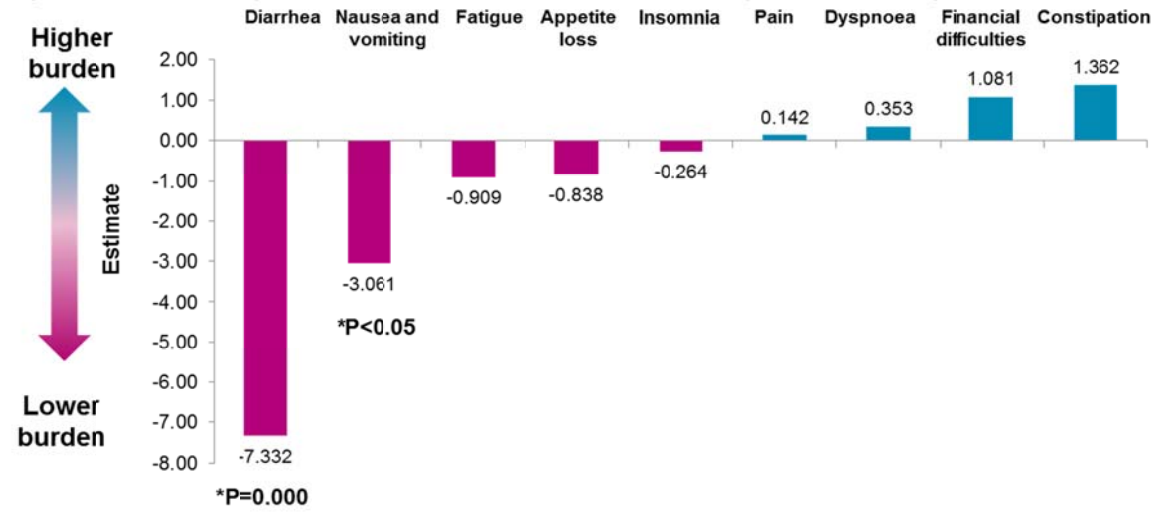
Patient burden of gastrointestinal adverse events was even more significantly lower for eribulin patients and is consistent with its known adverse event profile.

Figure 17 Eribulin Symptom Burden vs Capecitabine: Study 301 HER2 negative

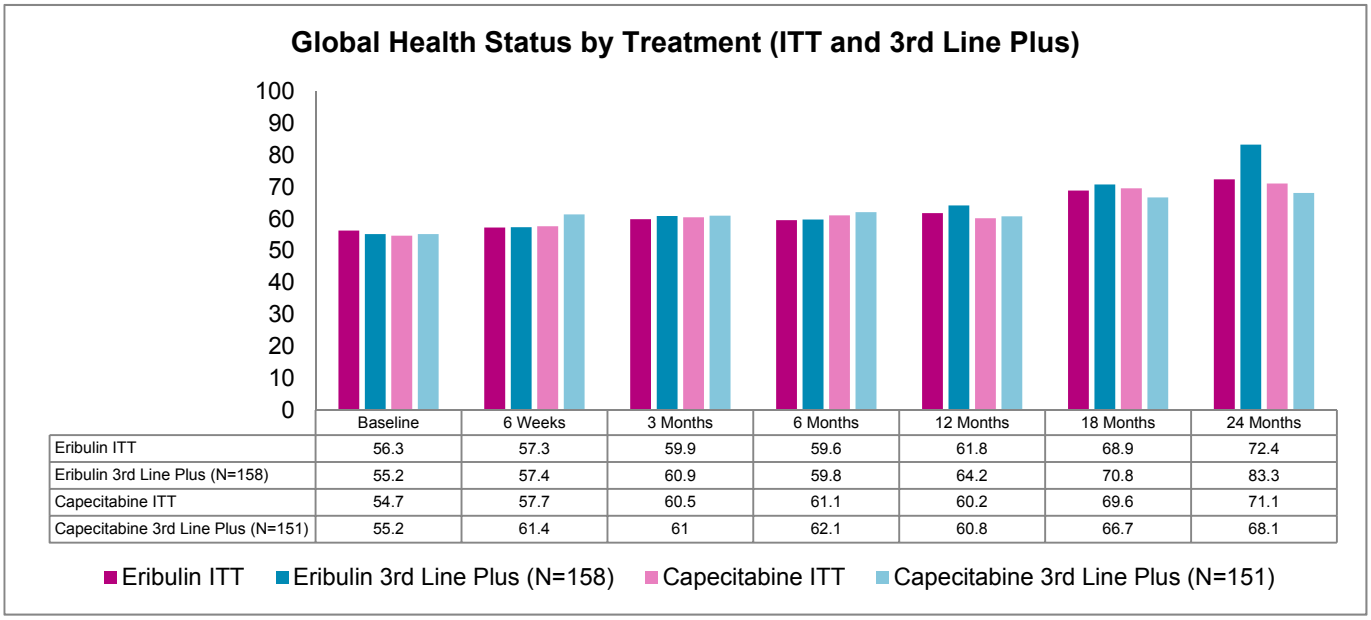


Subgroup 2

With regards to subgroup 2, although the study 301 population and comparator arm is different to those in study 305, a sub-analysis of the patient reported outcomes was conducted for patients that had received at least two prior chemotherapies (i.e. 3rd line plus)

to approximate the study 305 population. The results are again consistent with those in the overall population.

Figure 18 Global Health Status: ITT vs Third line plus in Study 301



	Baseline	6 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
Eribulin ITT	56.3	57.3	59.9	59.6	61.8	68.9	72.4
Eribulin 3rd Line Plus (N=158)	55.2	57.4	60.9	59.8	64.2	70.8	83.3
Capecitabine ITT	54.7	57.7	60.5	61.1	60.2	69.6	71.1
Capecitabine 3rd Line Plus (N=151)	55.2	61.4	61	62.1	60.8	66.7	68.1

4.8 Subgroup analysis

On the basis of current clinical practice and unmet clinical need, the submission considers two separate subgroups separately, as described in the decision problem (Table 1).

Subgroup 1

1. HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.

Study 301 was designed to further evaluate the effect of eribulin on prespecified subgroups including human epidermal growth factor receptor 2 [HER2/*neu*] negative) status. Therefore, patients were pre-stratified according to geographical region and HER2 status.

Patient demographics and baseline disease characteristics for this subgroup are provided in Table 30 overleaf. These are mostly consistent with those presented for the ITT population of study 301 in Table 19 and Table 20, with the exception of triple negative status.

Table 30 Patient demographics and Baseline disease Characteristics (HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting)

Trial no. (acronym) Characteristic	Eribulin	Capecitabine	Total
Study 301	**(n = 186)**	**(n = 206)**	**(n = 392)**
Age distribution, n (%)			
≤ 40 yrs	16 (8.6)	36 (17.5)	52 (13.3)
>40 to > 65 yrs	135 (72.6)	150 (72.8)	285 (72.7)
≥ 65 yrs	35 (18.8)	20 (9.7)	55 (14.0)
Race, n (%)			
White	163 (87.6)	191 (92.7)	354 (90.3)
Black or African American	6 (3.2)	1 (0.5)	7 (1.8)
Asian/Pacific Islander	7 (3.8)	8 (3.9)	15 (3.8)
Other	10 (5.4)	6 (2.9)	16 (4.1)
Geographic region, n (%)			
North America, Western Europe, Asia	46 (24.7)	56 (26.9)	100 (25.5)
Eastern Europe	99 (53.2)	112 (54.4)	211 (53.8)
Latin America, South Africa	41 (22.0)	38 (18.4)	79 (20.2)
ER Status, n (%)			
+	104 (55.9)	116 (56.3)	220 (56.1)
–	82 (44.1)	87 (42.2)	169 (43.1)
Not done	0	3 (1.5)	4 (1.0)
Triple negative (ER/PR/HER2-negative), n (%)	73 (39.2)	72 (35.0)	145 (37.0)
No. of organs involved, n (%)			
1	37 (19.9)	27 (13.1)	64 (16.3)
2	59 (31.7)	62 (30.1)	121 (30.8)
≥3	90 (48.4)	117 (56.8)	207 (52.8)

Abbreviations: ER, Oestrogen receptor; HER2, Human epidermal growth factor receptor 2; PR, progesterone receptor;
Source: Appendix 4

Summary of results

Full details of the results summarised below are available in Appendix 4.

[redacted]

Figure 19 Kaplan Meier analysis of overall survival: Study 301 (HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting)

Source: Appendix 4

Figure 20 Kaplan Meier analysis of progression-free survival: Study 301 (HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting)

Source: Appendix 4

Subgroup 2

2. Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated).

Since Study 305 (EMBRACE) was a global study, and recognising differences in clinical practice and drug availability, patients were pre-stratified by geographical region, HER2 status and prior capecitabine treatment. Pre-planned subgroup analyses explored the effect of these strata, as well as other characteristics commonly assessed in cancer studies. Pre-planned subgroup analyses included were as follows:

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

Patient demographics and baseline disease characteristics for this subgroup are provided in Table 31 overleaf. These are mostly consistent with those presented for the ITT population of study 305 in Table 19 and Table 20.

Table 31 Patient demographics and Baseline disease Characteristics (Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine if indicated)

Trial no. (acronym) Characteristic	Eribulin	TPC	Total
Study 305 (EMBRACE)	**(n = 370)**	**(n = 189)**	**(n =559)**
Age distribution, n (%)			
≤ 40 yrs	24 (6.5)	15 (7.9)	39 (7.0)
>40 to > 65 yrs	280 (75.7)	133 (70.4)	413 (73.9)
≥ 65 yrs	66 (17.8)	41 (21.7)	107 (19.1)
Race, n (%)			
White	346 (93.5)	174 (92.1)	520 (93.0)
Black or African American	13 (3.5)	10 (5.3)	23 (4.1)
Asian/Pacific Islander	1 (0.3)	2 (1.1)	3 (0.5)
Other	10 (2.7)	3 (1.6)	13 (2.3)
ER Status, n (%)			
+	257 (69.5)	130 (68.8)	387 (69.2)
–	99 (26.8)	54 (28.6)	153 (27.3)
Not done	13 (3.5)	5 (2.6)	18 (3.2)
Unknown	1 (0.3)	0	1 (0.2)
Triple negative (ER/PR/HER2-negative), n (%)	68 (18.4)	38 (20.1)	106 (19.0)
No. of organs involved, n (%)			
1	61 (16.5)	25 (13.2)	86 (15.3)
2	128 (34.6)	59 (31.2)	187 (33.4)
≥3	179 (48.4)	105 (55.6)	284 (50.8)
ECOG Performance status at screening,			
0	154 (41.6)	80 (42.3)	234 (41.9)
1	179 (48.4)	90 (47.6)	269 (44.9)
2	30 (8.1)	16 (8.5)	46 (8.2)

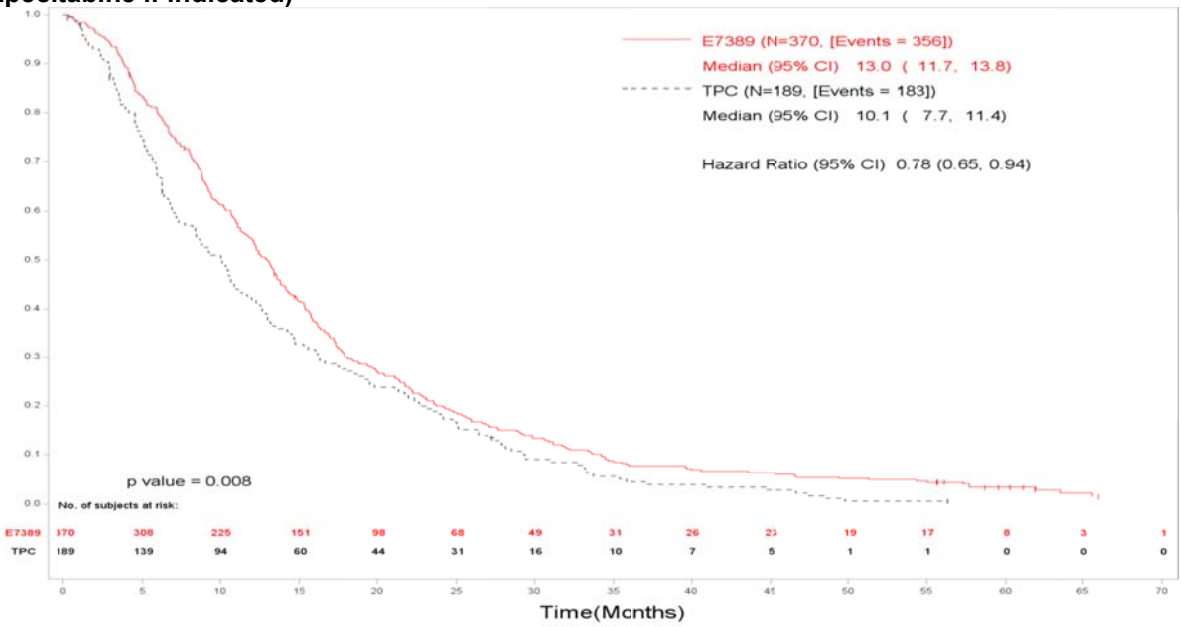
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, Oestrogen receptor; HER2, Human epidermal growth factor receptor 2; PR, progesterone receptor; TPC, Treatment of Physician's Choice

Summary of results

An updated OS analysis of Study 305 (EMBRACE) was carried out when 95% of patients had died. Results from this analysis in those patients who had received prior capecitabine therapy are summarised below and the full results are available in Appendix 4.

The median OS of the eribulin group (13.0 months/395 days) compared with the TPC group (10.1 months/308 days) improved by 2.9 months (87 days; HR 0.78; 95% CI: 0.65 to 0.94, p=0.008). (Figure 21, overleaf.)

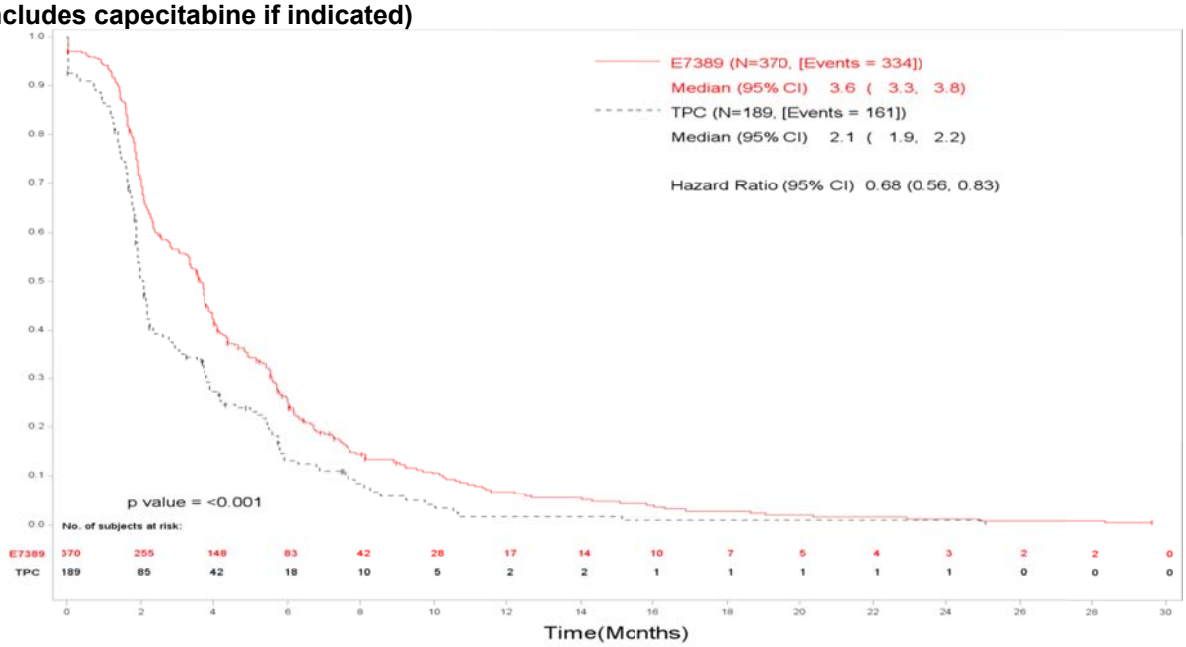
Figure 21 Kaplan Meier analysis of overall survival: Study 305 (Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine if indicated)



Source: Appendix 4

Median PFS as assessed by the investigator was 3.6 months in the eribulin group and 2.1 months in the TPC treatment group. (HR=0.68; 95% CI=0.56, 0.83;p<0.001). (Figure 22, below)

Figure 22 Kaplan Meier analysis of progression-free survival: Study 305 (Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine if indicated)



Source: Appendix 4

4.9 Meta-analysis

N/A

4.10 Indirect and mixed treatment comparisons

An indirect/mixed treatment comparison was not conducted because the Phase III eribulin RCTs (studies 305 and 301) provided direct head to head evidence versus the comparators listed in the scope.

4.11 Non-randomised and non-controlled evidence

No non-randomised and non-controlled evidence has been included in the submission.

4.12 Adverse reactions

Summary of safety

Eribulin's tolerability profile is comparable to other chemotherapeutic agents commonly used in clinical practice in LABC/MBC patients and healthcare professionals caring for these patients will be experienced in handling these adverse events.

Both Phase III RCTs (Study 305 and study 301) have demonstrated that eribulin is associated with a predictable and well-characterised safety profile and is generally well tolerated (7,11):

- Discontinuations due to AEs were lower in the eribulin group than in the control group for both Phase III studies (13.3% vs. 15.4% in Study 305 and 5.7% vs 6.2% in study 301, respectively).

In Studies 305 and 301 respectively, the mean dose intensities in the eribulin group were 0.84 and 0.87. Considering the relatively poor performance status of the patient population and the late stage of the disease, the relatively high dose intensity is another good indicator of eribulin's manageable safety profile. (7,11)

Patients received eribulin for almost twice as long as TPC in Study 305 and this is an important indicator that eribulin is better tolerated than current standard treatments in this late line setting and patients are less impacted by the types of side effects associated with eribulin. (7)

Overall rates of AEs experienced with eribulin in Study 305 and Study 301 are acceptable for a chemotherapeutic agent in the follow-on LABC/MBC setting. (7,11)

- The majority of AEs experienced with eribulin were mild or moderate (CTCAE Grade 1 or 2).
- The most frequently reported AEs (all grades) with eribulin therapy were asthenia/fatigue, neutropenia, alopecia, peripheral neuropathy and nausea.
- Febrile neutropenia (4.6% and 1.3%) and neutropenia (1.8% and 1.8%) were the most frequently reported SAEs, reported in eribulin patients in study 305 (EMBRACE), and study 301 respectively.
- Development of Grade 3/4 AEs of neutropenia occurred in 49.7% of patients in study 305 and 45.8% in Study 301. However, neutropenia led to discontinuation in only 0.9% and 1.7% of patients, while febrile neutropenia was infrequent. Primary prophylaxis with G-CSF for the prevention of neutropenia was not a requirement of the studies (unless defined by local practice protocols).

A patient preference study (65) has indicated that reducing the Grade 3/4 incidences of neuropathy and GI side effects such as nausea/vomiting make the most difference to MBC patients:

- Peripheral neuropathy, a common side effect seen with some chemotherapies, was generally mild/ moderate (Grade 1/2) with the occurrence of Grade 3/4 peripheral

neuropathy being low in both Phase III studies; the majority of those patients with peripheral neuropathy were able to continue treatment. It is important to note that peripheral neuropathy was defined differently in study 305 (EMBRACE) and study 301 (Table 33)

- In studies 305 and 301, the incidence of GI events such as constipation, diarrhoea, and vomiting with eribulin was low (< 25%); where these GI AEs occurred they were generally mild (CTCAE Grade 1).
- Palmar-plantar erythrodysaesthesia (hand-foot syndrome), commonly seen with certain chemotherapies, e.g. capecitabine occurred in only up to 1.4% of patients at any severity grade with eribulin in the RCTs.

Eribulin's well characterised and manageable tolerability profile is further supported by the fact that since launch, it has been given to approximately 85,000 women with MBC. In England to date, eribulin is the 7th most prescribed treatment in the Cancer Drugs Fund (CDF) and has been given to more than 2300 patients since it was first made available through the regional CDF panels in April 2011.

Recently published "real world" data from independent audits undertaken at three UK hospitals in over 200 patients (35,36,37) have shown that eribulin is well tolerated in a routine clinical practice setting and reflect that patients are not impacted greatly by eribulin's side effect profile:

- Majority of the patients received at least 5 cycles of eribulin
- Development of Grade 3/4 AEs of asthenia/fatigue, neutropenia, alopecia, peripheral neuropathy and nausea occurred in less patients than in Study 305 (EMBRACE)

Similar results were seen in "real world" audits undertaken in France (66) and Spain (67):

- In 258 French patients on eribulin, the incidence of Grade 3/4 side effects of neutropenia and peripheral neuropathy were less than in Study 305 (EMBRACE)
- In a heavily pre-treated group of 104 Spanish patients taking eribulin (50.9% had received ≥6 prior chemotherapy regimens for advanced disease), the incidence of the most common reported adverse events was lower than that of Study 305 (EMBRACE): (Asthenia/fatigue 44.2% vs 53.7%; Neutropenia 25% vs 51.7%; Alopecia: 17.3% vs 44.5%; Nausea: 10.6% vs 34.6%)

As discussed previously in Section 4.3, there are two Phase III studies (Study 305 and study 301) which contain relevant safety results for this submission. The methodology of each study has been described previously in Table 12. Unless specified, AE refers to TEAE throughout.

The main body of adverse event evidence is drawn from the pivotal phase III eribulin RCTs (Study 305, EMBRACE and Study 301) and is presented below, together with supportive "real world" evidence and information on patient preference.

Studies 305 and 301

Treatment exposure (7,11)

In study 305 (EMBRACE), overall exposure to study treatment was longer in the eribulin group compared with the TPC group (median 3.9 months/118 days vs. 2.1 months/64 days [chemotherapy] and 1 month/30 days [hormonal], respectively; Table 32, overleaf. More than half of patients (58.6%) received five or more cycles of eribulin treatment, with 22.7% (n=114) and 2.4% (n=12) of patients on treatment for > 6 months and > 1 year, respectively. Similar results were seen in Study 301. (Table 32, overleaf)

This longer duration of therapy with eribulin in Study 305 (EMBRACE) demonstrates the superior tolerability of eribulin compared with TPC. Patients received eribulin for almost twice as long as TPC, indicating that eribulin is better tolerated than current standard treatments in this late line setting and that patients are less impacted by the types of side effects associated with eribulin.

The mean dose intensity in the eribulin group, as seen in Table 32 overleaf was 0.84 in Study 305 (EMBRACE) and 0.87 in Study 301. Considering the relatively poor performance status of the patient population in both studies (91% and 98% of patients taking eribulin had an ECOG status of ≤1 in studies 305 and 301, respectively, Table 20, this is another good indicator of eribulin's manageable safety profile.

Further evidence of this manageable adverse event profile and the likely impact on patients in clinical practice can be found in recently published "real world" evidence (see below)

Table 32: Extent of exposure (Safety population)

Study 305 (EMBRACE)		
	Eribulin (N=503)	**TPC (Chemotherapy) (N=238)**
Duration of exposure, median days (min, max)	118 (21–497)	64.0 (1–644)
Number of cycles completed on study, n (%) 1–2 3–4 5–6 > 6 Range	 81 (16.1%) 127 (25.2%) 110 (21.9%) 185 (36.8%) 1–23 cycles	 NA
Relative dose intensity, mean (SD)	0.84 (0.178)	NA
Patients with dose interruption, n (%)	28 (5.6%)	21 (8.8%)
Study 301		
	Eribulin (N=544)	**Capecitabine (N=546)**
Duration of exposure, median days (min, max)	125 (21-1372)	119 (21-1442)
Number of cycles completed on study, n (%) 1–2 3–4 5–6 > 6 Range	 118 (21.7%) 120 (22.1%) 107 (19.7%) 199 (36.6%) 1-65 cycles	 151 (27.7%) 107 (19.6%) 73 (13.4%) 215 (39.4%) 1-61 cycles
Relative dose intensity, mean (SD)	0.87 (0.146)	0.86 (0.156)
Patients with dose interruption, n (%)	7 (1.3%)	NR

Abbreviations: NA, Not applicable; NR, Not reported; SD, Standard Deviation; TPC; Treatment of Physician's Choice.
Source: 7and 11

Brief overview

Both study 305 and 301 adequately characterised the safety profile of eribulin, demonstrating that eribulin is associated with a predictable and well-characterised safety profile and is generally well-tolerated.

Over 90% of patients in the studies (eribulin or TPC or capecitabine arms) experienced at least one AE, with SAEs reported for approximately 18% of eribulin patients and 21% of capecitabine patients in study 301 (Table 33). (11) The incidence of SAEs in the EMBRACE study was slightly higher, at approximately 25% in both groups (Table 33). (7) The rates of AEs and SAEs in the eribulin group are acceptable for a chemotherapeutic agent in the follow-on MBC setting.

Adverse events

AEs occurring in at least 10% of patients in either arm of both studies are shown in Table 34 (7,11). The most common AEs in studies 305 and 301 respectively were:

- asthenia/fatigue (53.7%, 32%), neutropenia (51.7%, 54.2%), alopecia (44.5%, 34.6%), peripheral neuropathy (34.6%, 13.4%) and nausea (34.6%, 22.2%) with eribulin.

- palmar-plantar erythrodysaesthesia syndrome (43.2%, 45.1%), asthenia/fatigue (38.6%, 30%), diarrhoea (27.3%, 28.8%), nausea (20.5%, 24.4%) and anaemia (22.7%, 17.6%) with capecitabine
- asthenia/fatigue (50.8%), neutropenia (49.2%), constipation (39.3%), nausea (31.1%) and diarrhoea (23.0%) with vinorelbine

It is important to note that peripheral neuropathy was defined differently in study 305 (EMBRACE) and study 301 (Table 33), with Study 305 including a broader definition versus study 301, which reported peripheral sensory neuropathy only.

A separate Phase II study compared the incidence and severity of neuropathy associated with eribulin (n=51) versus ixabepilone (n=50) in MBC (49) and included both a broad definition of neuropathy and a definition of peripheral neuropathy. In this study, the incidence of peripheral neuropathy in patients taking eribulin (31.4%) was similar to that reported in study 305 (EMBRACE).

SAEs

As described above, in study 301, less patients experienced SAEs in the eribulin arm vs the capecitabine group (18% vs. 21%, Table 33) (11). In study 305 (EMBRACE), the percentage of patients who experienced SAEs in both groups was similar (7).

In Study 305 (EMBRACE), the most frequently reported SAEs in the eribulin group were febrile neutropenia (4.2%) and neutropenia (1.8%), while the most frequently reported SAEs in the TPC group were dyspnoea (3.6%) and asthenia (2.4%) (7). These were similar to those SAEs reported in study 301, where, in the eribulin group, the most frequently reported SAEs were dyspnoea (2.4%), neutropenia (1.8%) and febrile neutropenia (1.3%). In the capecitabine group of study 301, the most frequently reported SAEs were dyspnoea (3.1%), diarrhoea (2.7%) and dehydration and vomiting (1.6%) (11).

Deaths

At the end of both studies 305 and 301, the rate of deaths in the eribulin groups was comparable to that in the control groups (53.9% [n=271] vs. 57.9% [n=143] and 81.3% [n=442] vs 83.9% [n=458], respectively). (7,11)

However, in terms of deaths related to toxicity, a lower proportion of patients had SAEs leading to death (only including SAEs that occurred during study treatment or within 30 days of the last study treatment) in the eribulin group compared with the capecitabine groups in both studies 305 and 301 (4.0% [n=20] vs. 9.1% [n=4], 4.8% [n=26] vs 6.6% [n=36], respectively) (7,11). In study 305, the proportion of patients who had SAEs leading to death was similar between the eribulin and vinorelbine groups (4.0% [n=20] vs 4.9% [n=3]). (7)

Treatment-related AEs

In Study 305, a total of 94.2% of patients reported AEs that were thought by the investigator to be treatment-related (Table 33) in the eribulin group compared to 77.7% of patients in the TPC group. (7) The incidence of treatment-related AEs in study 301 was slightly lower at 84.6% in the eribulin group vs 77.1% in the capecitabine group. (11)

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

Discontinuation due to AEs

In both studies 305 and study 301, the percentage of patients experiencing AEs that led to dose discontinuation was higher in the control group compared with the eribulin group (Table 33). The proportion of patients who discontinued from the eribulin and TPC groups due to AEs in Study 305 were 13.3% and 15.4%, respectively. In Study 301, the proportion of patients who discontinued from the eribulin and capecitabine groups due to AEs was 7.9% and 10.4%, respectively. (7,11)

In Study 305, while the most common AE leading to discontinuation of eribulin treatment was peripheral neuropathy (4.8% of patients), 63% (26/41) of the patients with Grade 3/4 peripheral neuropathy were able to continue treatment. Neutropenia led to eribulin discontinuation for only 0.6% patients. (7)

In Study 301, the most common AE leading to discontinuation was neutropenia, but as per study 305, the incidence was low ie only 1.7% of patients. The most common AE leading to discontinuation in the capecitabine group was palmar-plantar erythrodysaesthesia in 2.2% of patients. (11)

Table 33 Overall incidence of adverse events: Study 305 (EMBRACE) and Study 301 (Number of patients; Safety population)

	Study 305 (EMBRACE)					Study 301	
AEs	**Eribulin N=503 n (%)**	**TPC N=247 n (%)**	**TPC Group**			**Eribulin N=544 n (%)**	**Capecitabine N=546 n (%)**
			Vin. N=61 n (%)	**Gem. N=46 n (%)**	**Cape. N=44 n (%)**		
Any AE	497 (98.8%)	230 (93.1%)	57 (93.4%)	44 (95.7%)	41 (93.2%)	512 (94.1%)	494 (90.5%)
Any treatment-related AE	474 (94.2%)	192 (77.7%)	49 (80.3%)	35 (76.1%)	35 (79.5%)	460 (84.6%)	421 (77.1%)
Any SAEs	126 (25.0%)	64 (25.9%)	16 (26.2%)	12 (26.1%)	13 (29.5%)	95 (17.5%)	115 (21.1%)
Fatal SAEs	20 (4.0%)	18 (7.3%)	3 (4.9%)	4 (8.7%)	4 (9.1%)	26 (4.8%)	36 (6.6%)
Other SAEs	114 (22.7%)	56 (22.7%)	14 (23.0%)	10 (21.7%)	11 (25.0%)	97 (17.8%)	117 (21.4%)
Any treatment-related SAEs	59 (11.7%)	17 (6.9%)	5 (8.2%)	2 (4.3%)	4 (9.1%)	7.7%	8.1%
AEs that led to discontinuation	67 (13.3%)	38 (15.4%)	7 (11.5%)	5 (10.9%)	5 (11.4%)	43 (7.9%)	57 (10.4%)
Other AEs of interest							
AE that led to dose delay	177 (35.2%)	80 (32.4%)	27 (44.3%)	18 (39.1%)	10 (22.7%)	173 (31.8%)	195 (35.7%)
AEs that led to dose interruption	25 (5.0%)	25 (10.1%)	7 (11.5%)	5 (10.9%)	10 (22.7%)	10 (1.8%)	1 (0.2%)
AEs that led to dose reduction	85 (16.9%)	39 (15.8%)	12 (19.7%)	7 (15.2%)	8 (18.2%)	174 (32.0%)	174 (31.9%)
AEs of CTCAE Grade 3	308 (61.2%)	114 (46.2%)	40 (65.6%)	22 (47.8%)	14 (31.8%)	202 (37.1%)	183 (33.5%)
AEs of CTCAE Grade 4	148 (29.4%)	33 (13.4%)	12 (19.7%)	7 (15.2%)	1 (2.3%)	128 (23.5%)	32 (5.9%)
Asthenia/ fatigue	270(53.7%)	98(39.7%)	-	-	-	174 (32%)	163 (30%)
Neutropenia	260(51.7%)	73(29.6%)	-	-	-	295 (54.2%)	87 (15.9%)
Alopecia	224(44.5%)	24(9.7%)	-	-	-	188 (34.6%)	22 (4.0%)
Peripheral neuropathy[†]	174(34.6%)	40(16.2%)	-	-	-	73 (13.4%)	38 (7.0%)
Arthralgia/ myalgia	109(21.7%)	29(11.7%)				72 (12.2%)	39 (7.1%)
Febrile neutropenia	23(4.6%)	4(1.6%)				7 (1.3%)	4 (0.7%)

Abbreviations: AE, Adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, Serious adverse event; TPC, Treatment of Physician's Choice; In Study 305 (EMBRACE), peripheral neuropathy includes peripheral neuropathy, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and paraesthesia. Study 301 reported peripheral sensory neuropathy only.

Table 34 Most commonly reported adverse events by treatment group: Study 305 (EMBRACE) and Study 301 (Safety population; > 10% of patients in either study arm, all CTCAE grades)

	Study 305 (EMBRACE)					Study 301	
System organ class AEs	**Eribulin N=503 n (%)**	**TPC N=247 n (%)**	**Vin. N=61 n (%)**	**Gem. N=46 n (%)**	**Cape. N=44 n (%)**	**Eribulin N=544 n (%)**	**Capecitabine N=546 n (%)**
Any AE	497 (98.8 %)	230 (93.1)	57 (93.4%)	44 (95.7%)	41 (93.2%)	512 (94.1%)	494 (90.5%)
Blood and Lymphatic							
Neutropenia	260 (51.7%)	73 (29.6 %)	30 (49.2%)	17 (37.0%)	2 (4.5%)	295 (54.2%)	87 (15.9%)
Anaemia	94 (18.7%)	56 (22.7%)	13 (21.3%)	9 (19.6%)	10 (22.7%)	104 (19.1%)	96 (17.6%)
Leucopoenia	116 (23.1%)	28 (11.3%)	10 (16.4%)	8 (17.4%)	1 (2.3%)	171 (31.4%)	57 (10.4%)
Gastrointestinal							
Nausea	174 (34.6%)	70 (28.3%)	19 (31.1%)	18 (39.1%	9 (20.5%)	121 (22.2%)	133 (24.4%)
Constipation	124 (24.7%)	51 (20.6%)	24 (39.3%)	9 (19.6%)	6 (13.6%)	<10%	<10%
Diarrhoea	92 (18.3%)	45 (18.2%)	14 (23.0%)	9 (19.6%)	12 (27.3%)	78 (14.3%)	157 (28.8%)
Vomiting	91 (18.1%)	44 (17.8%)	13 (21.3%)	10 (21.7%)	10 (22.7%)	65 (11.9%)	92 (16.8%)
General disorders and administration site							
Asthenia/fatigue	270 (53.7%)	98 (39.7%)	31 (50.8%)	17 (37.0%)	17 (38.6%)	174 (32%)	163 (30%)
Pyrexia	105 (20.9%)	31 (12.6%)	6 (9.8%)	8 (17.4%)	6 (13.6%)	70 (12.9%)	31 (5.7%)
Mucosal inflammation	43 (8.5%)	25 (10.1%)	3 (4.9%)	3 (6.5%)	7 (15.9%)	<10%	<10%
Investigations							
Weight decreased	107 (21.3%)	35 (14.2%)	10 (16.4%)	5 (10.9%)	6 (13.6%)	<10%	<10%
Metabolism and nutrition							
Anorexia	98 (19.5%)	32 (13.0%)	11 (18.0%)	6 (13.0%)	6 (13.6%)	68 (12.5%)	81 (14.8%)
Musculoskeletal and connective tissue							
Arthralgia/ myalgia	109 (21.7%)	29 (11.7%)	7 (11.5%)	3 (6.5%)	8 (18.2%)	<10%	<10%
Back pain	79 (15.7%)	18 (7.3%)	7 (11.5%)	2 (4.3%)	4 (9.1%)	56 (10.3%)	43 (7.9%)
Bone pain	60 (11.9%)	23 (9.3%)	5 (8.2%)	4 (8.7%)	2 (4.5%)	<10%	<10%
Pain in extremity	57 (11.3%)	25 (10.1%)	11 (18.0%)	2 (4.3%)	8 (18.2%)	<10%	<10%
Nervous system							
Headache	97 (19.3%)	29 (11.7%)	9 (14.8%)	6 (13.0%)	8 (18.2%)	69 (12.7%)	57 (10.4%)
Peripheral neuropathy[†]	174 (34.6%)	40 (16.2%)	12 (19.7%)	2 (4.3%)	5 (11.4%)	73 (13.4%)	38 (7.0%)
Respiratory, thoracic and mediastinal							
Dyspnoea	79 (15.7%)	31 (12.6%)	7 (11.5%)	6 (13.0%)	3 (6.8%)	56 (10.3%)	59 (10.8%)
Cough	72 (14.3%)	21 (8.5%)	4 (6.6%)	7 (15.2%)	3 (6.8%)	<10%	<10%
Skin and subcutaneous tissue							
Alopecia	224 (44.5%)	24 (9.7%)	2 (3.3%)	3 (6.5%)	3 (6.8%)	188 (34.6%)	22 (4.0%)

	Study 305 (EMBRACE)					Study 301	
System organ class AEs	**Eribulin N=503 n (%)**	**TPC N=247 n (%)**	**Vin. N=61 n (%)**	**Gem. N=46 n (%)**	**Cape. N=44 n (%)**	**Eribulin N=544 n (%)**	**Capecitabine N=546 n (%)**
Palmar-plantar erythrodysaesthesia syndrome	7 (1.4%)	34 (13.8%)	0	0	19 (43.2%)	1 (0.2%)	246 (45.1%)

Abbreviations: AE, Adverse event; CTCAE, Common Terminology Criteria for Adverse Events; Treatment of Physician's Choice; † In Study 305 (EMBRACE), peripheral neuropathy includes peripheral neuropathy, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and paraesthesia. Study 301 reported peripheral sensory neuropathy only.

Real World Evidence

Eribulin is currently available in more than 60 countries worldwide and has been given to approximately 85,000 women with MBC.

Recently published data from audits undertaken in the UK (35,36,37), France (66) and Spain (67) have mirrored both the efficacy and safety results of Study 305 (EMBRACE). They have shown that eribulin is well tolerated in a routine clinical practice setting and reflect that patients are not impacted greatly by eribulin's side effect profile. This is further supported by the fact that in England to date, eribulin is the 7th most prescribed treatment in the Cancer Drugs Fund (CDF) and has been given to more than 2300 patients since it was first made available through the regional CDF panels in April 2011.

Three retrospective audits describe the outcomes of LABC/MBC patients who had progressive disease after at least two prior chemotherapeutic regimens in the advanced setting and received eribulin via the CDF at the Royal Marsden Hospital (n=108) (35), Christie Hospital NHS Foundation Trust (n=75) (36) and Imperial College Healthcare NHS Trust (n=25) (37).

The Table below (Table 35) summarises relevant patient characteristics and safety results from Study 305 (EMBRACE) and these audits.

Table 35 Summary of UK Audit Data

	Study 305 (EMBRACE)	**UK MARSDEN**	**UK CHRISTIE**	**UK IMPERIAL**
Patient Characteristics				
No. of patients on eribulin	508	108	75	25
No. of patients who previously received ≥3 prior chemotherapy regimens	86.6%	median 3 for MBC	NR[a]	median 3 for MBC
No of patients who previously received capecitabine	72.8%	>80%	85%	80%
Safety results				
Most common AEs				
Asthenia/fatigue: All Grades: Grades 3&4	 53.7% 8.7%	 65% 7%	 55% NR	 8% NR
Neutropenia All Grades: Grades 3&4	 51.7% 45.1%	 45% 32%	 17% NR	 32% None
Alopecia	44.5%	35%	NR	NR
Peripheral Neuropathy All Grades: Grades 3&4	 34.6% 8.2%	 NR NR	 33% NR	 20% 4%
Nausea All Grades: Grades 3&4	 34.6% 1.2%	 NR NR	 32% NR	 12% NR
Duration of treatment				
Cycles	≥ 5 = 58.6%	> 5 = 62%	≤ 6 = 57% > 6 = 43%	4 (median) range:1-15

[a] 70% of patients had previously received ≤3 prior chemotherapy regimens
Abbreviations: AEs, Adverse events; MBC, Metastatic breast cancer; NR, Not reported
Source: 7,35,36 and 37

In this real world evidence (35,36,37), the most common adverse events reported were consistent with Study 305 (EMBRACE). However, with the exception of asthenia/fatigue the incidence of these adverse events was lower than that of the Phase III evidence.

More importantly, the development of Grade 3 and Grade 4 AEs of asthenia/fatigue, neutropenia, alopecia, peripheral neuropathy and nausea occurred in less patients than in Study 305 (EMBRACE). In a cross-sectional study evaluating preferences associated with chemotherapy side effects in breast cancer patients (65), among Grade 3 and 4 side effects, a 5% reduction in motor neuropathy and nausea/vomiting made the most difference.

Similar results to the UK audits were seen in "real world" audits undertaken in France (66) and Spain (67).

The French retrospective clinical practice setting study (66) included 258 eribulin patients with MBC who had received a median of 4 prior chemotherapy regimens in the metastatic setting, with 85% who had previously received capecitabine. In this study, the incidence of Grade 3 and 4 side effects of neutropenia and peripheral neuropathy were less than in Study 305 (EMBRACE).

In Spain, 19 hospitals took part in an observational retrospective national study (67). One hundred and four patients on eribulin, of whom 81% had received prior capecitabine) were included in the analysis. Even in this heavily pre-treated group of patients (50.9% had received ≥6 prior chemotherapy regimens for advanced disease), the incidence of the most common reported adverse events were lower than that of Study 305 (EMBRACE):

- Asthenia/fatigue: 44.2% vs 53.7%
- Neutropenia: 25% vs 51.7%
- Alopecia: 17.3% vs 44.5%
- Nausea: 10.6% vs 34.6%

A study of patient preferences for the treatment of MBC has found that treatment effectiveness was rated as the most important attribute, more than 3 times more important than some side effects (68).

Given the outcome of this patient preference study and in combination with the safety data presented above for eribulin in both the phase III clinical trials and "real world" observational studies, it can be fairly argued that eribulin has a well-characterised and manageable safety profile which

- does not affect HRQoL and
- does not necessitate for patients making compromises between efficacy and safety

4.13 Interpretation of clinical effectiveness and safety evidence

Principal findings from the clinical evidence highlighting the clinical benefit and harms

Two phase III studies involving more than 1,800 patients form the basis of the current licensed indication for eribulin in MBC. (6,10) In the landmark Phase III study 305 (EMBRACE) where the primary endpoint was overall survival (6), eribulin was the first cytotoxic agent to improve overall survival in heavily pre-treated patients with MBC versus treatment of physicians' choice (TPC).

Overall survival is recognised as the most reliable cancer outcome (26) and is of most importance to patients when making decisions regarding treatment options (27). As identified by NICE, there is minimal high-quality evidence about the relative clinical effectiveness of current treatments (17) and none of the currently available NICE-approved monotherapies have demonstrated a survival benefit over any other (17,28), including the specific agents identified in the NICE scope (Table 1).

NICE identified that the level of evidence on the use of vinorelbine as a monotherapy is generally of very poor quality consisting mainly of low patient number, non-comparative phase II trials or small RCTs. None of the available data demonstrated an overall survival benefit over an alternative treatment (17). For capecitabine monotherapy, NICE concluded again that the level of evidence is generally of poor quality consisting mainly of low patient number, non-comparative phase II studies (17); although overall survival data for capecitabine is reported in these non-comparative studies, no comparative data on overall survival is available (17). Recommendations from NICE for gemcitabine are based on its use in combination with paclitaxel only (69), and we are not aware of any comparative overall survival data available for gemcitabine monotherapy.

In contrast, in the Phase III, randomised, controlled study 305 trial, median overall survival was significantly improved in women assigned to eribulin (13.1 months) compared with TPC (10.6 months), an increase in duration of survival of 23% (2.5 months) (p= 0.041). (7) The updated analysis performed after 77% of patients had died and on request of the regulatory authorities, confirmed these results; median OS (eribulin 13.2 months vs. TPC 10.5 months) was improved by 2.7 months (p=0.014). (8)

A further updated OS analysis of study 305 (EMBRACE) was performed after 95% of patients had died. In those patients who had received prior capecitabine treatment (73.4% of the trial population), the OS was statistically significant with a HR of 0.78 (95% CI: 0.65, 0.94). Median OS was 13.0 months for eribulin and 10.1 months for TPC, an extension in median survival of 2.9 months. (9)

A second Phase III study in earlier line metastatic breast cancer, Study 301, provides further supporting evidence for the efficacy and safety of eribulin in MBC. Eribulin demonstrated a trend favouring improved OS as compared with capecitabine but this improvement did not reach statistical significance. (10,11)

Importantly, the results of a HRQOL assessment conducted in study 301 show that eribulin does not adversely impact HRQOL (as assessed by EORTC QLQ-C30). The majority of patients (≥74%) in both treatment groups maintained or improved their global health status/HRQOL vs baseline. (83) In addition, separate sub-analyses in subgroup 1 and subgroup 2 show consistent results with those in the overall population.

Eribulin's safety profile is well characterised in the two global phase III studies in the MBC setting, which showed that eribulin had a manageable profile of adverse events which is similar to those of other chemotherapeutic agents used in this setting. Oncologists and associated healthcare professionals caring for patients with MBC are experienced in dealing with these adverse events.

Eribulin is generally well tolerated, with fewer discontinuations due to AEs than control in the Phase III studies. (7,11) Discontinuations due to AEs were lower in the eribulin group than in the control group for both phase III studies (13.3% vs. 15.4% in Study 305 and 5.7% vs 6.2% in study 301, respectively).

Haematological toxicity (e.g. neutropenia) with eribulin is evident although not dissimilar in frequency to some of the other chemotherapeutic drugs. Development of Grade 3/4 AEs of neutropenia occurred in 49.7% of patients in study 305 and 45.8% in Study 301 (6,10)

However, neutropenia led to discontinuation in only 0.9% and 1.7% of patients, while febrile neutropenia was infrequent. Primary prophylaxis with G-CSF for the prevention of neutropenia was not a requirement of the studies (unless defined by local practice protocols).

Common non-haematological AEs experienced during eribulin treatment in the phase III studies included asthenia/fatigue, alopecia, nausea and peripheral neuropathy; these were usually manageable with dose delays, dose reductions, or supportive therapies.

Eribulin's well characterised and manageable tolerability profile is supported by recently published "real world" data from audits undertaken at three UK hospitals in over 200 patients (35,36,37) which have shown that eribulin is well tolerated in a routine clinical practice setting and reflect that patients are not impacted greatly by eribulin's side effect profile

Strengths and limitations of clinical evidence

There is minimal high-quality evidence about the relative clinical effectiveness of current treatments for patients at this advanced stage of the disease, as acknowledged by NICE (17). The pivotal eribulin study 305 (EMBRACE) represents a high quality, large (> 750 patients), multi-centre, head to head RCT providing robust evidence for the statistically and clinically significant benefit of eribulin compared with current treatment options in pre-treated patients with LABC/MBC.

Study 305 compared the efficacy and safety of eribulin with TPC, a comparator arm that reflects the real life choices faced by physicians and patients. Although an RCT has not been performed versus one specific comparator, by following the recommendations supported by the EMA to use TPC, study 305 reflects clinical practice and the reality that there is no single standard treatment for patients beyond 2nd line in treatment in advanced breast cancer. It can be argued that practically speaking it would not be feasible to conduct large scale trials to compare eribulin with individual therapies due to the diversity of treatment used at this stage of the disease. Using TPC as a comparator allows treatment selection to be based on a number of factors including prior chemotherapy exposure and response, tolerability, patient preference, availability of drugs, and the patient's quality of life, representing how treatment decisions are made in clinical practice. Offering patients a choice of treatment and taking their preferences into account is crucial to this approach. NICE guidance to manufacturers on the technology appraisal process recognises that comparators for technology appraisals should be selected based on current standard of care, and that standard of care will vary across the NHS. The mixture of therapies currently used in clinical practice, and those chosen by physicians within study 305 would appear to validate the TPC approach for the study.

The second Phase III study in earlier line metastatic breast cancer, Study 301, was an open-label, randomised, study in patients with locally advanced or metastatic breast cancer to investigate the efficacy of eribulin monotherapy compared to capecitabine monotherapy. Patients had previously received up to three prior chemotherapy regimens, including both an anthracycline and a taxane and a maximum of two for advanced disease. The percentage of patients who had received 0, 1 or 2 prior chemotherapy treatments for metastatic breast cancer were 20.0%, 52.0% or 27.2% respectively, making this a predominantly second-line study.

Study 301 provides further supporting evidence for the efficacy and safety of eribulin in MBC. Eribulin demonstrated a trend favouring improved OS as compared with capecitabine but this improvement did not reach statistical significance.

Importantly, HRQoL was assessed in study 301 using the EORTC QLQ-C30 instruments and these results were then used in the cost effectiveness analysis (see section 5.4).

Both study 305 (EMBRACE) and study 301 employed primary and secondary efficacy outcomes, including OS, PFS and ORR, that are all accepted, objective, commonly used measures of efficacy for breast cancer drugs and clinically relevant.

The primary outcome of OS is considered the most reliable cancer outcome, particularly in the pre-treated population considered here (i.e. short life expectancy, where results are expected in a reasonable timeframe and there are limited effective next line therapies) (26). It is precise and easy to measure, documented by the date of death and thus is not subject to assessment bias.

The other secondary endpoint used to evaluate efficacy— objective tumour response rate using RECIST— is also a standard clinical outcome variable in oncology studies. In addition, the EORTC Questionnaire QLQ-C30 is an accepted method used routinely to evaluate a patient's health related quality of life which was derived from an advanced breast cancer population.

End-of-life criteria

Although therapeutic advances have been made, the overall prognosis for patients with MBC remains poor, with an average length of survival of 12 months for those receiving no treatment, compared to 18-24 months for those receiving chemotherapy (39)

Further information in Table 36 overleaf indicates that eribulin is suitable for consideration as a 'life-extending treatment at the end of life'.

Please note that, as per guidance received by Eisai during the decision problem meeting, the end-of life criteria has been amended to be as per the revised criteria proposed in the "Consultation on proposals for a new cancer drugs fund (CDF) operating model from 1st April 2016".

Table 36 End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months, and	The EMBRACE study reported a median OS of 13.1 months in the eribulin arm and a median OS of 10.6 months in the TPC arm (6). In study 301, the median OS in the eribulin arm was 15.9 months versus 14.5 months in the capecitabine arm (10). Therefore, eribulin is indicated for LABC/MBC patients who have a short life expectancy, normally less than 24 months.
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 cost effectiveness analysis in HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting (subgroup 1) show a mean overall survival benefit for eribulin of 4.61 months. (See section 5.3) The results of the cost effectiveness analysis in patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (subgroup 2) show a mean overall survival benefit for eribulin of 3.04 months. (See section 5.3) Therefore, eribulin offers an extension to life, **normally** of a mean value of at least an additional 3 months, compared with current NHS treatment.

Abbreviations: LABC, Locally advanced breast cancer; MBC, Metastatic breast cancer; OS, Overall survival; HER2, Human epidermal growth factor receptor 2; TPC, Treatment of Physician's Choice.

4.14 Ongoing studies

There are no completed or ongoing studies which would provide additional relevant evidence in the next 12 months.

5 Cost effectiveness

Summary of Cost Effectiveness

- The present economic evaluation was conducted for the two subgroups as described in Section 1.
- Two systematic reviews were conducted to retrieve relevant information from the published literature regarding the cost-effectiveness of eribulin in each of subgroup patient populations. None of the identified studies was found to be relevant for the purposes of this economic evaluation.
- In the absence of relevant economic evaluations found in the literature, a de novo cost effectiveness analysis was conducted for eribulin within the two subgroups identified.
- The economic evaluation was performed by developing a partition survival model similar to previous models developed in LABC/MBC as well as according to the NICE technical and clinical guidelines.
- Health outcomes were measured in in terms of quality adjusted life years (QALYs). Utility values for the estimation of the QALYs were based on patient reported outcomes collected in study 301.
- Cost assessment included the cost of treatments and their administration, the cost of treating AEs. The cost of healthcare resources utilised over stable and progressive disease as well as resources related to palliative care and end of life were also considered.
- In comparison to TA250, this economic evaluation of eribulin was based on patient-level data to model the survival functions and within-trial collected patient reported outcomes for the elicitation of the utilities. These two elements are very important in terms of reducing uncertainty around the outcomes.
- Apart from probabilistic and deterministic sensitivity analyses, additional sensitivity analysis scenarios were performed assessing variations in comparators for both subgroups, primary and secondary treatment duration, prevalence of the AEs considered and variations in time horizon of the analysis.
- In both subgroups, eribulin was associated with higher costs but provided additional quality-adjusted life years (QALYs) compared to capecitabine in subgroup 1 and TPC in subgroup 2. The basecase ICERs were found to be £36,244 per QALY for subgroup 1 and £35,624 for subgroup 2.
- All the sensitivity analyses conducted strongly indicate that the evaluation is very robust with all the ICER derivatives being a very narrow range from the basecase ICERs. The basecase ICERs for subgroup 1 and 2 are fairly close to the willingness to pay thresholds used for other treatments which have been recently approved by NICE. Considering the increased willingness to pay thresholds for treatments meeting the “end of life criteria”, both the observed basecase ICERs and sensitivity analysis ICERs fall below these thresholds given that eribulin meets the “end of life” criteria.
- Considering all of the above, the cost effectiveness analysis demonstrates that eribulin in the two specified subgroups has been robustly and conservatively demonstrated to meet all the accepted criteria for a cost-effective end of life treatment and could be considered good value for money for adoption by the NHS.

5.1 Published cost-effectiveness studies

As stated previously in the decision problem Table 1, the populations considered suitable for eribulin treatment within this submission consist of two separate subgroups, namely:

Subgroup 1

1. HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.

Subgroup 2

2. Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated).

Therefore, two systematic reviews were conducted to retrieve relevant information from the published literature regarding the cost-effectiveness of eribulin in each of the above patient populations. In both systematic reviews, 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 and restricted to English language only. This was supplemented by additional searching of clinicaltrials.gov and conference proceedings from ASCO, ESMO, AACR and ISPOR.

Using Boolean operators and specific syntax, the searches used terms (including MeSH headings as appropriate) for eribulin, including any alternative names (e.g. Halaven, E7389).

Full details of the search strategies used in both systematic reviews are provided in Appendix 2.

Identification of studies

Eligibility criteria

Studies identified were initially assessed based on title and abstract (Step 1). Publications not meeting inclusion criteria in in Step 1 were excluded and listed alongside the reason of study exclusion (Step 2). Full text publications were retrieved from those abstracts meeting inclusion criteria in Step1 and assessed based on the full text. (Step 3) After the full text review, all papers meeting inclusion were retained for data extraction, and those papers not meeting inclusion criteria were excluded and listed alongside the reason for the exclusion.

Inclusion and exclusion criteria for each of the two systematic reviews are shown in Table 37 and Table 38 overleaf.

Table 37 Eligibility criteria used in search strategy: HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.

	Inclusion	Exclusion
Population	Adult patients AND [MBC OR Advanced breast cancer (ABC)] AND HER2-negative AND Following one prior chemotherapy	Non-human OR Children OR Adolescents OR Males OR First line Not distinguished HER2 status
Intervention	Eribulin (monotherapy)	All other treatments
Comparator	Any	
Outcomes	All	
Study design	Cost OR Budget OR Budget impact OR Expenditure OR Utilization OR Cost effectiveness OR Cost utility OR Cost benefit OR Cost Minimization OR Cost/Burden of illness studies OR Resource utilisation	Editorials OR Notes OR Comments OR Letters OR Reviews OR Abstracts without full paper available
Language	English	Non-English studies

Abbreviations: ABC, Advanced breast cancer; HER2, Human epidermal growth factor receptor 2; MBC, Metastatic breast cancer;

Table 38 Eligibility criteria used in search strategy: Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated)

	Inclusion	Exclusion
Population	Adult patients AND [MBC OR Advanced breast cancer (ABC)] AND 3rd line plus	Non-human OR Children OR Adolescents OR Males OR First and second line
Intervention	Eribulin (monotherapy)	All other treatments
Comparator	Any	
Outcomes	All	
Study design	Cost OR Budget OR Budget impact OR Expenditure OR Utilization OR Cost effectiveness OR Cost utility OR Cost benefit OR Cost Minimization OR Cost/Burden of illness studies OR Resource utilisation	Editorials OR Notes OR Comments OR Letters OR Reviews OR Abstracts without full paper available
Language	English	Non-English studies

Abbreviations: ABC, Advanced breast cancer; HER2, Human epidermal growth factor receptor 2; MBC, Metastatic breast cancer;

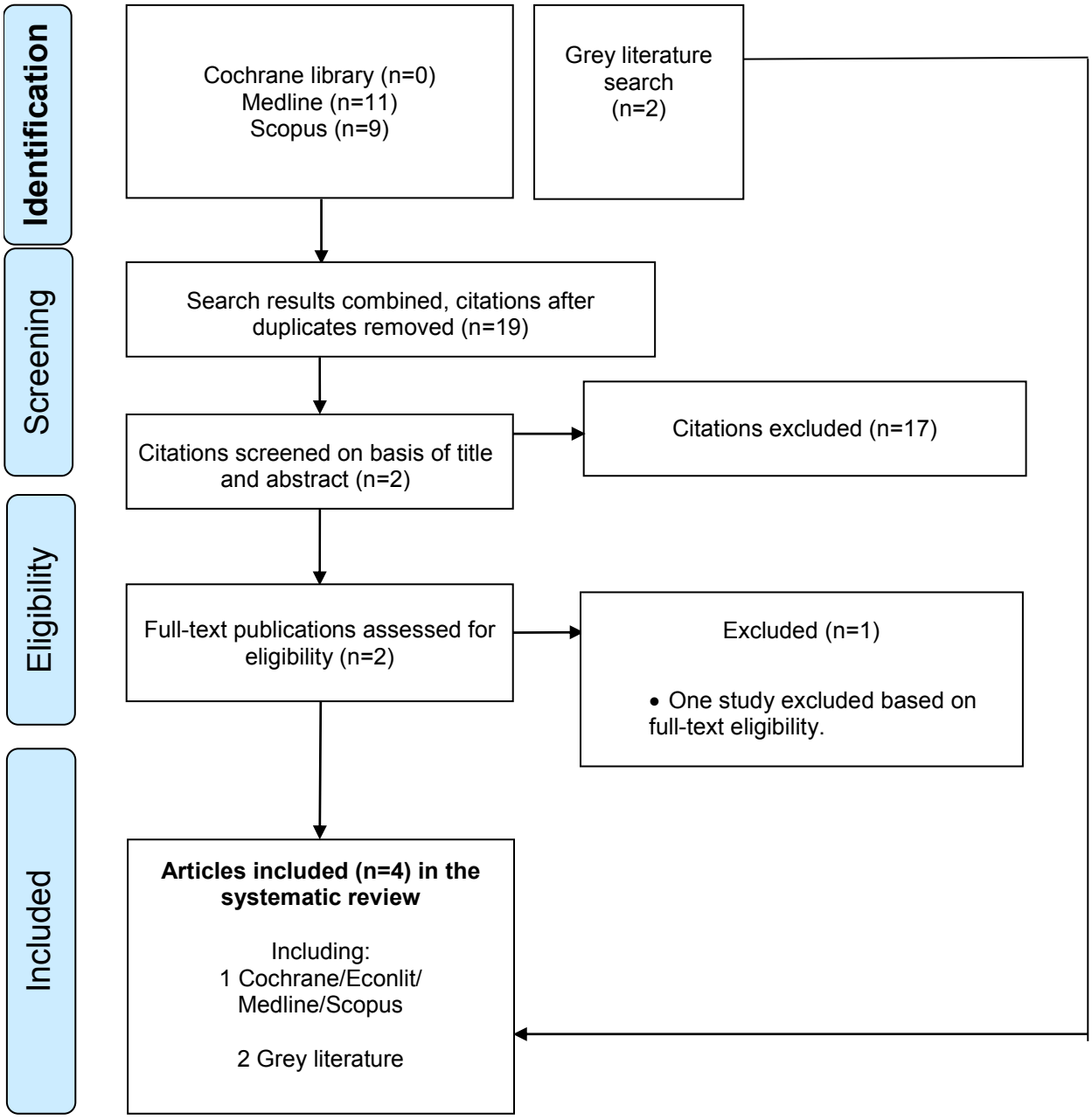
Flow Diagrams of included and excluded studies

1. *HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.*

Following assessment and exclusion of studies based on title, abstract and full text, 3 records from the systematic review were identified in total covering including two studies from the grey literature.

A list of excluded studies is provided in Appendix 2. The flow diagram for the systematic review is shown in Figure 23 below.

Figure 23 PRISMA Study Attrition Diagram used in search strategy: HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.

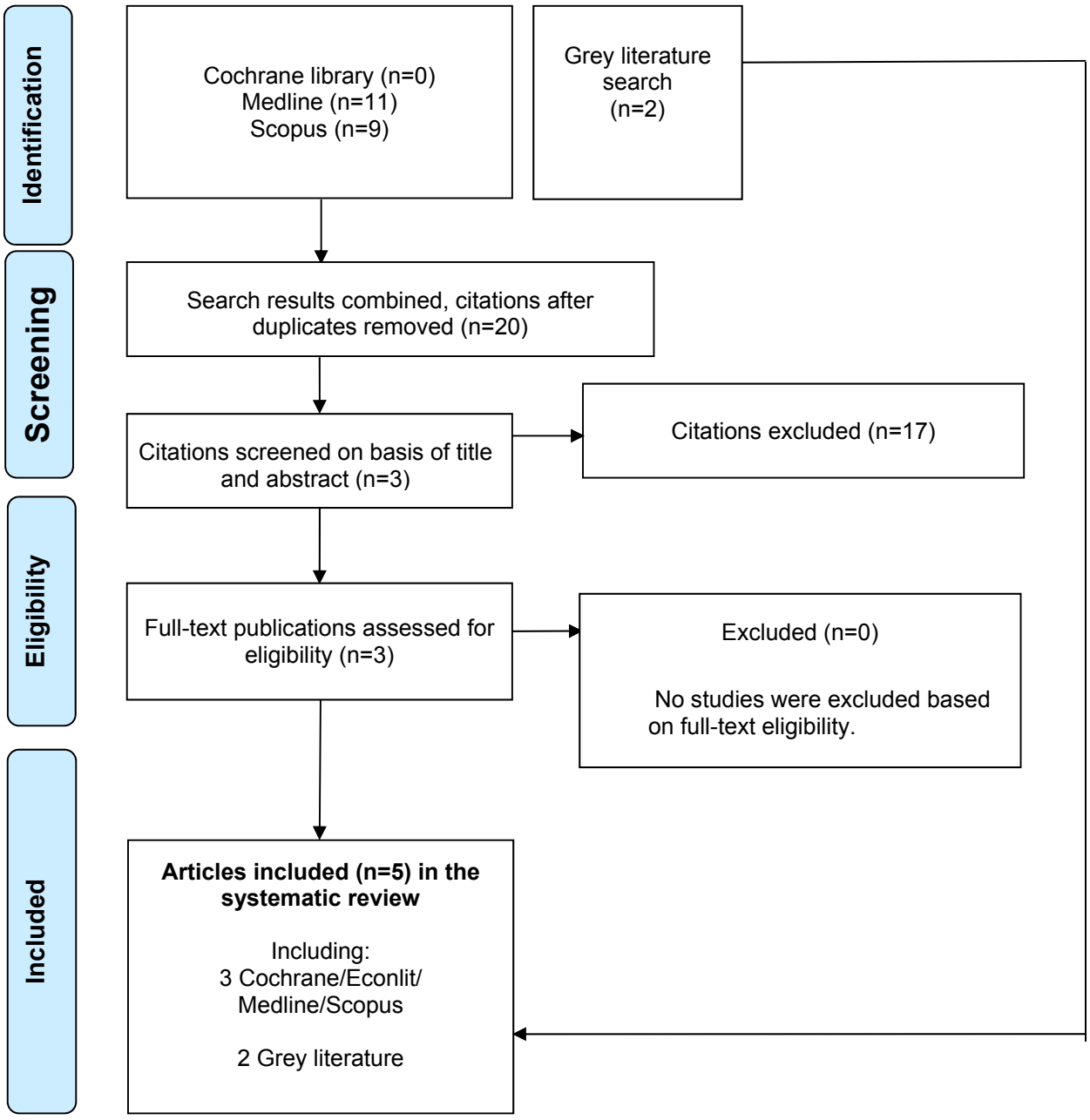


2. *Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated)*

Following assessment and exclusion of studies based on title, abstract and full text, 5 records from the systematic review were identified in total covering including two studies from the grey literature.

A list of excluded studies is provided in Appendix 2. The flow diagram for the systematic review is shown in Figure 24 below.

Figure 24 PRISMA Study Attrition Diagram used in search strategy: Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated)



Description of identified studies

The systematic reviews on the cost effectiveness of eribulin in the aforementioned subgroups identified the following studies:

Subgroup 1

1. Dranitsaris G, Beegle N, Kalberer T, et al. A comparison of toxicity and health care resource use between eribulin, capecitabine, gemcitabine, and vinorelbine in patients with metastatic breast cancer treated in a community oncology setting. J Oncol Pharm Pract. 2015;21(3): 170-177 (70)

2. Wan Y, Copher R, Corman S, et al. Indirect costs among metastatic breast cancer patients receiving eribulin. ISPOR 20th Annual International Meeting, 16-20 May, 2015, Philadelphia. PNC72 (71)

3. Tremblay G, Majethia U, Kontoudis I, et al. Cost Effectiveness Analysis of Eribulin Mesylate as a Treatment for Metastatic Breast Cancer in Spain: Management in the Later Line of Therapy. JHEOR 2015;3(2):180-93 (94)

From the three identified studies above, only one study, Tremblay et al (94) provides a cost effectiveness analysis of eribulin and provided a cost/QALY. However, the objective of this study was to evaluate the cost effectiveness of eribulin in Spain, it was not conducted in the UK from the perspective of the NHS and therefore it is not relevant to decision making in England.

Therefore, to address the lack of published evidence for the cost effectiveness of eribulin in subgroup 1, a de novo analysis has been carried out (see Section 5.2)

The studies by Dranitsaris et al (70) and Wan et al (71) discuss the direct and indirect costs associated with treatment of locally advanced or metastatic breast cancer with eribulin or its comparators. Therefore, the results of these studies are summarised in section 5.5.

Subgroup 2

1. Dranitsaris G et al. A comparison of toxicity and health care resource use between eribulin, capecitabine, gemcitabine, and vinorelbine in patients with metastatic breast cancer treated in a community oncology setting. J Oncol Pharm Pract. 2015 21: 170-177 (70)

2. Greenhalgh J et al. Eribulin for the treatment of advanced or metastatic breast cancer: a NICE single technology appraisal. Pharmacoeconomics. 2015 (73)

3. Lopes G, Glück S, Avancha K, Montero AJ.A cost effectiveness study of eribulin versus standard single-agent cytotoxic chemotherapy for women with previously treated metastatic breast cancer. Breast Cancer Res Treat. 2013 Jan;137(1):187-93. (74)

4. Tremblay G et al. Cost Effectiveness Analysis of Eribulin Mesylate as a Treatment for Metastatic Breast Cancer in Spain: Management in the Later Line of Therapy. JHEOR 2015;3(2):180-93. (94)

5. Jones TE et al. Cost Effectiveness Analysis of Eribulin Mesylate (Halaven®) as a Treatment for Metastatic Breast Cancer in Mexico Value Health. 2015 Nov;18(7):A822. (75)

From the five identified studies above, four studies (73,74,94,75) provide a cost effectiveness analysis of eribulin and provided a cost/QALY. Only one publication is conducted in the UK from the perspective of the NHS and is therefore relevant to decision making in England. However, this publication is the NICE STA conducted in 2011 (73) and can be considered out of scope given the subgroup populations assessed in this economic evaluation. Key conclusions mentioned in the publication have been summarised and addressed in section 1.

Therefore, to address the lack of published evidence for the cost effectiveness of eribulin in subgroup 2 and to address the concerns raised during the NICE STA conducted in 2011, a de novo analysis has been carried out (see Section 5.2)

As stated previously, the study by Dranitsaris et al (70) discusses the direct and indirect costs associated with treatment of locally advanced or metastatic breast cancer with eribulin or its comparators. Therefore, the results are summarised in section 5.5.

A summary of the above mentioned published cost effectiveness studies is included in the table overleaf (Table 39) and a quality assessment is provided in Appendix 5.

Table 39 Summary of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Tremblay et al (94)	2015	Markov model from the perspective of the **Spanish healthcare system** with a 5 year time horizon. Objective was to compare cost effectiveness of eribulin as second-line treatment for HER2-negative MBC vs third-line treatment after capecitabine. Three health states: Stable, Progression and Death. Transition probabilities and efficacy data were obtained from study 301 (11) and study 305 (7). Utilities were derived from study 301 (11).	Patients with MBC. Two pre-treated patient populations: HER2-negative patients eligible for second line therapy and patients who had progressed on/were refractory to capecitabine	**Second-line treatment for HER2-negative MBC:** 1.18 QALY (vs capecitabine and vinorelbine) **Third-line treatment after capecitabine:** 0.92 QALY (vs primary TPC)	Discounted: **Second-line treatment for HER2-negative MBC:** €19,400 (eribulin vs capecitabine and vinorelbine) **Third-line treatment after capecitabine:** €13,519 (vs primary TPC)	**Second-line treatment for HER2-negative MBC:** €37,152 **Third-line treatment after capecitabine:** €35,484
Greenhalgh et al (73)	2011	**Company submitted model:** semi-Markov model from the **perspective of the NHS** with a lifetime horizon. Three health states: Treated, Progressive and Dead. Efficacy data was obtained from 305 (7). Utilities were derived from published literature.	Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease	**Company submitted model:** 0.12 QALY (vs TPC)	**Company submitted model (PAS price):** Discounted: £5,472 (eribulin vs TPC)	**Company submitted model (PAS price)**: £45,106
Lopes et al (74)	2012	Markov model from the perspective of the **US healthcare system**. Time horizon was not reported. Transition probabilities and efficacy data were obtained 305 (7). Utilities were derived from published literature.	Patients with advanced breast cancer.	0.119 QALY (vs TPC)	Not discounted $25,458.86 (eribulin vs TPC)	$213,742
Jones et al (75)	2015	Markov model from the perspective of the **Mexican healthcare system** with a 5 year time horizon. Three health states: Stable disease, Progressive disease and Dead. Transition probabilities and efficacy data were obtained 305 (7). Utility information is not reported.	Patients with metastatic breast cancer previously treated with capecitabine.	QALY not reported 1.29 LY (vs vinorelbine)	Discounted: $MXN 132,345.67 (eribulin vs vinorelbine)	ICER per QALY gained not reported ICER (Cost per LY): $MXN 22,016.61

Abbreviations: LABC, Locally advanced breast cancer; MBC; metastatic breast cancer; PAS, Patient access scheme; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; TPC, Treatment of physician's choice

5.2 De novo analysis

An economic evaluation using a de novo cost utility analysis was performed to assess the cost effectiveness of eribulin in clinical scope as described in earlier sections.

Patient population

The de novo analysis was conducted for the patient subgroups as described in the decision problem (Table 1). In detail, the cost utility analysis model assesses eribulin cost effectiveness in:

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

Although the population described in the final NICE scope reflects in full eribulin's indication, the patient population included in the model differs for the following reasons:

1. Eribulin's clinical benefit has been assessed in two phase III pivotal trials (7,11). However, the two studies included patient populations with different characteristics and focused in slightly different disease settings (see section 4.3). In order to ensure an accurate assessment of eribulin's cost effectiveness, the model includes two specific subgroups allowing the utilisation of exact patient level data without having to pool data from the two studies which would have created uncertainty risks given the aforementioned studies characteristics. The diagram below (Figure 25) illustrates the overlap between the two trials and how the selection of the subgroups enables accurate cost-effectiveness assessment. Moreover Table 40 overleaf summarises the methodological issues that would arise by utilising the pooled data from the two studies compared to using individual studies' patient level data.

Figure 25 Management of LABC/MBC and patient population included in the model

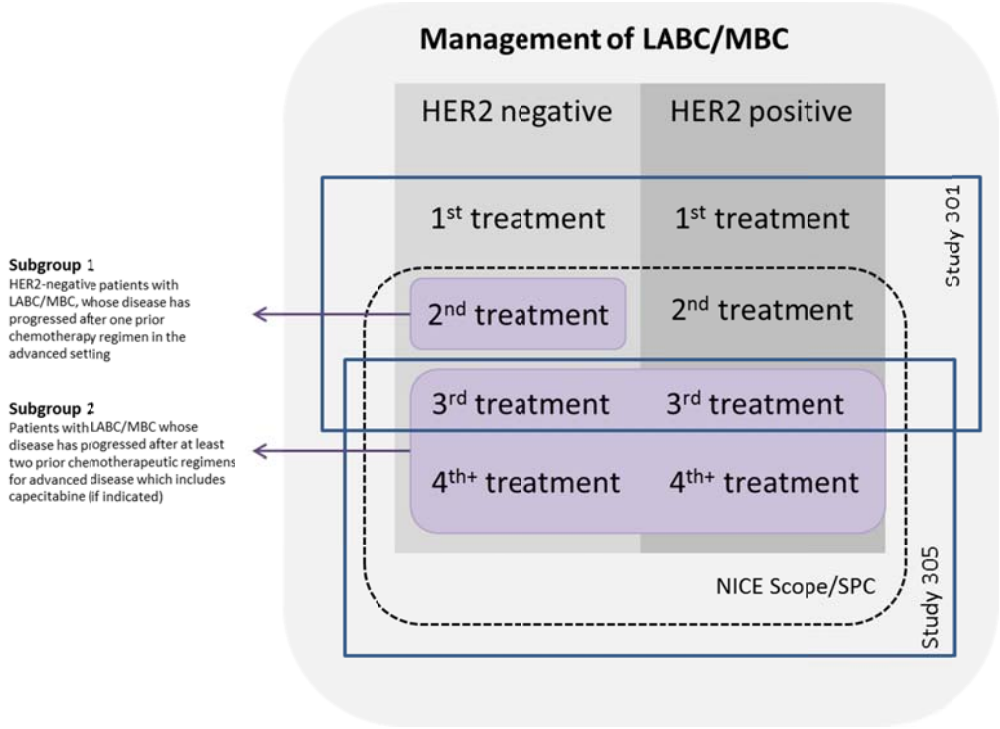


Table 40 Methodological issues of pooled patient data versus individual studies' patient level data

Parameters	*Pooled patient data*	*Individual Studies' patient data*
Trial effect bias	The pooled analysis is a combination of 301/305 trials patient-level datasets. Due to the different study characteristics between the two studies (e.g. lines of therapy, a "study" effect was tested in the Cox model considering different stratification factors (Study, prior cape, and region), and covariates (ER status and #organs involved) and it was found to be significant. While the trial effect can be managed properly in survival analysis using a parameter in the cox model, the data is less robust for extrapolation in a cost-effectiveness analysis model, because of different cut off points.	No trial effect in studies 301 and 305
Adverse events	Adverse events in each study were collected for the respective treatment arms of eribulin and capecitabine in study 301 and eribulin and TPC in study 305. The prevalence of the AEs, thus, is dependent on the proportions captured in each study. Pooling these proportions or making assumptions about them can lead to biases in the CEA results for TPC, so the adverse events prevalence will depend on the MS in the trial, but	Studies 301 and 305 area head-to-head trials and thus the adverse event profiles of each comparator are clean.

2. Different comparator arms were included in each of the studies - Study 301 included capecitabine whereas Study 305 included TPC. The selection of these comparators within the clinical trials was based on the current clinical practice at the time of the studies' design. The assessment of eribulin's cost-effectiveness in two specific subgroups allows for comparing eribulin to the most appropriate comparator instead of using a common control arm which would necessitate pooling patient data from the two studies.
3. The specific subgroups identified within the clinical trials are those where eribulin's greatest clinical benefit was observed.
4. Subgroup 2 reflects the current clinical practice in England as observed through the usage of eribulin through the CDF. Recently published data from audits undertaken at three UK hospitals (35,36,37) showed that more than 80% of patients had received prior capecitabine when prescribed eribulin under the CDF.

Model structure

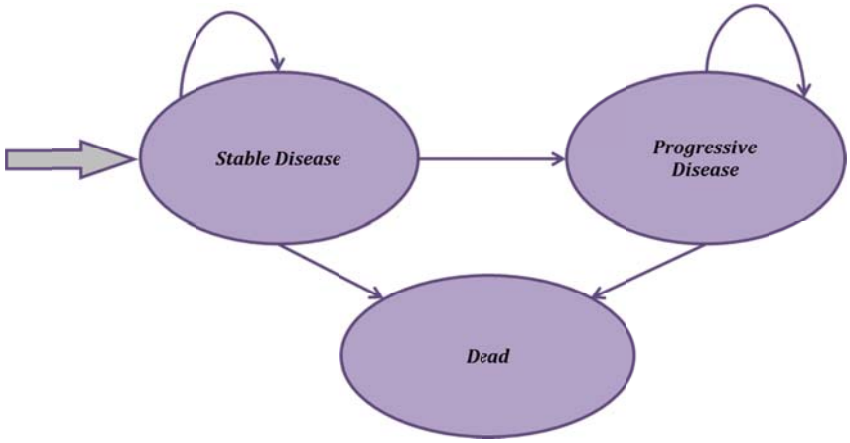
Structure Overview

A partition survival cost utility model was developed in Microsoft Excel to model the lifetime clinical and economic outcomes of eribulin and its comparators within the two aforementioned subgroups. This approach is similar to a traditional Markov model, except for phase III clinical trials efficacy data being used to estimate transition probabilities between health states.

Health States Structure

The model includes three health states (Figure 26):
- pre-progression or "Stable" health state which aims at capturing the progression free survival endpoint data,
- post-progression or "Progressive" health state and
- "Dead".

Figure 26 Patient Health States



Patients are assumed to transition between the three health states of "Stable", "Progressive" and "Dead", based on the patient level data. Patients enter the model in the "Stable" (or the progression free) health state when they initiate treatment with eribulin or the comparator arm. These patients stay at this health state until disease progression, when they enter into the "Progressive" (or post-progression) health state. Patients in the "Progressive" state are assumed to remain in this state until death. Patients in the "Stable" health state can transition directly to the "Dead" state without passing through the "Progressive State". Patients continue transitioning across health states until all patients are in the "Dead" state.

The "dead" state is the terminal state.

The PFS curve represents the frontier between the health states of "Stable" and "Progressive" disease, while the overall survival curve represents the frontier between "Progressive" disease health state and the terminal state.

Health states were defined in consistency with clinical outcomes reported in oncology clinical trials, including studies 301 and 305. The proportion of patients in each health state, over the course of time, was estimated based on the Kaplan-Meier survival functions associated with the clinical outcomes studied in the clinical trials.

Since the follow-up period in both studies was 5 years, the first 60 months were directly based on the Kaplan-Meier survivor function. Therefore, the 5 year time horizon has been selected as basecase scenario with the model being based exclusively on within trial patient level data. Two more time horizon options, 10 and 20 years have been considered in the model as sensitivity analysis scenarios. When these time horizons are selected, the tail of the OS curve is extrapolated.

While a partition survival model is based on the area under the curve and not transition rate, the expression "transition" is used to discuss about the transfer of a patient from one state to another. The use of the expression "transition", should not be confused with the classical expression of "Markov transition rate", which is fixed by nature, unlike in a partition model in which transition rate is based on patient level data rather than being fixed.

Model cycles

Markov cycle duration was set at 30.42[1] days (one Markov cycle). Every Markov cycle, patients face a risk of transition among health states based on disease status or death. As mentioned above, the transition of patient is derived from the clinical outcomes of studies 301 and 305 – Progression Free Survival (PFS) and overall survival (OS). One month cycle length was used for the purpose of convenience of calculations.

The Kaplan-Meier data was extracted on a monthly basis for this analysis i.e. at the end of the month. As an example, month 1 data is 30.43 days after day 0. A half-cycle correction was not used in this model so that the Kaplan-Meier data would be directly used without any additional correction. Therefore, the outcomes are based on the end-of the cycle, here a monthly cycle.

Model Time Horizon

The time horizon of the model was set at five years (60 months) beginning by the moment of treatment initiation. This timeframe approximates a lifetime projection in the model patient population.

As per the decision problem summary table (Table 1), ten and twenty year time horizons have been also included in the model as sensitivity scenarios allowing for all events to occur.

The 20 year horizon can be assumed to be a proxy for a lifetime model since both overall survival partitions corresponding to the two subgroups are below 1% at the end of twenty year time horizon

Costs & Utilities estimation

Costs and health-related quality of life (HRQoL) were assumed to be conditioned on treatment and expected time in the given health states. Patients were assumed to continue their primary treatment until disease progression and then switch to alternative treatments (secondary therapies) in the “Progressive” health state.

Model Perspective

The analysis was conducted from the perspective of NHS, and personal and social services in England & Wales, in line with current NICE guidelines. The analysis excluded patients' out-of-pocket expenses, carers’ costs and lost productivity derived costs.

Other Structural characteristics

Discounting: Costs and benefits were discounted at the rate of 3.5% annually according to the NICE guidelines. The monthly discounting rate for both costs and benefits was 0.29% and was generated using the cycle transition probability formula. i.e.
((1+Annual Discounting rate) ^ (1/12)-1).

Body Surface Area (BSA): BSA is an important factor for calculating the dose of chemotherapy regimens. As recommended by the Liverpool reviews and Implementation group (LRiG) STA report during the previous NICE assessment (TA250), the BSA for

[1] Markov cycle length: 365.25 / 12 = 30.4375 days per year

women in the UK was based on the paper by Sacco et al and assumed to be 1.74 m2 (CI: 1.72,1.76). (76) This BSA was assumed to be the same for both subgroups.

Dose Intensity: Chemotherapy treatment may require a dose reduction or dose delay in order to manage specific adverse events. The mean relative dose intensities of eribulin and capecitabine estimated in the study 301 were used for subgroup 1. For subgroup 2, the eribulin mean dose intensity was used for both eribulin and TPC arm for simplicity reasons since the TPC arm was comprised of more than one treatments. Regarding secondary therapies, TPC is assigned with the dose intensity of eribulin in each subgroup.

Table 41 Mean Dose Intensities used

	Eribulin	Capecitabine	Source
Subgroup 1	0.87	0.86	Study 301 (11)
	Eribulin	TPC	Source
Subgroup 2	0.84	0.84 (assumption)	Study 305 (7)

Wastage: The average BSA of patients in this model was 1.74 m2 (CI: 1.72,1.76). The average dose of treatment drugs was calculated for patients based on this BSA. The pack sizes of drugs available did not account for the exact amount of drug required for patients in each dose. Hence, a rounding was used for dose calculations to avoid drug wastage. The rounding was based on 10% of the smallest dose e.g. for gemcitabine, the pack sizes are 200 mg, 1000 mg and 2000 mg each. Based on the BSA, if the recommended drug dose of the patient was 1010 mg, the patient was given only 1 vial of 1000mg of gemcitabine to avoid wastage of the drug. But if the required dose of gemcitabine was 1020 mg or above, the patient was given an additional drug from the 200 mg vial and the remainder of the vial was accounted for as wasted drug. For the purpose of this economic evaluation, the costs of the wasted drug were also included in the model to be conservative.

Table 42 Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Basecase: 5years Sensitivity scenarios: 10 & 20 years	5 years time horizon reflects the follow up period of both study 301 and 305. 10 & 20 years time horizons were selected as sensitivity scenarios to project lifetime
Were health effects measured in QALYs; if not, what was used?	Yes QALYs was used	According to NICE guidelines
Discount of 3.5% for utilities and costs	Yes, 3.5% discounting rate was used	According to NICE guidelines
Perspective (NHS/PSS)	NHS England	No social services or indirect costs were included in the model as considered non relevant.

Abbreviations: PSS, personal social services; QALYs, quality-adjusted life years

Intervention technology and comparators

Primary Therapies

The model considers eribulin as the intervention technology. This is compared with different comparators for each of the subgroups mentioned above, as outlined below:

- **Subgroup 1:**
  - Basecase comparator – *Capecitabine*

Capecitabine was selected as the basecase comparator to reflect the design of study 301 of which patient level data are used in the model to estimate clinical and cost effectiveness outcomes.

- Sensitivity analysis scenario's comparators – *mix of 50% capecitabine and 50% vinorelbine (including both oral and IV formulation)*
  The mix of capecitabine and vinorelbine was selected as an alternative set of comparators for subgroup 1 in order to reflect the scope (Table 1) and the current NICE clinical guidelines (29). In the absence of clinical evidence of vinorelbine in the specific disease setting, the assumption of equal efficacy and safety between capecitabine and vinorelbine needed to be made. Although gemcitabine was also included in the NICE scope as a potential comparator, this is outside of the NICE clinical guidelines. Moreover, no clinical evidence exists for gemcitabine in this specific disease setting and a small number of UK clinical experts have validated that it is not routinely used in this setting. Therefore, further assumption would need to be made, something that would enhance the bias of the analysis and increase the uncertainty of the results.

- **Subgroup 2:**
  - Basecase comparator - Treatment of Physician's Choice (TPC), excluding capecitabine
    As described in section 4.3, this is the basis of the approach taken for the comparator arm of study 305, and reflects a pragmatic approach to compare eribulin in a disease setting of such late treatments, consisting of a variety of therapeutic options instituted by practicing physicians on a day-to-day basis.
    The proportion of treatment utilisation of the different therapies making up the TPC arm are based on the utilisation rates of the therapies included in the TPC arm of study 305, excluding capecitabine and treatments with less than a 10% share.

  - Sensitivity analysis scenario's comparators – The mix of vinorelbine and gemcitabine extracted from TPC arm was considered as an alternative comparator for eribulin in subgroup 2. The two treatments were selected to reflect the comparators listed in the scope (Table 1). Capecitabine was excluded for the aforementioned reasons.

Secondary Treatments

Patients of both subgroups transitioning from "Stable" to "Progressive" health state are assumed to receive secondary treatment comprised of the TPC arm mentioned above excluding capecitabine and treatments with less than a 10% share in the TPC arm. The breakdown of the TPC drugs as secondary treatment was obtained from the study 305 (7) and is estimated as the proportion of treatment utilisation in subgroup 2 as illustrated in Table 43 overleaf.

Table 43 Treatment proportion for TPC (primary or secondary therapy)

	Study 305	
Drug Name	Market Shares (excluding capecitabine)	Study 305 patients
Chemotherapies		
Gemcitabine	27.71%	46
Vinorelbine	36.75%	61
Taxanes		
Docetaxel	6.02%	10
Paclitaxel	15.66%	26
Doxorubicin	13.86%	23
Total	***100%***	***166***

Source: Study 305 CSR (7)

Treatment Duration

The treatment duration of eribulin and the comparator arms in both subgroups is until disease progression as indicated in the clinical protocols of studies 301 and 305 respectively (7,11). Nevertheless, patients may receive subsequent therapies (i.e. secondary therapies) following progression on primary treatments.

In order to cover both potential scenarios, the model allows for the user to select between the two options: treatment duration until progression and treatment duration capped at a maximum number of cycles. The latter has been considered as the basecase scenario. The maximum number of cycles was based on data obtained in the treatment architecture of MBC in Europe published by Kantar Health (77).

In respect of subgroup 1, the treatment duration for “Stable” and “Progressive” health states in combination is set to a maximum of eight months based on the Kantar Health data. According to this data, the aggregated average number of cycles of after one chemotherapy and onwards (second line plus) is estimated at 7.3494 and rounded up to eight months, as presented in Table 44 overleaf. Therefore, the treatment duration of secondary treatment following eribulin or capecitabine in the “Progressive” state is linked with the treatment duration of the “Stable” health state.

Table 44 Number of Lines of therapy in second line plus

		HR positive, and HER2-	% patients	Sum of cycle
	Average number of cycle per line	5.77		
Second line	Patients who received second line of systemic therapy	100%	100%	5.77
	Patients who died before receiving next line of therapy	24%		
Second- to Third-Line	Patients who are alive but did not receive next line of systemic therapy	18%		
	Patients who received Third line of systemic therapy	58%	58%	3.33
	Patients who died before receiving next line of therapy	44%		
Third- to Fourth-Line	Patients who are alive but did not receive next line of systemic therapy	19%		
	Patients who received fourth line of systemic therapy	37%	21%	1.23
	Patients who died before receiving next line of therapy	66%		
Fourth- to Fifth-Line	Patients who are alive but did not receive next line of systemic therapy	13%		
	Patients who received fidth line of systemic therapy	22%	5%	0.26
	Patients who died before receiving next line of therapy	66%		
Line 6 (assumption equal to 5)	Patients who are alive but did not receive next line of systemic therapy	13%		
	Patients who received fidth line of systemic therapy	22%	1%	0.06
Sum of the number of cycle		***In cycles***	***10.65***	***In months***	***7.3494***

Source: CancerMPact® Western Europe, March 2014, Note: Line 6 assumed equal to 5

For subgroup 2, the treatment duration for "Stable" and "Progressive" health states in combination is set to a maximum of six months. The aggregated average number of cycles after two prior chemotherapies (i.e. third line plus) is estimated at 5.6312 and rounded up to six months, as presented in Table 45 below. Therefore, the treatment duration of secondary treatment following eribulin or TPC in the "Progressive" state is linked with the treatment duration of the "Stable" health state.

Table 45 Number of Lines of therapy in third line plus

		HR positive, and HER2-	% patients	Sum of cycle	
	Average number of cycle per line	5.77			
	Patients who received third line of systemic therapy	100%	100%	5.77	
	Patients who died before receiving next line of therapy	44%			
Third- to Fourth-Line	Patients who are alive but did not receive next line of systemic therapy	19%			
	Patients who received fourth line of systemic therapy	37%	37%	2.12	
	Patients who died before receiving next line of therapy	66%			
Fourth- to Fifth-Line	Patients who are alive but did not receive next line of systemic therapy	13%			
	Patients who received fidth line of systemic therapy	22%	8%	0.46	
	Patients who died before receiving next line of therapy	66%			
Line 6 (assumption equal to 5)	Patients who are alive but did not receive next line of systemic therapy	13%			
	Patients who received fidth line of systemic therapy	22%	2%	0.10	
Sum of the number of cycle				***8.45***	***5.8324***
Source: CancerMPact® Western Europe, March 2014, Note: Line 6 assumed equal to 5				***cycles***	***months***

5.3 Clinical parameters and variables

The clinical outcomes considered for the estimation of the patient transition among health states were PFS (independent review) and OS. Expected PFS and OS were calculated as the area under their respective survival curves.

According to partitioned survival analysis, this patient transition among health states is time-dependent and based on time-to-event non-parametric Kaplan-Meier estimator. They reflect the curves derived by the Kaplan-Meier survival functions estimated based on patient-level data from the two eribulin Phase III pivotal trials, Study 301 and 305. The Kaplan-Meier Survivor functions for each treatment were extracted with Stata 13 for both OS and PFS.

Subgroup 1

For subgroup 1, the patient data considered were extracted from Study 301 of the patients with HER2 negative locally advanced or metastatic breast cancer who have progressed after one chemotherapeutic regimen only. The clinical results of this specific subgroup have been described in section 4.8.

Overall, the study was initiated in 01 Apr 2006; at the date of data cutoff (12 Mar 2012), 10 subjects (5 subjects [0.9%] each in the eribulin and capecitabine arms) were still on treatment while 152 patients were still alive on both arms (13.8% of the total population).13.8% was also the proportion of patients still alive in subgroup 1 (Appendix 4). This indicates that the survival data in study 301 were very close to being complete. Given that and as instructed by NICE DSU technical guidelines (78), the basecase analysis time horizon was set at 5 years imposing no need for extrapolation and, hence, only the Kaplan-Meier survival functions were used to estimate the corresponding transition probabilities as it can be seen in Figure 27 and Figure 28 below. Figure 29 overleaf shows the mean PFS and OS of the patients in the two treatment groups.

Figure 27 Subgroup 1 – PFS KM curves of patients in different treatment groups

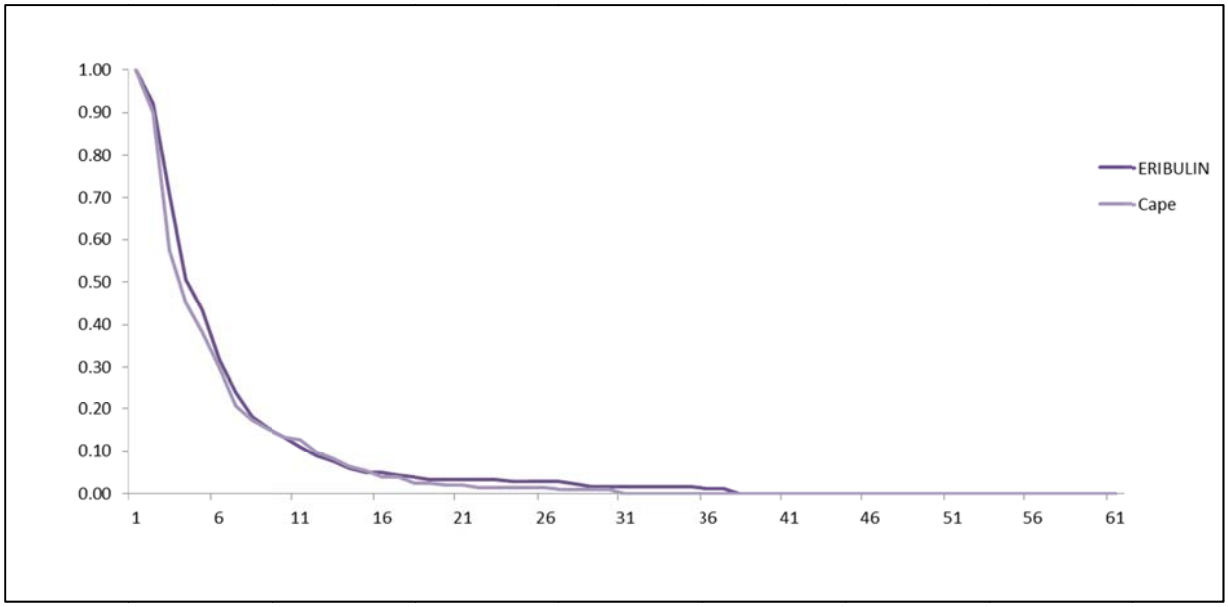


Figure 28 Subgroup 1 – OS KM curves of patients in different treatment groups

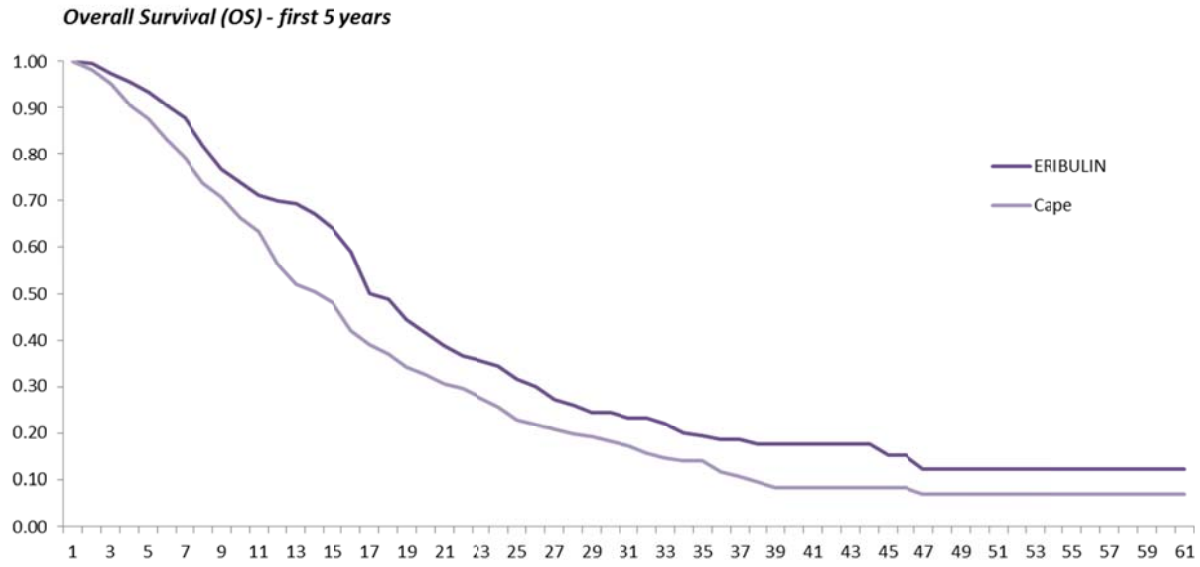
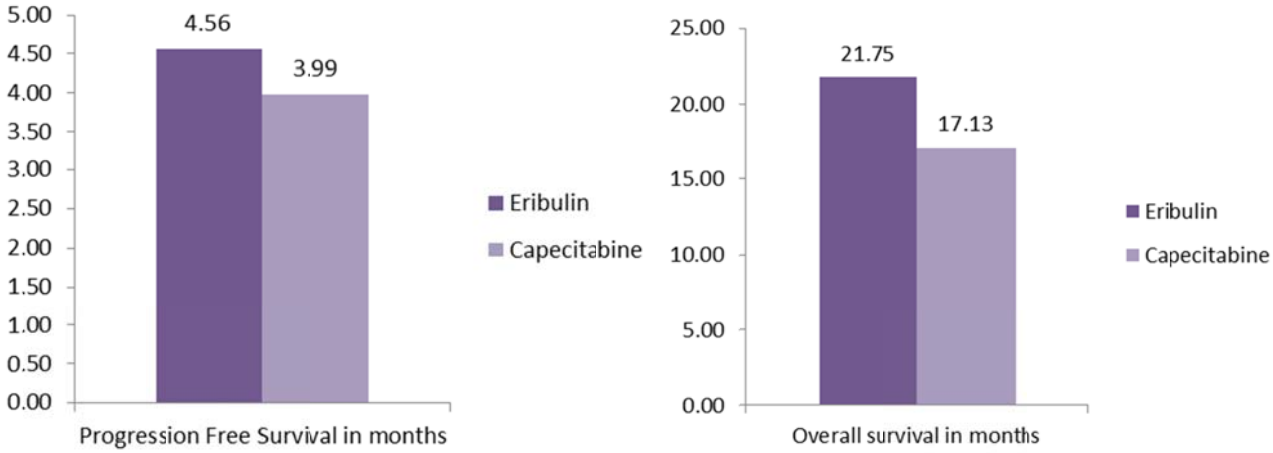


Figure 29 Subgroup 1 – PFS and OS of patients in different treatment groups



Sensitivity analysis scenarios depending on comparator:

Considering the NICE clinical guidelines, an additional sensitivity scenario was considered assuming a mix of comparators for subgroup 1 as mentioned in section 5.2. In detail, the mix of capecitabine and vinorelbine was selected as an alternative set of comparators for subgroup 1 in order to reflect the current NICE clinical guidelines. In the absence of clinical evidence of vinorelbine in the specific disease setting, the assumption of equal efficacy and safety between capecitabine and vinorelbine needed to be made. Therefore all of the aforementioned results apply for this mix of comparators as well.

Vinorelbine component of the mix is assumed to be comprised of 50% oral formulation and 50% IV formulation.

Sensitivity analysis scenarios depending on time horizon:

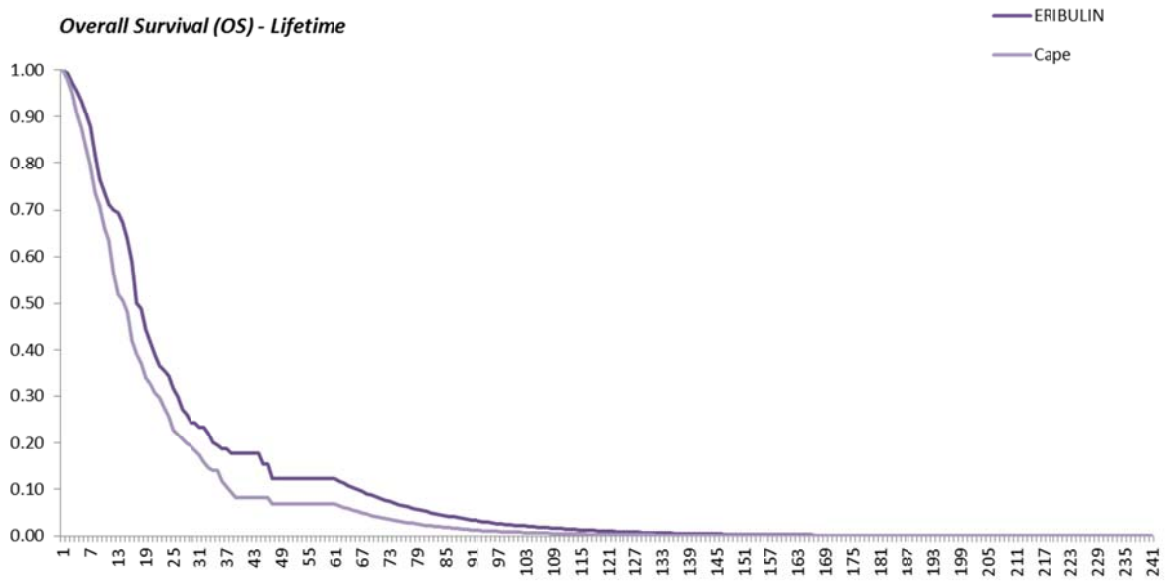
Despite the completeness of the study 301 OS data, 10 and 20 year time horizons were included in the model to approximate lifetime and meet the NICE Decision Problem requirements. To address that, data were extrapolated at the end of the Kaplan-Meier OS curve.

In detail, exponential and Weibull parametric functions including treatment covariate were used to extrapolate the OS curves of eribulin and capecitabine. The extrapolation was performed over 20 years. The parametric functions were then used to extrapolate the tail of the Kaplan-Meier curves used in the model.

The resulting piecewise model uses the Kaplan-Meier for the first 5 years (within trial) and attaches an extrapolated tail at 60 months (cut-off). In other words, the parametric function are not directly used as OS partition, but used to map the tail attached to the Kaplan-Meier curve only:

- **10-year time horizon:** Kaplan Meier survival function until the end of the follow-up. OS patient-level data were then extrapolated using an exponential and Weibull function attached at the end of the Kaplan-Meier curve until the month 120.
- **20-year time horizon:** Kaplan Meier survival function until the end of the follow-up. OS patient-level data were then extrapolated using an exponential and Weibull functions attached at the end of the Kaplan-Meier curve until month 240.

Figure 30 Subgroup 1 – Extrapolated OS curves of patients in different treatment groups



To assess the extrapolation performed, a PH global test was performed while the log-log plots were assessed visually. As illustrated in Figure 31 overleaf, the log-log plots present relatively parallel curves, while the results of the PH global test in Table 46 indicate that there is no proof that the PH assumption has been violated.

Figure 31 Proportional hazard testing for subgroup 1

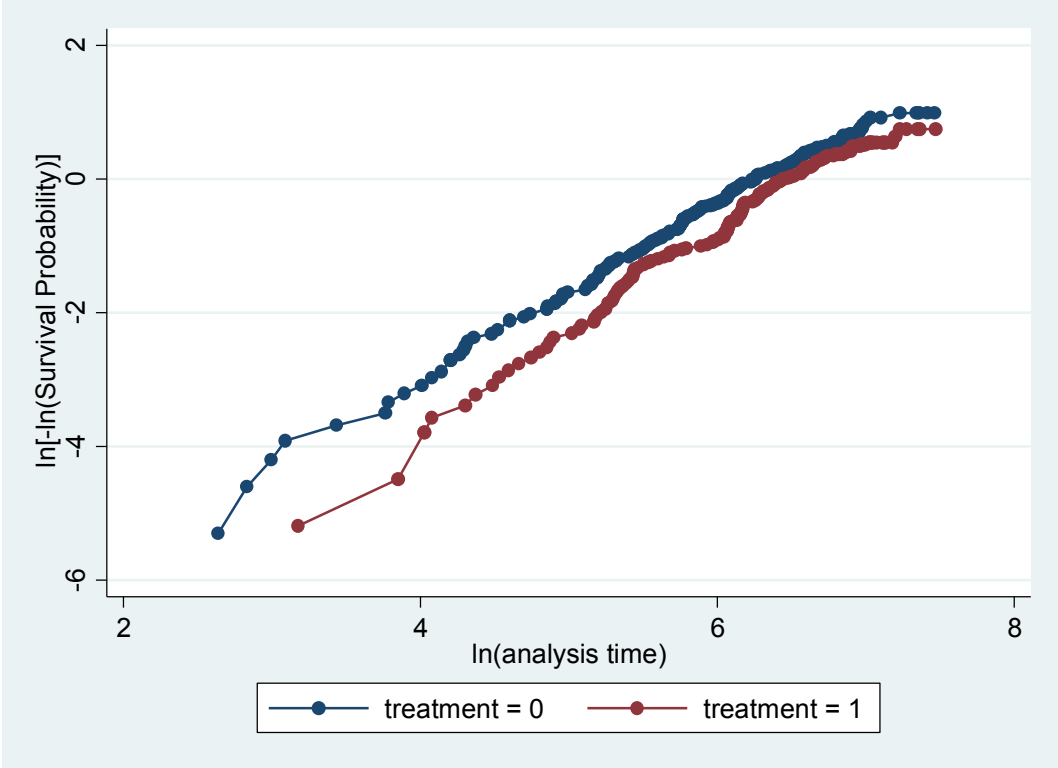


Table 46 PH Global Test results for subgroup 1

Test of proportional-hazards assumption

Time: Time

	chi2	df	Prob>chi2
global test	0.65	1	0.4188

Although the Kaplan-Meier is used for the first 60 months and the extrapolation is used only for the tail, a hazard fitting test was performed to allow for visual inspection (Figure 32, overleaf). Moreover, the AIC/BIC test indicated a slightly better fitting for Weibull function as presented in Table 47.

Figure 32 Hazard fitting in subgroup 1

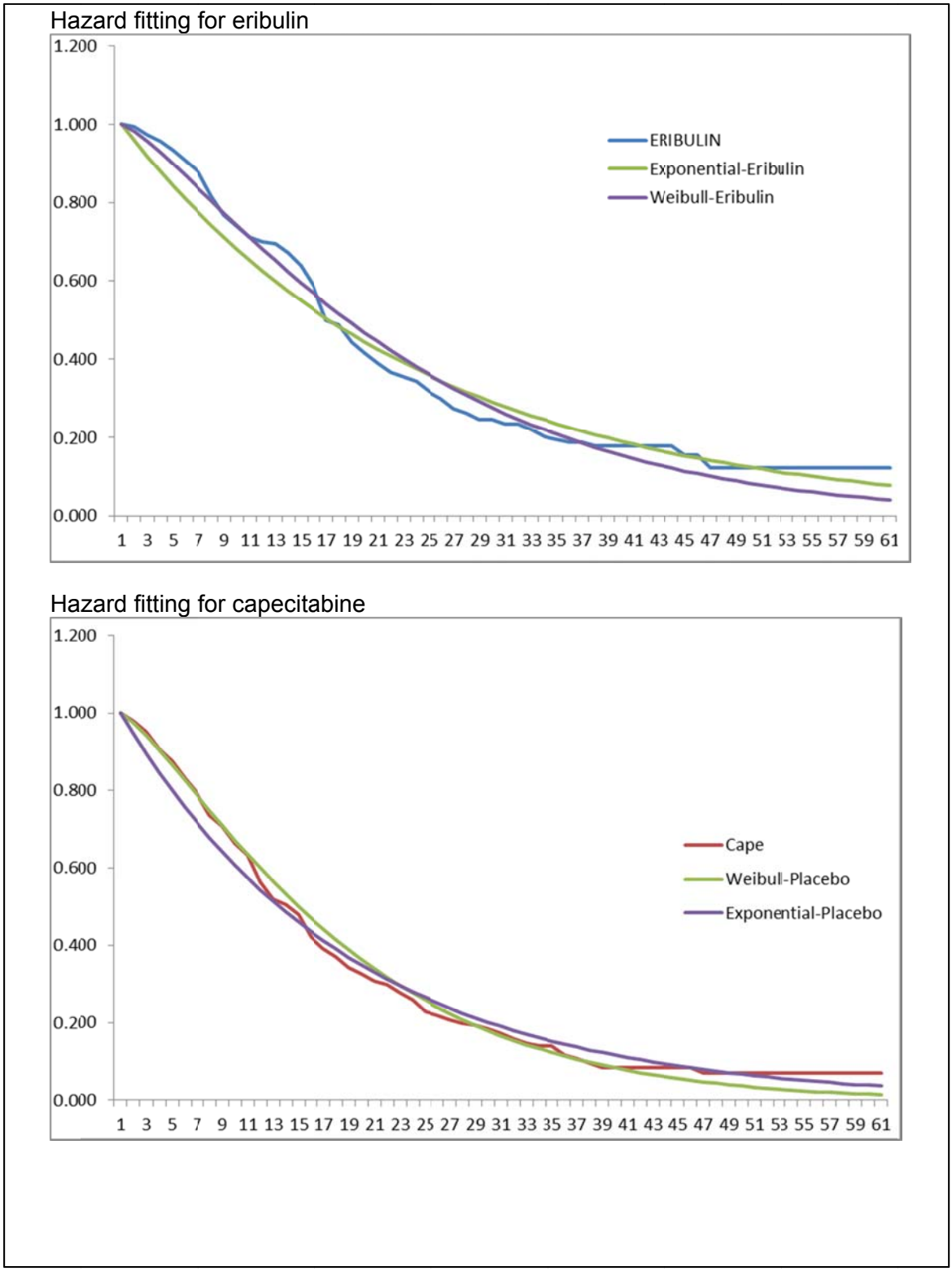


Table 47 Statistical criteria for subgroup 1

Akaike's information criterion and Bayesian information criterion

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
Weibull	552	-744.6285	-740.9258	3	1487.852	1500.792
EXP	552	-761.0157	-758.3723	2	1520.745	1529.372

Interpretation: The PH assumption seems to be appropriate for this dataset. While the AIC/BIC test indicates a slightly better fit Weibull, exponential curve were selected as the primary sensitivity scenario based on the visual inspection. As a reminder, the within trial hazard is likely to be a weak decision criterion here as the parametric function is only used for tail extrapolation.

Subgroup 2

For subgroup 2, the patient data considered were extracted from Study 305 of the patients with locally advanced or metastatic breast cancer who have progressed after two chemotherapeutic regimens and had received capecitabine previously. The clinical results of this specific subgroup have been described in section 4.8

In comparison to TA250, the model for the purposes of this assessment was based using data from the 95% data cut off indicating the completeness of the survival data considered. In further detail, the study was initiated in 16 Nov 2006 (first subject entered) while 95% of events occurred by 17 Jun 2013. By that latter date, only 3% of the patients were still alive in both arms of the study within the specific subgroup (Appendix 4). Given that and as instructed by NICE DSU technical guidelines (78), the basecase analysis time horizon was set at 5 years imposing no need for extrapolation and, hence, only the Kaplan-Meier survival functions were used to estimate the corresponding transition probabilities as it can be seen in Figure 33 and Figure 34. Figure 35 overleaf shows the mean PFS and OS of the patients in the two treatment groups.

Figure 33 Subgroup 2 – PFS KM curves of patients in different treatment groups

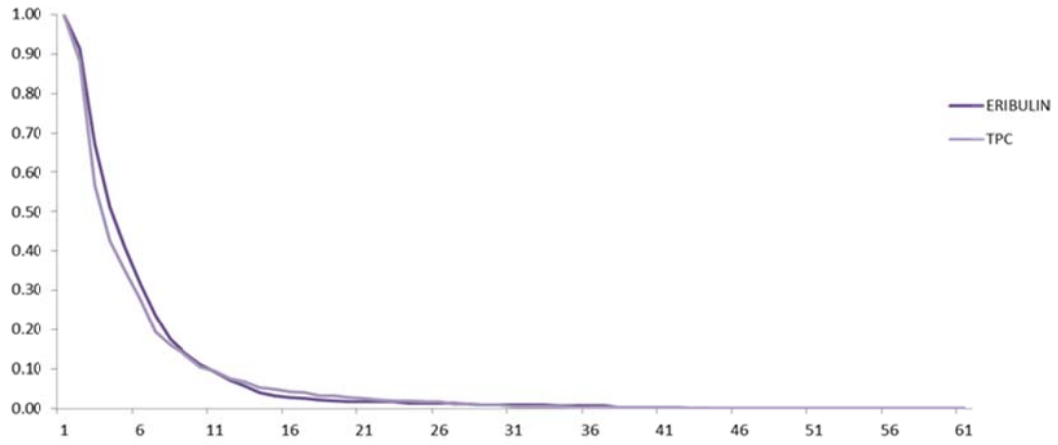


Figure 34 Subgroup 2 – OS KM curves of patients in different treatment groups

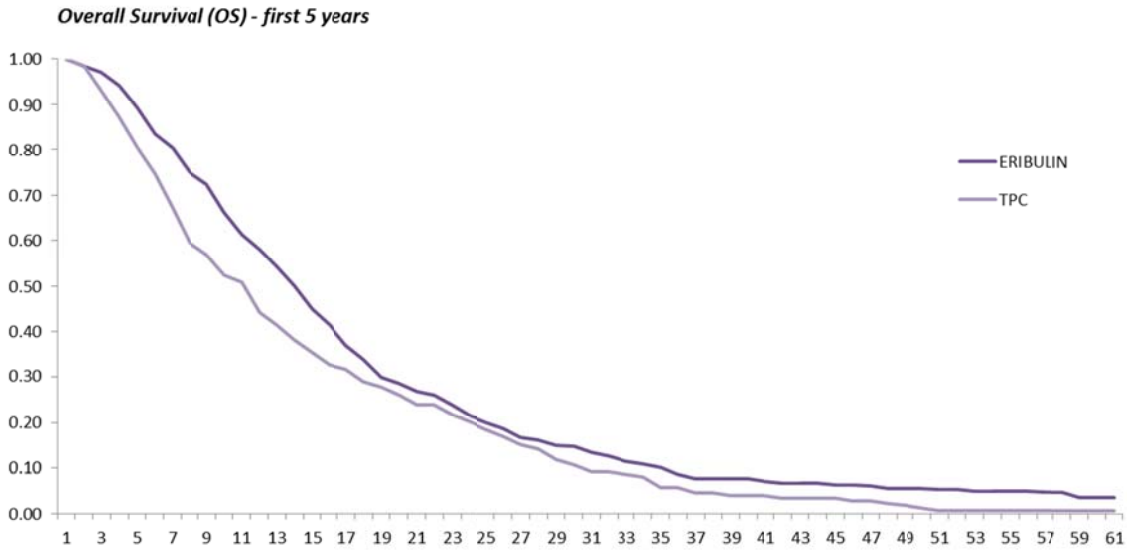
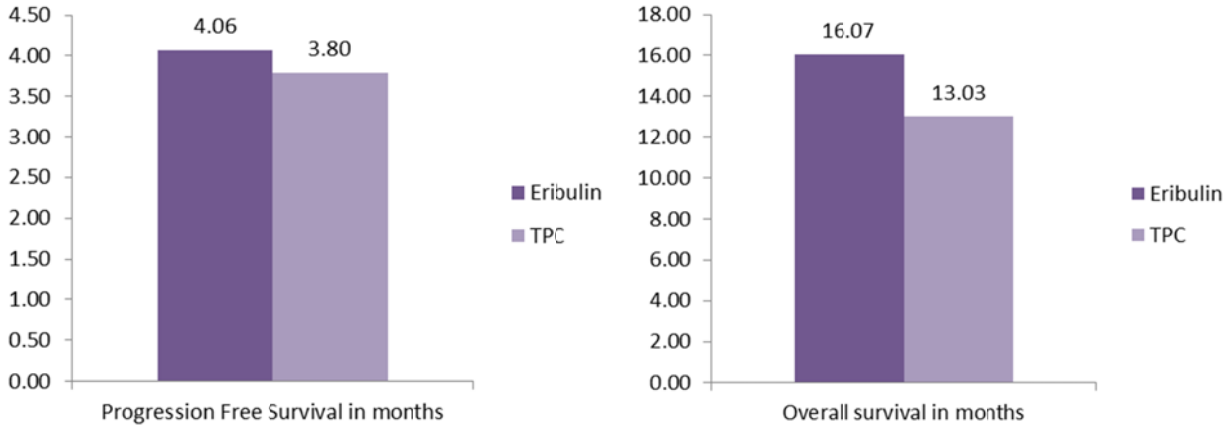


Figure 35 Subgroup 2 – PFS and OS of patients in different treatment groups



Sensitivity analysis scenarios depending on comparator:

Considering the selection of comparators within the NICE Scope and the Decision problem, the mix of vinorelbine and gemcitabine extracted from TPC arm was considered as an alternative comparator for eribulin in subgroup 2. Capecitabine was excluded given the reasons mentioned in section 5.1.

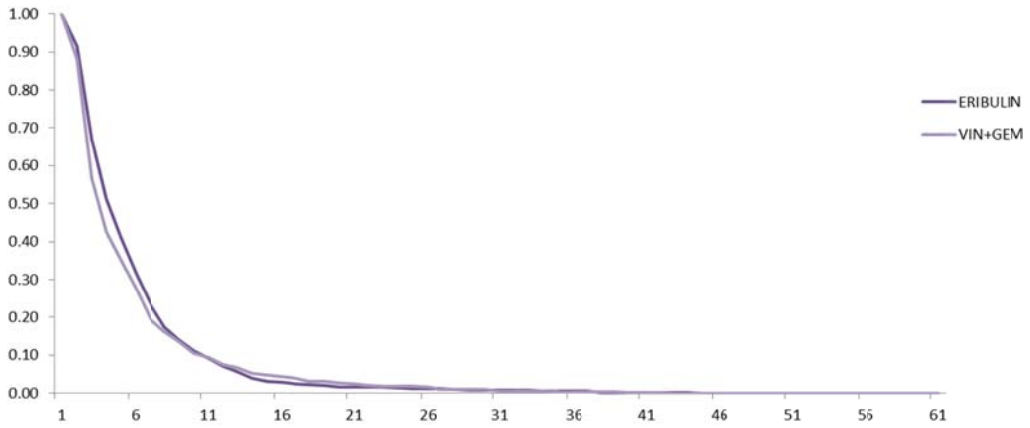
Vinorelbine component of the mix is assumed to be comprised of 50% oral formulation and 50% IV formulation.

Although the PFS results resemble the results those of the TPC comparator arm, the OS benefit is greater in absolute terms when eribulin is compared to the mix of vinorelbine and gemcitabine (mean OS eribulin vs TCP: 16.07 vs 13.03, mean OS eribulin vs Vin/Gem 16.07 vs 11.48).

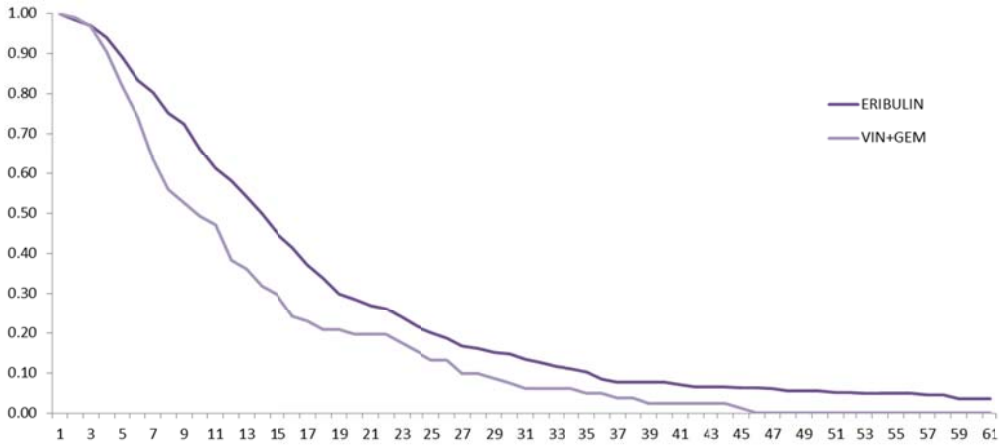
The figures overleaf summarise the efficacy results of this sensitivity scenario.

Figure 36 Subgroup 2 – PFS & OS KM curves with alternative mix of comparators

PFS KM curve for eribulin vs vinorelbine/gemcitabine



OS KM curve for eribulin vs vinorelbine/gemcitabine



Sensitivity analysis scenarios depending on time horizon:

Despite the completeness of the study 305 OS data, 10 and 20 year time horizons were included in the model to approximate lifetime and meet the NICE Decision Problem requirements. To address that, data were extrapolated at the end of the Kaplan-Meier OS curve.

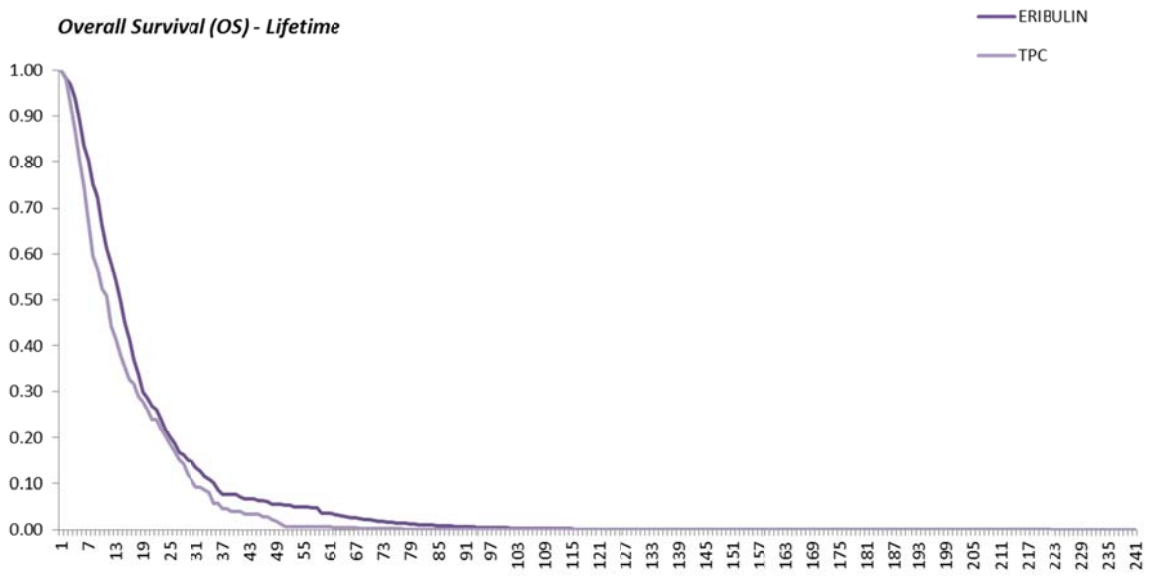
In detail, exponential and Weibull parametric functions including treatment covariate were used to extrapolate the OS curves of eribulin and TPC. The extrapolation was performed over 20 years. The parametric functions were then used to extrapolate the tail of the Kaplan-Meier curves used in the model.

The resulting piecewise model uses the Kaplan-Meier curve until the 95% data cut off point (within trial) and attach an extrapolated tail afterwards. In other words, the parametric

function are not directly used as OS partition, but used to map the tail attached to the Kaplan-Meier curve only.

- **10-year time horizon:** Kaplan Meier survival function until the end of the follow-up. OS patient-level data were then extrapolated using an exponential and Weibull function attached at the end of the Kaplan-Meier curve until the month 120.
- **20-year time horizon:** Kaplan Meier survival function until the end of the follow-up. OS patient-level data were then extrapolated using an exponential and Weibull functions attached at the end of the Kaplan-Meier curve until month 240.

Figure 37 Subgroup 2 – Extrapolated OS curves of patients in different treatment groups



To assess the extrapolation performed, a PH global test was performed while the log-log plots were assessed visually. As illustrated in Figure 38 overleaf, the log-log plots present relatively parallel curves, while the results of the PH global test in Table 48 overleaf indicate that there is no proof that the PH assumption has been violated.

Figure 38 Proportional hazard testing for subgroup 2

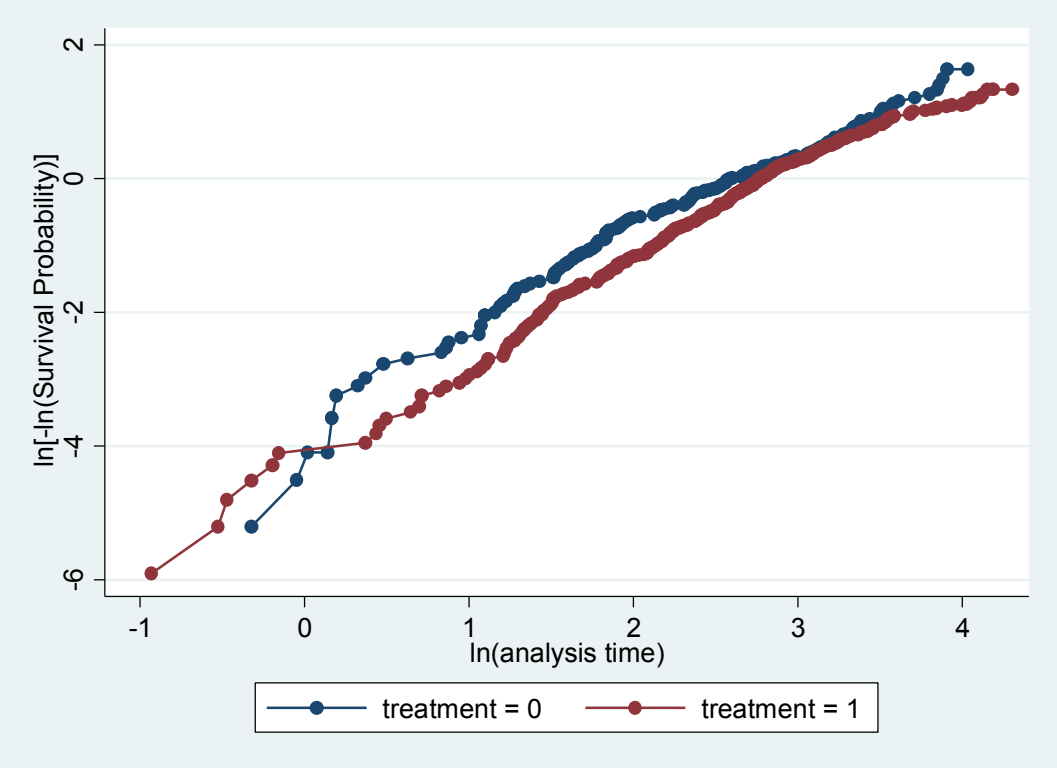


Table 48 PH Global Test results for subgroup 2

Test of proportional-hazards assumption

Time: Time

	chi2	df	Prob>chi2
global test	0.00	1	0.9891

Although the Kaplan-Meier is used for the first 60 months and the extrapolation is used only for the tail, a hazard fitting test was performed to allow for visual inspection. Moreover, the AIC/BIC test indicated a slightly better fitting for Weibull function as presented in Table 49.

Figure 39 Hazard fitting in subgroup 1

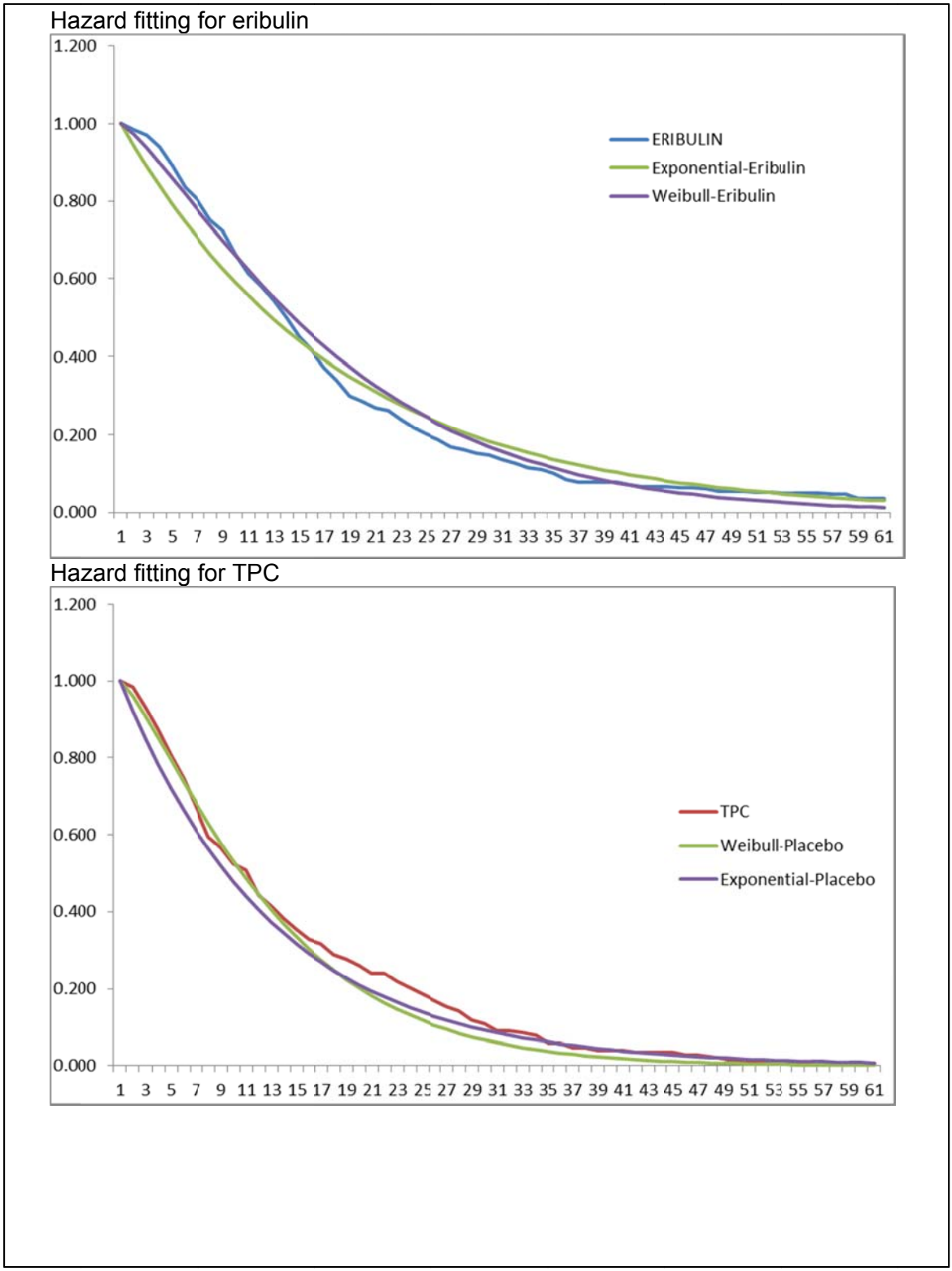


Table 49 Statistical criteria for subgroup 2

Akaike's information criterion and Bayesian information criterion

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
Weibull	552	-744.6285	-740.9258	3	1487.852	1500.792
EXP	552	-761.0157	-758.3723	2	1520.745	1529.372

Note: N=Obs used in calculating BIC; see **[R] BIC note**

Interpretation: The PH assumption seems to be appropriate for this dataset. While the AIC/BIC test indicates a slightly better fit Weibull, exponential curve were selected as the primary sensitivity scenario based on the visual inspection. As a reminder, the within trial hazard is likely to be a weak decision criterion here as the parametric function is only used for tail extrapolation.

5.4 Measurement and valuation of health effects

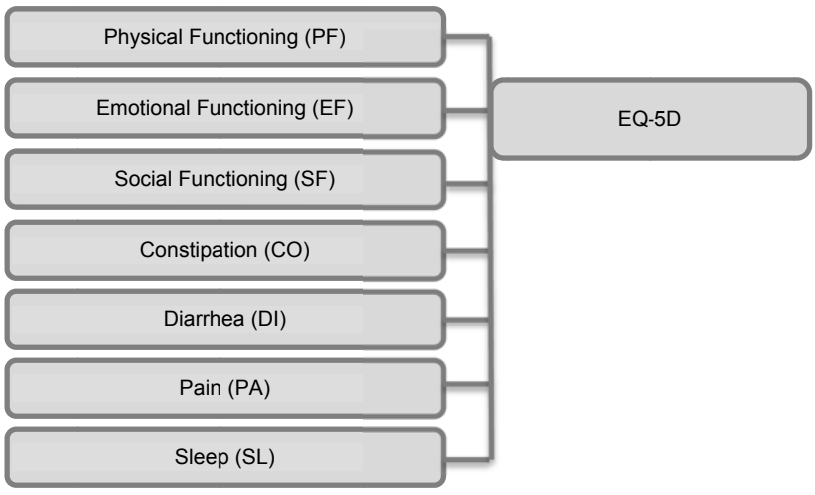
Health-related quality-of-life data from clinical trials

HRQOL data were collected in study 301 but not in study 305. The results of the patient reported HRQOL collected in study 301 have been reported and discussed in section 4.7. Therefore this section is focused on the elicitation of the utility values used in the model through the usage of a mapping algorithm.

Mapping

HRQOL data from study 301 using QLQ-C30 were mapped to EQ-5D derived utility scores using a published regression algorithm (equation 1) (81). This algorithm was developed in female patients with locally advanced breast cancer with good baseline health status, as a part of a randomised clinical trial, to convert the QLQ-C30 questionnaire results into EQ-5D. Ordinary least-squares (OLS) regression was used to predict overall EQ-5D dependent variable from QLQ-C30 scores (explanatory variables). The EQ-5D utilities were constructed using the original UK Tariff (82).

Figure 40 Mapping estimates



Equation 1: Utility Mapping Algorithm

$$\textbf{EQ-5D} = 0.85927770 - 0.0069693*\textbf{PF} - 0.0087346*\textbf{EF} - 0.0039935\ \textbf{SF} + 0.0000355*\textbf{PF}^2 + 0.0000552*\textbf{EF}^2 + 0.0000290*\textbf{SF}^2 + 0.0011453*CO + 0.0039889*DI + 0.0035614*PA - 0.0003678*SL - 0.0000540*\ DI^2 + 0.0000117*\ SL^2$$

Statistical Analyses

Mapped EQ-5D values were used to estimate the mean (standard deviation [SD]) for the following health states:

- baseline stable disease status,
- Tumour responder,
- disease progression and
- dis-utility for each of the major AEs.

A linear mixed-effects model was used to regress explanatory variables including baseline transformed health utility score and specific adverse event of interest against the change in health utility scores. In all models, the timing of QLQ-C30 administration and patient was included as random effects to control for unobserved, patient-specific characteristics and multiple observations per patient. All other predictors were included in the model as fixed effects.

Derived Health State Utilities and Dis-utilities

The results of the utility and dis-utility analysis are presented in the tables below and overleaf.

Table 50 Utility scores of patients on eribulin and capecitabine

	Eribulin Utility scores (SD)	Capecitabine Utility scores (SD)	Total Study Population scores (SD)
Baseline	0.704 [0.228]	0.691 [0.238]	0.697 [0.233]
Tumour Response	0.780 [0.194]	0.783 [0.185]	0.782 [0.189]
Progression (per treatment arm)	0.705 [0.211]	0.651 [0.250]	0.679 [0.232]

Abbreviations: SD, Standard deviation
Source: 84

Table 51 Disutility scores of patients on eribulin and capecitabine

Adverse Event	Total Study Population Disutilities (CI)
Anaemia	-0.010 (-0.035,0.015)
Nausea	-0.021 (-0.061,0.019)
Neutropenia	-0.007 (-0.014,0.000)
Febrile Neutropenia	-0.012 (-0.041,0.017)
Alopecia (all grade)	0.000
Leukopenia	-0.003 (-0.015,0.009)
Diarrhoea	-0.006 (-0.026,0.014)
Asthenia/fatigue	-0.029 (-0.044,-0.014)
Peripheral Neuropathy	-0.014 (-0.030,0.002)
Dyspnoea	-0.027 (-0.047,-0.007)
Palmar-Plantar Erythro-Dysaesthesia Syndrome	0.000 (-0.013,0.012)

Abbreviations: CI, 95% Confidence Intervals
Source: 84

Health-related quality-of-life studies

As stated previously in the decision problem Table 1, the populations considered suitable for eribulin treatment within this submission consist of two separate subgroups, namely:

Subgroup 1

1. HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.

Subgroup 2

2. Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated).

Therefore, two systematic reviews were conducted to identify HRQOL studies from the published literature for each of the above patient populations. In both systematic reviews, 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 and restricted to English language only. This was supplemented by additional searching of clinicaltrials.gov and conference proceedings from ASCO, ESMO, AACR and ISPOR.

Full details of the search strategies used in both systematic reviews are provided in Appendix 2.

Identification of studies

Eligibility criteria

Studies identified were initially assessed based on title and abstract (Step 1). Publications not meeting inclusion criteria in in Step 1 were excluded and listed alongside the reason of study exclusion (Step 2). Full text publications were retrieved from those abstracts meeting inclusion criteria in Step1 and assessed based on the full text. (Step 3) After the full text

review, all papers meeting inclusion were retained for data extraction, and those papers not meeting inclusion criteria were excluded and listed alongside the reason for the exclusion. Inclusion and exclusion criteria for each of the two systematic reviews are shown in Table 52 and Table 53 below and overleaf.

Table 52 Eligibility criteria used in search strategy: HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.

	Inclusion	Exclusion
Population	Adult patients AND [MBC OR Advanced breast cancer (ABC)] AND HER2-negative AND Following one prior chemotherapy	Non-human OR Children OR Adolescents OR Males OR First line Not distinguished HER2 status
Intervention	Eribulin (monotherapy)	All other treatments
Comparator	Any	
Outcomes	Utilities/disutilities/QALYs for health states of adverse events OR Quality of life assessment including EQ-5D, QLQ-C30, BR-23, FACT, SF-36, SF-6D	All others
Study design	Reports of mapping exercises for any outcome measure to utility OR Reports of utility elicitation exercises OR Reports for utility validation exercises OR Reports of economic evaluations using utility measures elicited during the studies OR Reports of clinical trials assessing HRQOL	Editorials OR Notes OR Comments OR Letters OR Reviews OR Abstracts without full paper available
Language	English	Non-English studies

Abbreviations: ABC, Advanced breast cancer; HER2, Human epidermal growth factor receptor 2; MBC, Metastatic breast cancer; ORR, Objective response rate; OS, Overall survival; PFS, Progression free survival, RCT, randomised, controlled trial; TTP, Time to progression; TTR, Time to response

Table 53 Eligibility criteria used in search strategy: Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated)

	Inclusion	Exclusion
Population	Adult patients AND [MBC OR Advanced breast cancer (ABC)] AND 3L+	Non-human OR Children OR Adolescents OR Males OR First-Second line
Intervention	Eribulin (monotherapy)	All other treatments
Comparator	Any	
Outcomes	Utilities/disutilities/QALYs for health states of adverse events OR Quality of life assessment including EQ-5D, QLQ-C30, BR-23, FACT, SF-36, SF-6D	All others
Study design	Reports of mapping exercises for any outcome measure to utility OR Reports of utility elicitation exercises OR Reports for utility validation exercises OR Reports of economic evaluations using utility measures elicited during the studies OR Reports of clinical trials assessing HRQOL	Editorials OR Notes OR Comments OR Letters OR Reviews OR Abstracts without full paper available
Language	English	Non-English studies

Abbreviations: ABC, Advanced breast cancer; HER2, Human epidermal growth factor receptor 2; MBC, Metastatic breast cancer; ORR, Objective response rate; OS, Overall survival; PFS, Progression free survival, RCT, randomised, controlled trial; RWE, Real world evidence; TTP, Time to progression; TTR, Time to response

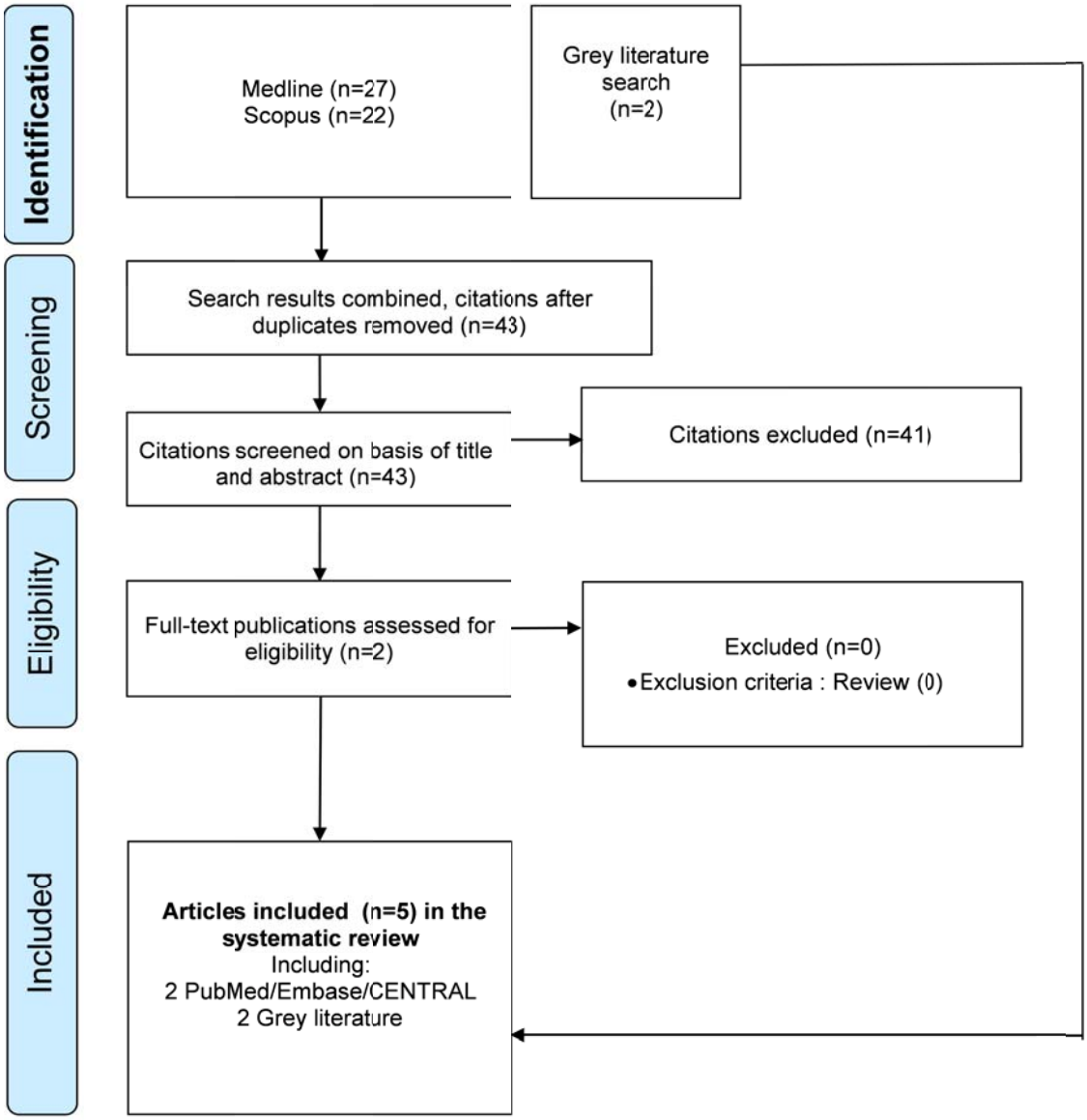
Flow Diagrams of included and excluded studies

1. *HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.*

Following assessment and exclusion of studies based on title, abstract and full text, 4 records from the systematic review were identified in total covering including two studies from the grey literature.

A list of excluded studies is provided in Appendix 2. The flow diagram for the systematic review is shown in Figure 41 overleaf.

Figure 41 PRISMA Study Attrition Diagram used in search strategy: HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting.

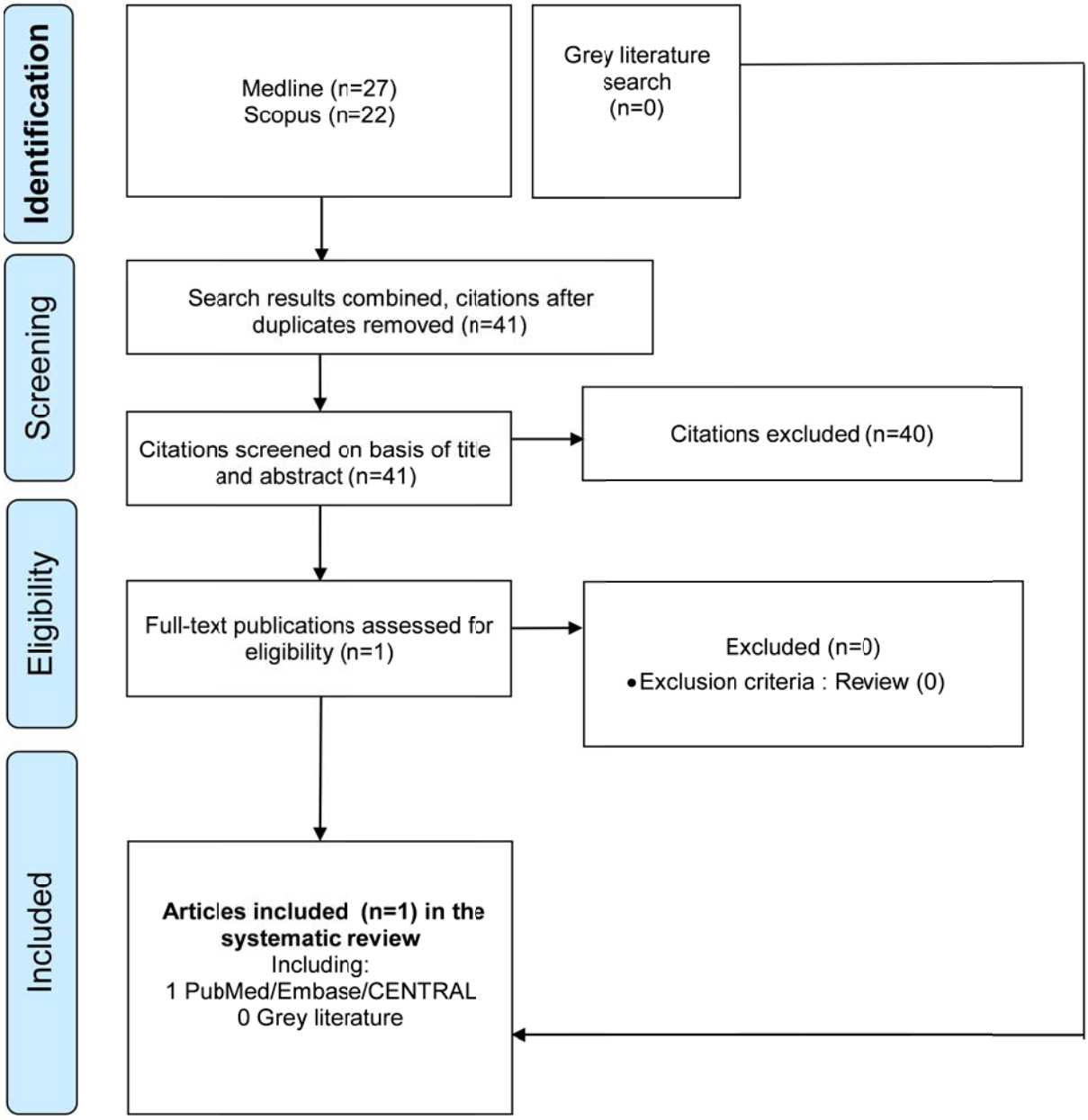


2. *Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated)*

Following assessment and exclusion of studies based on title, abstract and full text, 1 record from the systematic review was identified in total.

A list of excluded studies is provided in Appendix 2. The flow diagram for the systematic review is shown in Figure 42 overleaf.

Figure 42 PRISMA Study Attrition Diagram used in search strategy: Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated)



Description of identified studies

The systematic reviews on HRQoL in the aforementioned subgroups identified the following studies:

Subgroup 1

1. Cortes J, Hudgens S, Twelves C, et al. Health-related quality of life in patients with locally advanced or metastatic breast cancer treated with eribulin mesylate or capecitabine in an open-label randomized phase 3 trial. Breast Cancer Res Treat. 2015 Dec;154(3):509-20. (83)

2. Hudgens S, Briggs A, Velikova G, et al. Impact of treatment with eribulin (ERI) or capecitabine (CAP) for metastatic breast cancer (MBC) on EQ–5D utility derived from EORTC QLQ–C30. Annals of Oncology 2014;25(suppl 4): iv360–iv360. Poster 1046P (84)

3. Kaufman PA, Awada A, Twelves C, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2015;33(6):594-601 (10)

4. Velikova G, Hudgens, Forsythe A, et al. Health-related quality of life (HRQOL) and disease symptoms in patients (pts) with locally advanced or metastatic breast cancer (MBC) treated with eribulin (ERI) or capecitabine (CAP) in a post anthracycline and taxane setting. Presented at the European Society for Medical Oncology Congress ESMO, 26-30 September, 2014. Poster 392P (63)

Subgroup 2

1. Greenhalgh J, Bagust A, Boland A, et al. Eribulin for the treatment of advanced or metastatic breast cancer: a NICE single technology appraisal. Pharmacoeconomics 2015;33:137-148 (73)

A summary of the above mentioned published studies is included in the table overleaf (Table 54, except for the publication by Greenhalgh et al (73), which summarises the NICE STA conducted in 2011. For this submission, the company extracted HRQoL data from the published literature, specifically Lloyd et al (95). As relevant patient reported outcomes are now available for inclusion in this submission, these values are no longer needed, although they have been assessed in the deterministic sensitivity analysis (see section 5.8).

Of the four publications summarised overleaf, all report data from Study 301. Cortes et al (83), Kaufman et al (10) and Velikova et al (63) report the results of the patient reported outcomes in study 301 and these results are described previously in section 4.7.

The publication by Hudgens et al (84) provides information on utility scores from study 301 and these results are used in the model. (Table 50)

Table 54 Summary of HRQOL studies

Study	Country	Population	Interventions and comparators	Sample size	Method of elicitation	Health states	Utility score
Cortes et al (83)	As per Study 301 (see section 4.3)	Patients included in Study 301 (see section 4.3, Table 8)	Eribulin (n=554, randomised) Capecitabine (n=548, randomised)	Eribulin: n = 536 Capecitabine: n = 526	Not reported. HRQoL was assessed using EORTC QLQ-C30 and the breast module QLQ-BR23	Not reported	Not reported
Hudgens et al (84)	As per Study 301 (see section 4.3)	Patients included in Study 301 (see section 4.3, Table 8)	Eribulin (n=554, randomised) Capecitabine (n=548, randomised) Post-hoc analysis using a published regression algorithm to convert EORTC QLQ-C30 to EQ-5D	Eribulin: n = 536 Capecitabine: n = 526	EQ-5D	Baselines/Stable disease	Eribulin: 0.70 Capecitabine: 0.69
						Tumour response	Eribulin: 0.78 Capecitabine: 0.78
						Disease progression	Eribulin: 0.71 Capecitabine: 0.65
Kaufman et al (10)	24 countries (see section 4.3)	Patients included in Study 301 (see section 4.3, Table 8)	Eribulin (n=554, randomised) Capecitabine (n=548, randomised)	Eribulin: n = 536 Capecitabine: n = 526	Not reported. HRQoL was assessed using EORTC QLQ-C30 and the breast module QLQ-BR23	Not reported	Not reported
Velikova et al (63)	As per Study 301 (see section 4.3)	Patients included in Study 301 (see section 4.3, Table 8)	Eribulin vs Capecitabine	Eribulin: n = 536 Capecitabine: n = 526	Not reported. HRQoL was assessed using EORTC QLQ-C30	Not reported	Not reported

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; HRQoL, Health related quality of life

Adverse reactions

In Study 301, eribulin and capecitabine treatments displayed different safety profiles. Adverse events (AEs) including neutropenia, leukopenia, anaemia, alopecia, peripheral sensory neuropathy, and fatigue were more commonly observed in the eribulin treatment arm, while AEs including hand-foot syndrome, thrombocytopenia, diarrhoea, nausea, vomiting, and decreased appetite were more commonly observed in patients treated with capecitabine (Figure 43). (11)

For the purposes of the estimation of the dis-utilities, all grades AEs with prevalence greater than 10% and Grade ¾ AEs with prevalence greater than 2% were considered.

Figure 43 Incidence of common AEs in Study 301 >10% (all grades) or 2% (Grade 3 or higher) in either arm

AEs more common to ERI
AEs more common to CAP

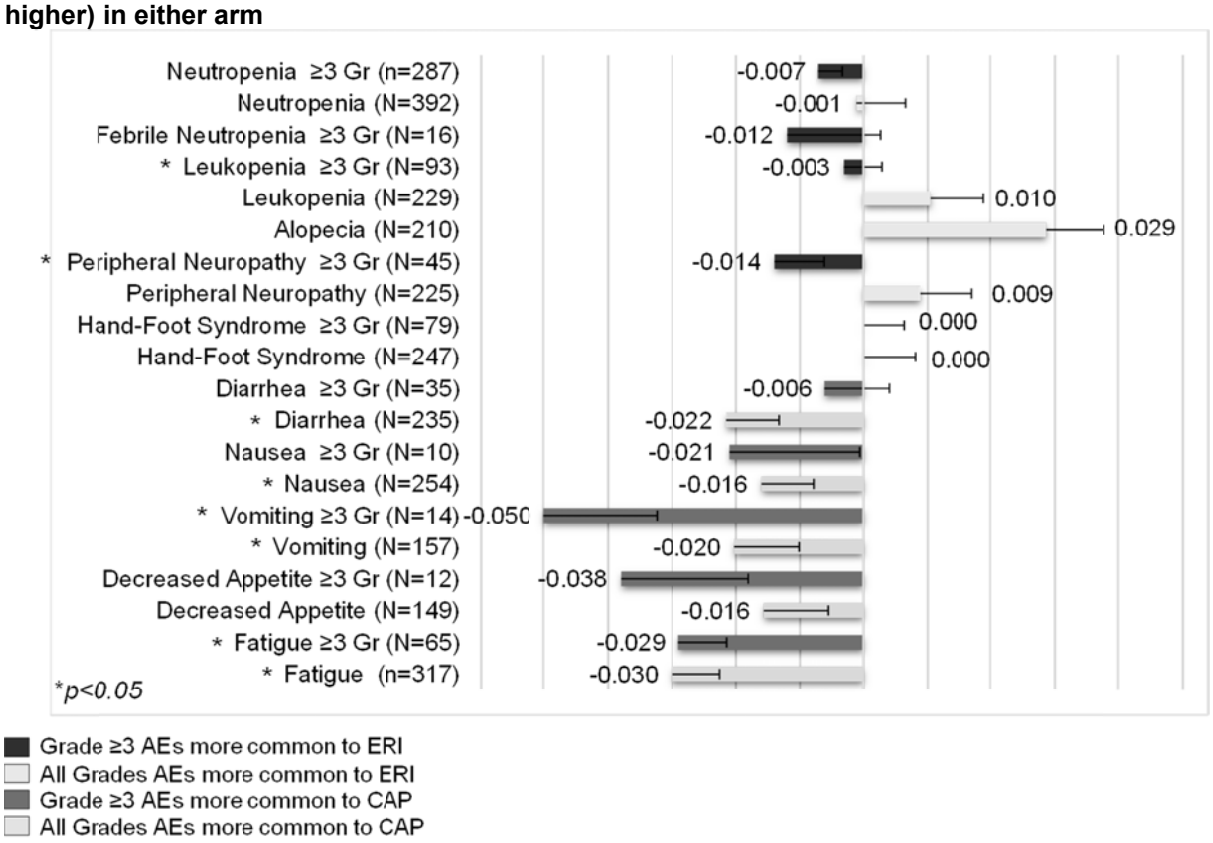
	Eribulin (n=503)		Capecitabine (n=247)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Neutropenia	54%	46%	16%	5%
Febrile Neutropenia	2%	2%	1%	1%
Leukopenia	31%	15%	10%	2%
Alopecia (hair loss)	35%	0%	18%	0%
Peripheral Neuropathy	13%	3%	7%	1%
Hand-foot syndrome	0%	0%	45%	14%
Diarrhea	14%	1%	29%	5%
Nausea	22%	0%	24%	2%
Vomiting	12%	0%	17%	2%
Decreased appetite	13%	1%	15%	2%
Fatigue	17%	2%	15%	2%

Disutility Analysis

A linear mixed-effects model was used to regress explanatory variables including baseline transformed health utility score and specific AEs (run individually for this specific analysis) of interest against the change in health utility scores. Most toxicities led to a decline in utility scores. Vomiting, decreased appetite, fatigue, nausea, and diarrhoea led to the highest disutility decrements (Figure 44, overleaf).

Specifically, the overall disutility value in common AEs including vomiting, decreased appetite, fatigue/asthenia, and diarrhoea were in favour of eribulin treatment and AEs including dyspnoea, peripheral neuropathy, febrile neutropenia, neutropenia, and leukopenia were in favour of capecitabine treatment. In this analysis, alopecia was associated with improvement in utility, which is consistent with a previously published study showing that patients with alopecia had significantly longer overall survival and progression-free survival compared with patients without alopecia. However, as the EORTC QLQ-C30 scale does not assess hand foot syndrome, alopecia or peripheral neuropathy, disutility scores should be interpreted with caution.

Figure 44 Disutility values for common AEs in Study 301 >10% (all grades) or 2% (Grade 3 or higher) in either arm



Health-related quality-of-life data used in cost-effectiveness analysis

In the absence of more appropriate utility values identified through the systematic literature review, the converted utility values extracted from study 301 dataset were used for the purposes of this economic model. However, certain adjustments and/or assumptions related to the estimated utility scores needed to be made in order for:

1) the utility scores to reflect the model's health states,

2) the AEs experienced by patients within the specific subgroups to be reflected in the utility values utilised within each version of the model and

3) to account for the different comparator arms used in the two versions of the model reflecting the corresponding subgroups. The following sections provide detailed description of the utility scores considered for each of the subgroups.

Subgroup 1

Although the "Progressive" state utility value included in the model was assumed to be equal to the progressive state pooled for both treatment arms score of the study 301, there was a need to calculate the utility score of the "Stable" health state of the model combining the utility scores of the "Baseline" and "Tumour response" health states of Study 301 HRQOL analysis.

This conversion was conducted through a stepwise approach, as follows: at first the incremental utility was calculated by subtracting the baseline utilities from the tumour response utilities (Table 50).

Incremental Utility = Tumour Response – Baseline

Incremental Utility (eribulin) = 0.780- 0.704=0.076
Incremental Utility (capecitabine) = 0.783- 0.691=0.092

The incremental utility was then multiplied with the tumour objective response rate obtained from Study 301 data (as reported by the independent review) and added to the baseline utilities. Different objective response rates were available for patients on eribulin and capecitabine (11% and 11.5% respectively).

Stable state Utility (eribulin) = Incremental Utility (eribulin) x Tumor Response Rate (eribulin)]+Baseline Utilities

Stable state Utility (eribulin) = [0.076 x 0.11] +0.704 = 0.712

Stable state Utility (capecitabine) =Incremental Utility (capecitabine) x Tumor Response Rate (capecitabine)]+Baseline Utilities

Stable state Utility (capecitabine) = [0.092 x 0.115] +0.691 = 0.702

The adverse event dis-utilities were then subtracted to obtain the utilities in the “Stable” health state. The dis-utilities considered for the estimation of the final utility values were only those associated with Grade ¾ AEs that occurred in more than 2% of the patients in either treatment arm as presented in Table 55 overleaf. Although no Grade ¾ AE of alopecia was observed, alopecia was included in the calculations in response to feedback received during the assessment of TA250.

Table 55 Adverse events disutility scores (yearly)

		Yearly adverse event rate (grade 3/4)		Disutility calculation	
AE	Disutility	Eribulin	Capecitabine	Eribulin	Capecitabine
Anemia	-0.010	2.02%	1.10%	0.000	0.000
Nausea	-0.021	0.18%	1.65%	0.000	0.000
Neutropenia	-0.007	45.77%	4.95%	-0.003	0.000
Febrile Neutropenia	-0.012	2.02%	0.92%	0.000	0.000
Alopecia (all grade)	0.000	34.56%	17.58%	0.000	0.000
Leukopenia	-0.003	15.07%	2.01%	0.000	0.000
Diarrhea	-0.006	1.10%	5.31%	0.000	0.000
Asthenia/fatigue	-0.029	6.25%	6.04%	-0.002	-0.002
Peripheral Neuropathy	-0.014	3.49%	0.55%	0.000	0.000
Dyspnoea	-0.027	2.21%	3.85%	-0.001	-0.001
Palmar-Plantar Erythro-Dysaesthesia Syndrom	0.000	0.00%	14.47%	0.000	0.000
Total disutility				**-0.007**	**-0.004**

Decision inclusion criteria: AEs with greater than 2% Grade 3/4 prevalecene; Alopecia was included in alignement with feedback received during TA150

Source AEs prevalence: Study 301 patient level data

Source disutility values: Hudgens et. Al. (2014) ESMO 2014

Given that, the final utility values for stable disease are as follows:

"Stable" Utility (eribulin) = 0.712 – Adverse Event Disutilities

"Stable" Utility (eribulin) = 07.12 - 0.007 = 0.705

"Stable" Utility (capecitabine) = 0.702 – Adverse Event Disutilities

"Stable" Utility (capecitabine) = 0.702 - 0.004 = 0.698

For the "Progressive" health state, the utility values for eribulin and capecitabine differed, with the value related to eribulin being slightly higher. However, it would be ambiguous to accept that there is a treatment effect on patient HRQOL following progression. Therefore, in order to limit uncertainty, a more conservative approach was considered as the basecase scenario assuming that both arms should be assigned with the aggregated utility value of the total study population, equal to 0.679. Table 56 overleaf summarises the utility values used for subgroup 1.

Table 56 Utility values calculation for subgroup 1

Utility scores as per Study 301		
	Eribulin	**Capecitabine**
Baseline	0.704	0.691
Tumour Response	0.780	0.783
Disease progression	0.679	0.679
Source: 84		
Stable disease utility scores adjusted for tumour response and disutility		
	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 Adverse events	-0.0071	-0.0042
Stable disease QALY	***0.705***	***0.697***
Source: 11; 84		
Utility scores per health states		
	Eribulin	**Capecitabine**
Stable disease	0.705	0.697
Progressive disease	0.679	0.679

Subgroup 2

In the absence of HRQOL data captured in Study 305, the converted utility scores extracted from the 301 study dataset were also used for this subgroup. Recognising the differences between the two studies, the following conservative assumptions were made in order to limit the uncertainty:

- "Stable" health state:
    - o The 'Baseline' and 'Tumor response' utility values of eribulin were assigned to both treatment groups of eribulin and TPC for the estimation of the "stable" health state as described above.
    - o Tumor objective response rates of eribulin and TPC from study 305 were considered for the estimation of the "stable" health state as described above.
    - o Dis-utility values were calculated as per algorithm for Grade ¾ AEs with prevalence greater than 2% as reported in study 301 to limit the bias.

- "Progressive" health state: the aggregated utility value of the total study population, equal to 0.679, was assigned to both treatment groups.

Following the same calculation process illustrated above for subgroup 1, Table 57 below presents the utility values considered for subgroup 2.

Table 57 Utility values calculation for subgroup 2

Utility scores as per Study 301		
	Eribulin	**Capecitabine**
Baseline	0.704	0.691
Tumour Response	0.780	0.783
Disease progression	0.679	0.679
Source: 84; baseline utility assumed equal to Eribulin		
Stable disease utility scores adjusted for tumour response and disutility		
	Eribulin	**TPC**
Baseline*	0.704	0.704
Tumour Response*	0.780	0.780
Incremental Utility of response	0.076	0.076
Tumour Response rate	12.2%	4.7%
Disutility of Adverse events	-0.0071	-0.0066
Stable disease QALY	***0.706***	***0.701***
Source: 7; 84		
*TPC assumed equal to Eribulin for baseline and tumour response utility values		
Utility scores per health states		
	Eribulin	**TPC**
Stable disease	0.706	0.701
Progressive disease	0.679	0.679

Table 58 Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Utilities Subgroup 1				
Eribulin stable disease	0.705	CIs and SDs for the original utilities used to calculate the CEA utilities are provided in the tables above	page 164	As calculated following the mapping exercise from QLQ-C30 to EQ-5D utilising the data collected in study 301.
Eribulin progressive disease	0.679		page 164	
Capecitabine stable disease	0.697		page 164	
Capecitabine progressive disease	0.679		page 164	
Utilities Subgroup 2				
Eribulin stable disease	0.706	CIs and SDs for the original utilities used to calculate the CEA utilities are provided in the tables above	page 165	As calculated following the mapping exercise from QLQ-C30 to EQ-5D utilising the data collected in study 301.
Eribulin progressive disease	0.679		page 165	
TPC stable disease	0.701		page 165	
TPC progressive disease	0.679		page 165	
Disutilities for Subgroup 1 & 2				
Anaemia	-0.010	CIs and SDs for the original utilities used to calculate the CEA utilities are provided in the tables above	page 163	As calculated following the mapping exercise from QLQ-C30 to EQ-5D utilising the data collected in study 301.
Nausea	-0.021		page 163	
Neutropenia	-0.007		page 163	
Febrile Neutropenia	-0.012		page 163	
Alopecia (all grade)	0.000		page 163	
Leukopenia	-0.003		page 163	
Diarrhoea	-0.006		page 163	
Asthenia/fatigue	-0.029		page 163	
Peripheral Neuropathy	-0.014		page 163	
Dyspnoea	-0.027		page 163	
Palmar-Plantar Erythro-Dysaesthesia Syndrome	0.000		page 163	

Abbreviations: CEA, Cost effectiveness analysis; CI, Confidence interval; SD. Standard deviation, TPC, Treatment of physician's choice;

5.5 Cost and healthcare resource use identification, measurement and valuation

Resource identification, measurement and valuation studies

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

As described previously, two systematic reviews were conducted to retrieve relevant information from the published literature regarding the cost-effectiveness of eribulin. Full information on the systematic literature reviews was mentioned in section 5.1.

In further detail, the systematic literature reviews identified the following studies for each subgroup that looked at resource utilisation and costs of management of LABC/MBC treated with eribulin or its comparators.

1. Dranitsaris G, Beegle N, Kalberer T, et al. A comparison of toxicity and health care resource use between eribulin, capecitabine, gemcitabine, and vinorelbine in patients with metastatic breast cancer treated in a community oncology setting. J Oncol Pharm Pract. 2015;21(3): 170-177 (70)

2. Wan Y, Copher R, Corman S, et al. Indirect costs among metastatic breast cancer patients receiving eribulin. ISPOR 20th Annual International Meeting, 16-20 May, 2015, Philadelphia. PNC72 (71)

Both studies present resource utilisation and cost information from the perspective of the US healthcare system and did not provide relevant data for England. A summary of both studies is provided overleaf in Table 59.

Therefore, the healthcare resource use and the associated unit costs were identified through UK specific sources and validated through clinical experts since the systematic literature review did not provide results that could be utilised in this de novo analysis given the aforementioned characteristics.

Overall, the identification of resource use was predominantly based on the NICE Clinical Guidelines for advanced breast cancer, CG81 (17), in line with feedback received during the TA250 consultation and validated through expert opinions. Further information is provided below.

Costs for the identified resource use were estimated based on the NHS Reference costs 2014 to 2015 (88), the PSSRU Unit Costs of Health and Social Care 2015 report (89) and the NICE Clinical Guidelines for advanced breast cancer, CG81. (17) Drug costs and administration costs were extracted from the electronic market information tool (eMit) database (85), MIMS (86) and NHS Reference Costs 2014 to 2015 (88). The costs associated with the treatment of adverse events were obtained from the NHS Reference costs (88) and/or the PSSRU Unit Costs of Health and Social Care 2015 report (89). Further detailed information on costs is included below.

Cancer services such as those for delivery of chemotherapy and radiotherapy are not currently covered by PbR tariffs. Also, neither the intervention nor the comparator arms within the two subgroups are subjected to PbR tariffs.

Table 59 Summary of published resource identification, measurement and valuation studies

Study	Date of Study	Country	Summary of study	Cost valuations	Costs for use in economic analysis	Technology costs	Healthcare Resource use
Dranitsaris et al (70)	2010-2012	US	Retrospective observational study of US patients in a community oncology setting with MBC who received capecitabine, vinorelbine, gemcitabine or eribulin. Toxicity and associated healthcare resource use were compared.	Not reported	Not reported	Not reported	Healthcare resource data collection included visits to an emergency department or unscheduled clinic visits as a result of treatment-related toxicity.
Wan et al (71)	2008-2012	US	Retrospective analysis of MarketScan Health and Productivity Management Database. Study examined indirect costs in terms of productivity loss among patients receiving eribulin vs other commonly used chemotherapies in the treatment of MBC.	Not reported	Not reported	Not reported	Study identified adult MBC patients eligible for ≥1 month employee benefits of short term disability and calculated the difference in STDI days and related costs between study cohorts

Abbreviations: MBC, Metastatic breast cancer

Intervention and comparators' costs and resource use

As mentioned above, eribulin's cost effectiveness is assessed within two specific subgroups. Despite the fact that the comparator arm differs in the two subgroups (capecitabine for subgroup 1 and TPC for subgroup 2), drug and administration costs remain the same in both of the corresponding versions of the model. This is because all of the treatments included in the relevant costs estimation are used either as primary or secondary therapies in the model. Table 60 below summarises the primary and secondary treatments used in each subgroup.

Table 60 Primary and secondary treatments used in subgroups

Subgroup 1	Subgroup 2
Primary treatments	
Intervention: eribulin	Intervention: eribulin
Comparator arm: capecitabine as Basecase mix of capecitabine & vinorelbine as Sensitivity scenario (a 50%/50% split was assumed for vinorelbine oral and IV)	Comparator arm: TPC comprised of
	Vinorelbine (oral/IV)
	Gemcitabine
	Docetaxel
	Paclitaxel
	Doxorubicin
Secondary treatments	
TPC comprised of	*TPC comprised of*
Vinorelbine (oral/IV)	Vinorelbine (oral/IV)
Gemcitabine	Gemcitabine
Docetaxel	Docetaxel
Paclitaxel	Paclitaxel
Doxorubicin	Doxorubicin

Unit Drug Costs

Drug Prices: Eribulin price was considered with the approved Patient Access Scheme. Since almost all of the rest of the treatments have been genericised, prices have been extracted from the electronic market information tool (eMit) database (85), with the exception of the oral formulation of vinorelbine, the price of which was obtained from MIMS (86). All of the prices are summarised per package/formulation in Table 61 overleaf.

Table 61 Drug pack sizes and prices

Drug	Package/Vial size	Package Type	Price (£)
Eribulin	2ml (0.88mg)	Solution Vial	[redacted]
	3ml (1.32mg)	Solution Vial	[redacted]
Vinorelbine Oral	10 capsules x 20mg	Soft capsules	439.80
	10 capsules x 30mg	Soft capsules	659.80
	10 capsules x 80mg	Soft capsules	1,759.20
Vinorelbine IV	10mg	Solution Vial	5.04
	50mg	Solution Vial	18.24
Capecitabine	60 tablets x 150mg	Tablets	7.73
	120 tablets x 500mg	Tablets	29.59
Gemcitabine	200mg	Powder Vial	3.99
	1000mg	Powder Vial	30.89
	2000mg	Powder Vial	21.39
Docetaxel	20mg	Solution Vial	4.92
	80mg	Solution Vial	12.47
	160mg	Solution Vial	34.83
Paclitaxel	30mg	Solution Vial	3.41
	100mg	Solution Vial	8.50
	150mg	Solution Vial	11.50
	300mg	Solution Vial	21.48
Doxorubicin	10mg	Solution Vial	1.53
	50mg	Solution Vial	4.04
	200mg	Solution Vial	20.30

Source: MIMS and eMIT database

Dosage and scheduling information for the estimation of the costs was extracted from the corresponding individual drug SPC's (87). BSA, dose intensity and wastage assumptions have also been incorporated into the drug costs estimation as mentioned under section 5.2.

Secondary therapy: secondary therapy is comprised of the TPC included treatments as mentioned before. Therefore, secondary therapy drug costs are the same as those mentioned above. Inclusion of secondary therapy costs is dependent on the option considered above in the "Treatment duration" sub-section of section 5.2 regarding the maximum number of treatment cycles applied.

Table 62 overleaf provides a brief summary of the drug costs per monthly Markov cycle. The calculations done were based on the assumptions listed below. The following parameters were considered for the estimation of these costs.

Table 62 Drug costs per monthly Markov cycle

Drug Name	Dosage Form	Dosage and Scheduling: Dose (mg/m2)	Dosage and Scheduling: Number of doses per cycle	Dosage and Scheduling: Cycle length (Days)	Number per Markov cycles	Market share in treatment arms[1]: Primary therapy market share	Market share in treatment arms[1]: Post primary therapy market share	Drug utilization based on BSA distribution: Total dose per treatment (mg)	Drug utilization based on BSA distribution: Drug costs per treatment cycle (21 to 28 days)	Drug utilization based on BSA distribution: Drug costs per Markov cycle (1 month)
Eribulin Arm										
Eribulin	IV	**1.23**	**2**	21	1.45			1.87	[redacted]	[redacted]
Comparator Arm (primary therapy for subgroup 1)										
Capecitabine	Oral	**2500**	**14**	21	1.45	100.0%		3,741.00	**24**	**35**
Comparator Arm (primary therapy for subgroup 2) and Secondary therapy										
Chemotherapies										
Vinorelbine IV	IV	**30**	**3**	21	1.45	0.0%	18.4%	45.94	**55**	**79**
Vinorelbine Oral	Oral	**75**	**3**	21	1.45	0.0%	18.4%	45.94	**7**	**10**
Gemcitabine	IV	**1250**	**2**	21	1.45	0.0%	27.7%	1,892.94	**43**	**62**
Taxanes										
Docetaxel	IV	**100**	**1**	21	1.45	0.0%	6.0%	151.99	**35**	**50**
Paclitaxel	IV	**175**	**1**	21	1.45	0.0%	15.7%	265.25	**21**	**31**
Anthracyclines										
Doxorubicin	IV	**75**	**1**	21	1.45	0.0%	13.9%	113.58	**11**	**16**
Primary therapy average costs per arm										**35**
Secondary therapy average costs										**44**

1 Source: Study 305 CSR Table 14.1.1.4 - TPC arm distribution: 5 most prevalent drugs excluding capecitabine
2 Source: NHS reference cost 2014/2015 (Paclitaxel has complex IV administration cost)

Administration Costs

Drug administration costs were based on NHS Reference Costs 2014 to 2015 (88). As a simplifying assumption, all chemotherapy was considered part of ongoing therapy, eliminating the need for separate initial and subsequent HRG codes.

Chemotherapy administration costs were estimated according to the HRG codes in the table below. Oral chemotherapy costs have been considered for capecitabine and oral vinorelbine. Accordingly, simple parenteral chemotherapy costs have been considered for eribulin, gemcitabine, docetaxel and doxorubicin. Complex IV administration with infusion costs have been considered for paclitaxel only due to the long infusion time.

These administration costs have been applied to the estimation of primary and secondary therapies costs at the first Markov cycle of each treatment.

Table 63 Administration costs

Type of chemotherapies	UK (NHS) cost code	Average cost (£)	Source
Oral chemotherapy	SB11z	**171**	*NHS ref costs 2014-15*
Simple parenteral chemotherapy (first attendance)	SB12Z	**239**	*NHS ref costs 2014-15*
IV complex with infusion	SB14z	**389**	*NHS ref costs 2014-15*

Health-state unit costs and resource use

The type and frequency of resources utilised for routine medical monitoring across the pre and post progression period (i.e. "Stable" and "Progressive" health states) were predominantly based on the NICE Clinical Guidelines for advanced breast cancer, CG81 (17), in line with feedback received during the TA250 consultation and validated through expert opinions as follows:

Costs were estimated based on the NHS Reference costs 2014 to 2015 (88), the PSSRU Unit Costs of Health and Social Care 2015 report (89) and the NICE Clinical Guidelines for advanced breast cancer, CG81. (17)

In the "Progressive" health state, apart from the direct medical costs related to routine medical monitoring, the following costs have been taken into consideration for a specific period of time:

- Palliative care costs: accounted for 6 Markov cycles prior to transitioning into the "Dead" health state
- End of life care costs: accounted for 0.5 Markov cycles prior to transitioning into the "Dead" health state. According to the NICE Clinical Guidelines for advanced breast cancer, CG81 (17), 40% of metastatic breast cancer patients spend their two weeks leading up to death in a hospital, while 10% die in a hospice and 50% die at home. Estimates of these end of life costs were also provided in the full CG81 published in 2009 (17). These costs were inflated to reflect 2014 to 2015 prices according to the hospital & community health services (HCHS) index for 2014, which is published in the PSSRU Unit Costs of Health and Social Care 2015 report (89).

The inputs were validated by four NHS England practising clinical experts. These were selected based on their expertise in MBC and the number of patients treated within their site

of practice (Royal United Hospitals Bath, The Newcastle Upon Tyne Hospitals, University Hospitals of North Midlands and the Christie). The validation was conducted through telephone interviews. The clinical experts were presented with the resource utilisation estimates, related costs and the rationale around them. Following that, they were asked to confirm or rejects the inputs. In case of rejection, experts were asked to provide their rationale. The majority of the experts confirmed that the inputs below generally reflect the current clinical practice in NHS England.

Table 64 below summarises the three categories of costs considered in the model.

Table 64 Summary of Direct Medical Costs

Direct Medical costs					
Stable and progressive disease costs	**Unit cost**	**Usage**	**Unit**	**Cost per month**	**References**
Medical Oncologist - follow-up	158.54	1	Monthly	158.54	NHS Reference Costs 2014-15
GP Contact	44.00	1	Monthly	44.00	PSSRU, 2015 - 10.8b GP
CT scan	92.03	0.33	Monthly	30.68	NHS Reference Costs 2014-15
Supportive palliative care costs	**Unit cost**	**Usage**	**Unit**	**Cost per month**	**References**
Medical Oncologist - follow-up	158.54	1	Monthly	158.54	NHS Reference Costs 2014-15
GP Home visit	44.00	1	Monthly	44.00	PSSRU, 2015 - 10.8b GP
Clinical nurse specialist	88.00	1	Monthly	88.00	PSSRU, 2015 - 10.7 Nurse advanced
Community nurse home visit	58.00	0.67	Monthly	38.67	PSSRU, 2015 - 10.4 Nurse per patient hours
End of life costs	**% of patients**	**End of Life Unit Costs**	**End of Life Costs†**	**References**	
Hospital/Medical institution	40%	5135.25	2054.10	NICE Breast Cancer Guidance (2009), Marie Curie report on End of Life Costs	
Hospice	10%	6402.15	640.22	NICE Breast Cancer Guidance (2009), Marie Curie report on End of Life Costs	
At home (with community support)	50%	2649.47	1324.73	NICE Breast Cancer Guidance (2009), Marie Curie report on End of Life Costs	

Source: NICE CG81, NHS Reference costs; PSSRU, 2015; NICE Breast Cancer Guidance (2009), Marie Curie report on End of Life Costs. †Inflated to 2014-2015; Source inflation: PSSRU 2015, The hospital & community health services (HCHS) index for 2014, table 16.3 (Pay + prices).

Adverse reaction unit costs and resource use

Adverse Event (AE) data included in the model for each of the subgroups were derived from the two pivotal studies 301 and 305. The AEs considered were only grade 3/4 AEs with a prevalence greater than 2% requiring treatment and/or hospitalisation. Alopecia was included in alignment with feedback received during TA250 consultation but no grade3/4 was observed. Table 65 presents the AEs considered for each of the subgroups.

Table 65 Proportion of patients with >2% Grade ¾ AEs treated or hospitalised

Toxicity	All G3-4 AEs >2%			
	Subgroup 1		Subgroup 2	
	% Patients Eribulin	% Patient Capecitabine	% Patients Eribulin	% Patient TPC
Anaemia	1.50%	0.90%	1.99%	3.24%
Nausea	0.20%	1.70%	1.19%	2.43%
Neutropenia	16.80%	2.00%	14.51%	5.26%
Febrile Neutropenia	2.02%	2.80%	1.60%	4.17%
Alopecia (all grade)	34.56%	0.00%	0.00%	0.00%
Leukopenia	5.90%	1.10%	4.17%	1.62%
Diarrhoea	1.10%	7.30%	0.00%	0.00%
Asthenia/fatigue	6.25%	2.50%	1.90%	1.59%
Peripheral Neuropathy	3.49%	3.30%	0.00%	3.78%
Dyspnoea	3.50%	5.10%	3.38%	2.83%
Palmar-Plantar Erythro-Dysaesthesia Syndrome	0.00%	0.00%	6.10%	0.40%
	Source: Study 301 patient level data		Source: Study 305 patient level data	

It is important to note that the adverse event collected probability data within the studies 301 and 305 were based on the entire duration for which the patients were administered each treatment. Hence, the following formula was used to calculate monthly rates of AEs.

$$\boldsymbol{Monthly\ probability} = \left\{(\mathbf{1} + \boldsymbol{CTP})^{\left(\frac{(365/12)}{CTL}\right)}\right\} - \mathbf{1}$$

The costs associated with the treatment of adverse events were obtained from the NHS Reference costs (88) and/or the PSSRU Unit Costs of Health and Social Care 2015 report (89). The list of adverse events and the relevant costs associated with the management of these adverse events are listed in Table 66 overleaf.

Table 66 Adverse Event costs

Toxicities Grade 3/4	Costs 2014-2015	HRG Code	Description
Anaemia	516.55	SA04K	Iron deficiency anaemia with cc score 2-5 non elective short stay
Nausea	399.42	JA12L	Malignant Breast Disorders without Interventions, with CC Score 0-1 (Non-elective short stay)
Neutropenia	127.7	XD25Z	Neutropenia drugs band 1
Febrile Neutropenia*†	6060	PA45Z (2012-2013)	Febrile Neutropenia with Malignancy
Alopecia (all grade)	0		Assumption - no cost
Leukopenia	127.7	XD25Z	Neutropenia drugs band 1
Diarrhoea	399.42	JA12L	Malignant Breast Disorders without Interventions, with CC Score 0-1 (Non-elective short stay)
Asthenia/Fatigue**	38	N/A	1hr community nurse visit per day for duration of adverse event
Peripheral Neuropathy*†	146.33	AB05Z (2013-2014)	procedures in outpatient Intermediate pain procedures (Code no longer exists)
Dyspnoea	490	DZ20E	Pulmonary Oedema without Interventions, with CC Score 6+
Palmar-Plantar Erythro-Dysaesthesia Syndrome	429.65	JD07J	Skin Disorders without Intervention, with cc score 2-5 (non-elective inpatient short stay)

Source: NHS Reference Costs 2014-2015

**Source: Other year for NHS Reference Costs - see HRG cost for year*

***PSSRU 2015*
†Inflated to 2014-2015; Source inflation: PSSRU 2015, The hospital & community health services (HCHS) index for 2014, table 16.3 (Pay + prices)

Considering the aforementioned information, Table 67 and Table 68 overleaf present the monthly average AE costs for each of the subgroups.

Table 67 Monthly costs per AE for Subgroup 1

Toxicity	Monthly adverse events rates - Patient treated		Monthly cost of adverse events (£)	
	% AE's per month, Eribulin	%AE's per month Capecitabine	Eribulin	Capecitabine
Anaemia	0.27%	0.16%	1.39	0.81
Nausea	0.04%	0.30%	0.14	1.19
Neutropenia	2.84%	0.35%	3.62	0.45
Febrile Neutropenia	0.50%	0.28%	30.22	16.95
Alopecia (all grade)	0.00%	0.00%	0.00	0.00
Leukopenia	1.04%	0.19%	1.33	0.25
Diarrhoea	0.20%	1.25%	1.11	7.01
Asthenia/fatigue	0.45%	0.33%	0.17	0.13
Peripheral Neuropathy	0.59%	0.00%	0.86	0.00
Dyspnoea	0.62%	0.88%	3.04	4.30
Palmar-Plantar Erythro-Dysaesthesia Syndrome	0.00%	1.05%	0.00	4.50

Table 68 Monthly costs per AE for Subgroup 2

Toxicity	Monthly adverse events rates - Patient treated		Monthly cost of adverse events (£)	
	% AE's per month, Eribulin	%AE's per month TPC	Eribulin	TPC
Anaemia	0.44%	0.99%	2.26	5.09
Nausea	0.26%	0.74%	1.05	2.96
Neutropenia	3.05%	1.59%	3.89	2.03
Febrile Neutropenia	0.91%	0.37%	55.20	22.56
Alopecia (all grade)	0.00%	0.00%	0.00	0.00
Leukopenia	0.91%	0.50%	1.16	0.63
Diarrhoea	0.00%	0.00%	0.00	0.00
Asthenia/fatigue	0.35%	0.62%	0.13	0.24
Peripheral Neuropathy	0.83%	0.86%	1.21	1.26
Dyspnoea	0.74%	0.86%	3.62	4.23
Palmar-Plantar Erythro-Dysaesthesia Syndrome	0.09%	0.74%	0.38	3.19

Miscellaneous unit costs and resource use

No miscellaneous costs were included in the model.

5.6 Summary of base-case de novo analysis inputs and assumptions

Summary of base-case de novo analysis inputs

Table 69 overleaf summarises all the inputs and variables used in the economic model.

Table 69 Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI/SE (distribution)	Reference to section in submission
Utility values	**Mean values**	**SD/SE/CI**	
Study 301 Utility Scores & Variables used for the estimation of Utility Values included in the model			
Baseline - Eribulin	0.704	SD=0.228	Section 5.4
Tumor Response – Eribulin	0.780	SD=0.194	
Tumor objective response rate - Eribulin	11.0%	CI= 8.5, 13.9	
Baseline – Capecitabine	0.691	SD=0.238	
Tumor Response – Capecitabine	0.783	SD=0.185	
Tumor objective response rate - Capecitabine	11.5%	CI= 8.9, 14.5	
Progression – Total study population	0.679	SD=0.23	
Study 305 Variables used for the estimation of Utility Values included in the model			
Tumor objective response rate - Eribulin	12.2%	CI=9.4, 15.5	Section 5.4
Tumor objective response rate - TPC	4.7%	CI= 2.3, 8.4	
Basecase Utility values for Subgroup 1			
Eribulin stable disease	0.705	N/A	Section 5.4
Eribulin progressive disease	0.679	N/A	
Capecitabine stable disease (applied to the additional sensitivity scenario of mix of capecitabine/vinorelbine comparator)	0.697	N/A	
Capecitabine progressive disease (applied to the additional sensitivity scenario of mix of capecitabine/vinorelbine comparator)	0.679	N/A	
Basecase Utility values for Subgroup 2			
Eribulin stable disease	0.706	N/A	Section 5.4
Eribulin progressive disease	0.679	N/A	
TPC stable disease (applied to the additional sensitivity scenario of mix of gemcitabine/vinorelbine comparator)	0.701	N/A	
TPC progressive disease (applied to the additional sensitivity scenario of mix of gemcitabine/vinorelbine comparator)	0.679	N/A	
Disutilities Values			
Anemia	-0.010	CI= -0.035,0.015	Section 5.4

Nausea	-0.021	CI= -0.061,0.019	Section 5.4
Neutropenia	-0.007	CI= -0.014,0.000	
Febrile Neutropenia	-0.012	CI= -0.041,0.017	
Alopecia (all grade)	0.000		
Leukopenia	-0.003	CI= -0.015,0.009	
Diarrhea	-0.006	CI = -0.026,0.014	
Asthenia/fatigue	-0.029	CI= -0.044,-0.014	
Peripheral Neuropathy	-0.014	CI= -0.030,0.002	
Dyspnea	-0.027	CI= -0.047,-0.007	
Palmar-Plantar Erythro-Dysaesthesia Syndrome	0.000	CI= -0.013,0.012	
Drug & Acquisition Costs	**Cost (£) / Value**	**SD**	
Treatments			
Eribulin 2ml vial (PAS price)	[redacted]	N/A	Section 5.5
Eribulin 3ml vial (PAS price)	[redacted]	N/A	
Vinorelbine oral 20 mg	439.80 per pack	N/A	
Vinorelbine oral 30 mg	659.80 per pack	N/A	
Vinorelbine oral 80 mg	1,759.20 per pack	N/A	
Vinorelbine IV 10mg	5.04 per vial	N/A	
Vinorelbine IV 50mg	18.24 per vial	N/A	
Capecitabine 150mg	7.73 per pack	N/A	
Capecitabine 500mg	29.59 per pack	N/A	
Gemcitabine 200mg	3.99 per vial	N/A	
Gemcitabine 1000mg	30.89 per vial	N/A	
Gemcitabine 2000mg	21.39 per vial	N/A	
Docetaxel 20mg	4.92 per vial	N/A	
Docetaxel 80mg	12.47 per vial	N/A	
Docetaxel 160mg	34.83 per vial	N/A	
Paclitaxel 30mg	3.41 per vial	N/A	
Paclitaxel 100mg	8.50 per vial	N/A	
Paclitaxel 150mg	11.50 per vial	N/A	

Paclitaxel 300mg	21.48 per vial	N/A	
Doxorubicin 10mg	1.53 per vial	N/A	
Doxorubicin 50mg	4.04 per vial	N/A	
Doxorubicin 200mg	20.30 per vial	N/A	
Relative Dose Intensity for eribulin in Subgroup 1	0.87	SD=0.146	Section 5.2
Relative Dose Intensity for capecitabine in Subgroup 1	0.86	SD=0.156	Section 5.2
Relative Dose Intensity for TPC as secondary therapy in Subgroup 1	0.87		Section 5.2
Relative Dose Intensity for eribulin and TPC in Subgroup 2 (TPC used as both primary and secondary therapy)	0.84	SD=0.178	Section 5.2
Body Surface Area	1.74	SD=0.01	Section 5.2
Administration			
Oral chemotherapy	£171	N/A	Section 5.5
Simple parenteral chemotherapy (first attendance)	£239	N/A	Section 5.5
IV complex with infusion	£389	N/A	Section 5.5
Treatment proportion for TPC arm			
Gemcitabine	27.71%	N/A	Section 5.2
Vinorelbine	36.75%	N/A	
Docetaxel	6.02%	N/A	
Paclitaxel	15.66%	N/A	
Doxorubicin	13.86%	N/A	
Maximum number of treatment cycles for primary and secondary therapy			
Subgroup 1	7.3494 months	N/A	Section 5.3
Subgroup 2	5.8282 months	N/A	
Resource Utilization	**Cost (£)**		
Medical Oncologist - follow-up	£ 158.54 per visit @ 1visit per month	N/A	Section 5.5
GP Contact	£ 44 per visit @ 1visit per month	N/A	
CT scan	£ 92.03 per scan, once every 3 months	N/A	
GP Home visit	£ 44 per visit @ 1visit per month	N/A	
Clinical nurse specialist	£ 88 per visit @ 1visit per month	N/A	
Community nurse home visit	£ 58 per visit @ 2visits per 3 months	N/A	

Terminal care costs - Hospital/Medical institution	£ 2054.10	N/A	Section 5.5
Terminal care costs - Hospice	£ 640.22	N/A	
Terminal care costs - At home (with community support)	£ 1324.73	N/A	
AE Management	**Cost (£)**		
Grade 3/4 Anemia	£ 517	N/A	Section 5.5
Grade 3/4 Nausea	£ 399	N/A	
Grade 3/4 Neutropenia	£ 128	N/A	
Grade 3/4 Febrile Neutropenia	£ 6060	N/A	
Grade 3/4 Alopecia	£ 0	N/A	
Grade 3/4 Leukopenia	£ 128	N/A	
Grade 3/4 Diarrhea	£ 562	N/A	
Grade 3/4 Asthenia/Fatigue	£ 38	N/A	
Grade 3/4 Peripheral Neuropathy	£ 146	N/A	
Grade 3/4 Dyspnea	£ 490	N/A	
Grade 3/4 PPEDS	£ 430	N/A	

Abbreviations: CI, Confidence interval; PAS, Patient access scheme; PPEDS, S Palmar-Plantar Erythro-Dysaesthesia Syndrome; SD, Standard deviation; TPC, Treatment of physician's choice

Assumptions

Table 70 overleaf provides a brief overview of the main structural assumptions made by the economic model, and a summary of the justification for the decision. Please refer to the referenced section for a full overview of the assumptions in the context where they are discussed.

Table 70 Key model assumptions

Assumption	Justification	Reference to section:
Equal efficacy and safety between capecitabine and vinorelbine assumed for the Subgroup 1 sensitivity analysis scenario's comparators – mix of 50% capecitabine and 50% vinorelbine (including both oral and IV formulation)	The mix of capecitabine and vinorelbine was selected as an alternative set of comparators for subgroup 1 in order to reflect the scope (Table 1) and the current NICE clinical guidelines (29). Although gemcitabine was also included in the NICE scope as a potential comparator, this is outside of the NICE clinical guidelines. Moreover, no clinical evidence exists for gemcitabine in the specific disease setting. Therefore, further assumption would need to be made, something that would enhance the bias of the analysis and increase the uncertainty of the results.	Section 5.2
A 50%/50% split was assumed for vinorelbine oral and IV when vinorelbine is considered in the additional sensitivity scenarios.	This assumption was made in order to allow for both formulations of vinorelbine to be included in the model. The split between oral and IV was verified by clinical experts reflecting real clinical practice.	Section 5.2, Section 5.5
Equal utility values between capecitabine and vinorelbine assumed for the Subgroup 1 sensitivity analysis scenario's comparators – mix of 50% capecitabine and 50% vinorelbine (including both oral and IV formulation)	In the absence of specific HRQOL data linked to a mix of capecitabine and vinorelbine, the converted utility scores extracted from the 301 study dataset were also used for this additional sensitivity scenario.	Section 5.4
Baseline and Tumour response utilities values for eribulin assumed to equal to TPC.	In the absence of HRQOL data captured in Study 305, the converted utility scores extracted from the 301 study dataset were also used for this subgroup too. Recognising the differences between the two studies, these conservative assumptions were made in order to limit the uncertainty.	Section 5.4
Patients assumed to receive secondary therapy for a capped maximum number of cycles.	This assumption was made to allow for patients receiving secondary therapies following progression on primary therapies.	Section 5.2

5.7 Base-case results

Base-case incremental cost effectiveness analysis results

As mentioned above, the basecase include the following characteristics for the two subgroups.

Parameter	Subgroup 1	Subgroup 2
Comparator	Capecitabine	TPC
Time horizon	5 years	
Wastage	Included	
Total treatment duration threshold	Set maximum number of cycles	
Discounting costs & benefits	3.5%	
Cost of AEs applied to	Proportion of patients with >2% prevalence G3/4 adverse events that required treatment and/or hospitalisation	
Utility values	As per Table 56	As per Table 57

Table 71 and Table 72 overleaf summarise the basecase results for each of the assessed subgroups including the estimation of the incremental benefits and costs.

Table 71 Subgroup 1 Basecase incremental cost effectiveness results

Incremental benefits in years

Treatment	Eribulin	Capecitabine arm	Difference
LYG	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]

Incremental costs

Treatment	Eribulin	Capecitabine arm	Difference
Drug costs	[redacted]	[redacted]	[redacted]
Direct medical costs	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Incremental Cost-Effectiveness Ratio

Treatment	ICER
Cost per LYG	24,994
Cost per QALY	36,244

Table 72 Subgroup 2 Basecase incremental cost effectiveness results

Incremental benefits in years

Treatment	Eribulin	TPC arm	Difference
LYG	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]

Incremental costs

Treatment	Eribulin	TPC arm	Difference
Drug costs	[redacted]	[redacted]	[redacted]
Direct medical costs	[redacted]	[redacted]	[redacted]
Adverse events costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Incremental Cost-Effectiveness Ratio

Treatment	ICER
Cost per LYG	24,525
Cost per QALY	35,624

Clinical outcomes from the model

The tables below illustrate the study 301 and 305 medians as well as the model estimated medians and means for PFS and OS.

Overall, all median estimates from the model are within the 95% confidence intervals of the study 301 and study 305 estimates, with the only exception being PFS estimates in study 301. These results demonstrate that the modelled figures are comparable to the clinical trial results observed. The aforementioned exception may be due to a combination of the following factors: a) patients that discontinued or were lost to follow up were excluded from the data used in the economic model, b) study 301 PFS HR is estimated after stratification of region and adjusted by the number of organs and ER status covariates.

Outcome	Study 301 – subgroup analysis median (months, 95% CIs)		Subgroup 1 Model results – median (months)	
	Eribulin	Capecitabine	Eribulin	Capecitabine
PFS	4.2 (3.5, 4.5)	4.0 (3.2, 4.5)	3.02	2.71
OS	16.1 (15.2, 18.6)	13.5 (10.9, 14.9)	15.97	13.24

Outcome	Study 305 – subgroup analysis median (months, 95% CIs)		Subgroup 2 Model results – median (months)	
	Eribulin	TPC	Eribulin	TPC
PFS	3.6 (3.3, 3.8)	2.1 (1.9, 2.2)	3.53	1.91
OS	13.00 (11.7, 13.8)	10.1 (7.7, 11.4)	12.88	9.73

Disaggregated results of the base case incremental cost effectiveness analysis

Table 73 and Table 74 below present the disaggregated benefit results for the basecase analysis by health state for each subgroup.

Table 73 Summary of QALY gain by health state for Subgroup 1

Health state	Eribulin QALYs	Capecitabine QALYs	Increment	Absolute increment	% absolute increment
Stable	0.26	0.23	0.03	0.03	14%
Progressive	0.92	0.70	0.21	0.21	86%
Total	1.18	0.93	0.24	Total absolute increment	100%

Abbreviations: QALY, quality-adjusted life year;

Table 74 Summary of QALY gain by health state for Subgroup 2

Health state	Eribulin QALYs	TPC QALYs	Increment	Absolute increment	% absolute increment
Stable	0.24	0.22	0.02	0.02	11%
Progressive	0.65	0.50	0.15	0.15	89%
Total	0.88	0.72	0.16	Total absolute increment	100%

Abbreviations: QALY, quality-adjusted life year;

Table 75 and Table 76 below present the disaggregated cost results for the basecase analysis by health state for each subgroup.

Table 75 Summary of costs by health state for subgroup 1

Health state	Cost Eribulin	Cost Capecitabine	Increment	Absolute increment	% absolute increment
Stable disease	[redacted]	[redacted]	[redacted]	[redacted]	99.55%
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	0.45%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Table 76 Summary of costs by health state for subgroup 2

Health state	Cost Eribulin	Cost TPC	Increment	Absolute increment	% absolute increment
Stable disease	[redacted]	[redacted]	[redacted]	[redacted]	98.62%
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	1.38%
Total	[redacted]	[redacted]	[redacted]	[redacted]	100%

Table 77 below and Table 78 overleaf present the disaggregated resource use related cost results for the basecase analysis by resource use item for each subgroup.

Table 77 Summary of predicted resource use by category of cost for subgroup 1

Item	Cost eribulin	Cost capecitabine	Increment	Absolute increment	% absolute increment
Drug and administration costs					
Primary therapy cost	[redacted]	[redacted]	[redacted]	[redacted]	70.51%
Secondary therapy - TPC costs	[redacted]	[redacted]	[redacted]	[redacted]	0.06%
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	18.84%
Direct medical costs					
Medical costs	[redacted]	[redacted]	[redacted]	[redacted]	11.25%
Palliative care costs	[redacted]	[redacted]	[redacted]	[redacted]	0.07%
End-of-life costs	[redacted]	[redacted]	[redacted]	[redacted]	2.59%
Adverse events costs	[redacted]	[redacted]	[redacted]	[redacted]	2.01%
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	***100.00%***

Table 78 Summary of predicted resource use by category of cost for subgroup 2

Item	Cost eribulin	Cost TPC	Increment	Absolute increment	% absolute increment
Drug and administration costs					
Primary therapy cost	[redacted]	[redacted]	[redacted]	[redacted]	76.79%
Secondary therapy - TPC costs	[redacted]	[redacted]	[redacted]	[redacted]	0.04%
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	9.75%
Direct medical costs					
Medical costs	[redacted]	[redacted]	[redacted]	[redacted]	10.44%
Palliative care costs	[redacted]	[redacted]	[redacted]	[redacted]	1.37%
End-of-life costs	[redacted]	[redacted]	[redacted]	[redacted]	2.31%
Adverse events costs	[redacted]	[redacted]	[redacted]	[redacted]	3.91%
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	***100.00%***

5.8 Sensitivity analyses

Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis, the utility of each health state and the time spent in each health state were considered as probabilistic and follow Gamma (utility) or normal distributions (survival and stable disease). Gamma distribution was selected for the utility variables because it is more flexible and can be bounded. On the other side, normal distribution was selected in order to avoid considering assumptions which would restrict the robustness of the PSA. The table overleaf (Table 79) presents the parameters considered in the PSA for both subgroups as well as the justifications related to these.

For unit costs and resource utilisation in particular though, stochasticity will depend on the survival and progression stochasticity. Unit costs are assumed to be fixed in the model like in most economic analysis (90). The utilisation is derived by the survival and therefore directly correlated. The cost per patient will therefore change as utilisation differs.

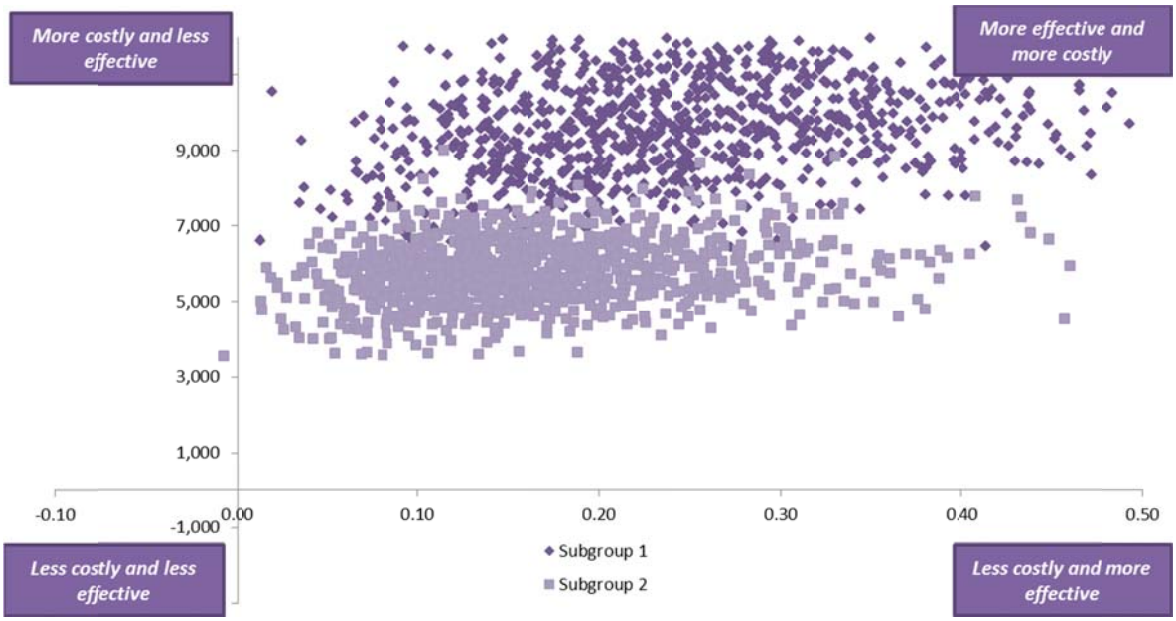
The ICERs in the Probabilistic Model were observed to be between £27,000 and £48,000 for subgroup 1 and between £20,000 and £60,000 for subgroup 2. These were obtained by varying all the utility and survival parameters such as Baseline Utility, Tumour Response Utility, Progression Utility, Pre-progression Survival, Post-Progression Survival and End of Life. The results of the probabilistic sensitivity analysis are presented in Table 79 and Figure 45 overleaf.

Table 79 Probabilistic Parameters for Subgroups 1 & 2

Parameters		Subgroup 1 Point estimate	Subgroup 1 Standard Error	Subgroup 1 Distribution	Subgroup 2 Point estimate	Subgroup 2 Standard Error	Subgroup 2 Distribution	Justification
Utility	Baseline - Eribulin	0.704	0.23	Gamma	0.70	0.23	Gamma	
	Tumour Response - Eribulin	0.78	0.19	Gamma	0.78	0.19	Gamma	Data extracted from the study 301 HRQOL analysis results
	Disease progression - Eribulin	0.679	0.23	Gamma	0.68	0.23	Gamma	
	Baseline - Comparator	0.691	0.24	Gamma	0.69	0.24	Gamma	
	Tumour Response - Comparator	0.783	0.19	Gamma	0.78	0.19	Gamma	
	Disease progression - Comparator	0.679	0.23	Gamma	0.68	0.23	Gamma	
Unit Costs and resource utilization								Survival and progression stochasticity dependent*
	Primary and secondary therapy drug cost		+/-10%	Normal		+/-10%	Normal	
Survival	Stable disease - Eribulin	4.06	0.44	Normal	4.06	0.14	Normal	Point estimate from the parametric simulation and SE from the studies 301 & 305 data
	Progressive disease - Eribulin	12.00	0.91	Normal	12.00	0.72	Normal	
	Stable disease - Comparator	3.80	0.35	Normal	3.80	0.20	Normal	
	Progressive disease - Comparator	9.23	0.84	Normal	9.23	0.72	Normal	
	End of life							

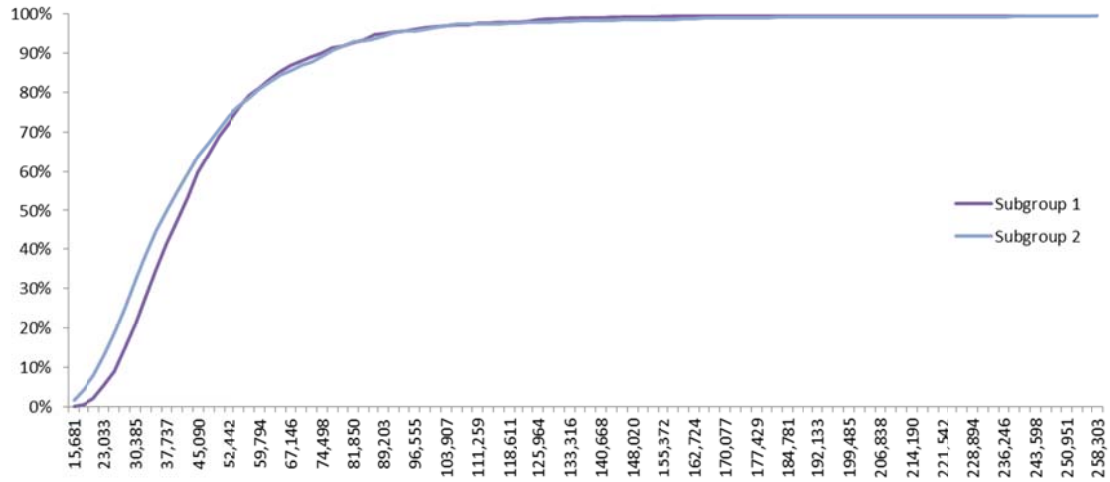
**Source: Briggs, A.H. and Goeree, R. and Blackhouse, G. and O'Brien, B.J. (2002) Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. Medical Decision Making 22(4):pp. 290-308 (90)*

Figure 45 Cost Effectiveness Planes of the Probabilistic Sensitivity Analysis



A cost effectiveness acceptability curve was created to understand the probability of eribulin being cost effective within each subgroup. Figure 46 below showed that there is 8%, 20% and 70% probability that eribulin would be cost effective at an ICER threshold of £25,000, £30,000 and £50,000 per QALY for subgroup 1. Accordingly, that there is 17%, 30%, 72% probability that eribulin would be cost effective at an ICER threshold of £25,000, £30,000 and £50,000 per QALY for subgroup 2.

Figure 46 Cost Effectiveness Acceptability Curves



Deterministic sensitivity analysis

The deterministic sensitivity analysis (SA) was used as a tool to evaluate the variables that seemed sensitive, but were not evaluated directly in the studies 301 & 305. As the model is developed according to a partition survival framework, it was considered that a deterministic SA would be most suited to evaluate their sensitivity. The sensitivity of OS, PFS and utility variables were only analysed in the PSA. The variables used in the deterministic SA and the range of variance associated with each variable for each subgroup are presented in Table 80 below.

With regards to the ranges used in the deterministic sensitivity analysis, the following rationale was followed:

- Scenarios 1,2,3: Discounting rate ranges from 0 to 6% according to NICE guidelines
- Scenarios 4,5,6,7,8: Although a range of +/- 10% change is usually indicated as best practice according to the certain acknowledged CUA guidelines (91,92), a broader range of +/- 20% change was selected in order to enhance robustness and limit uncertainty of the analysis.
- Scenario 9: The upper limit was set at 0.705 assuming almost equal value to stable disease. The lower limit was the lowest value mentioned in previous NICE submissions. The value 0.50 was used in NICE guidance TA371 for trastuzumab emtansine in HER2-positive, unresectable locally advanced or metastatic breast cancer (93).

Table 80 Deterministic Sensitivity Analysis - Scenario Presentation for Subgroups 1 & 2

Scenario Presentation	*Optimistic*	*Basecase*	*Conservative*
Scenario 1: Benefits discounting rate	0.0%	3.5%	6.0%
Scenario 2: Costs discounting rate	6.0%	3.5%	0.0%
Scenario 3: Costs and benefits discounting rates	0.0%	3.5%	6.0%
Scenario 4: Halaven price	-20.0%	0.0%	20.0%
Scenario 5: Comparator price	20.0%	0.0%	-20.0%
Scenario 6: Administration costs	-20.0%	0.0%	20.0%
Scenario 7: Direct Healthcare costs	-20.0%	0.0%	20.0%
Scenario 8: Prevalence of Adverse events	-20.0%	0.0%	20.0%
Scenario 9: Progressive disease utility	0.705	0.695	0.500

The results of the scenarios for subgroup 1 are discussed below and summarised in Table 81 overleaf.

1. Scenario 1: Benefits Discounting Rate: The benefits discounting rate range spanned from 0% to 6% resulting in an ICER range between £ 33,499 and £ 38,232.
2. Scenario 2: Costs Discounting Rate: The costs discounting rate range spanned from 0% to 6%, resulting in an ICER range between £ 35,583 and £ 37,255.
3. Scenario 3: Costs and Benefits Discounting Rates: The costs and benefits discounting rate range spanned from 0%-6% resulting in an ICER range between £ 34,433 and £ 37,535.
4. Scenario 4: Eribulin Price: The Eribulin price range spanned from -20% to 20% resulting in an ICER between £ 32,095 and £ 40,394. A difference of £ 8,299 indicated that the price of eribulin is the second biggest factor influencing the

ICER in this economic model.

5. Scenario 5: Price of the comparator: The comparator price range spanned from -20% to 20% resulting in an ICER between £ 36,132 and £ 36,356.
6. Scenario 6: Administration Costs: The administration costs range spanned from -20% to 20 resulting in an ICER range between £ 34,879 and £ 37,610.
7. Scenario 7: Direct Healthcare costs: The direct healthcare costs range spanned from -20% to 20% resulting in an ICER between £ 35,622 and £ 36,866
8. Scenario 8: Prevalence of AEs: The prevalence of AEs range spanned from -20% to 20% resulting in an ICER between £ 36,098 and £ 36,390.
9. Scenario 9: HRG costs of adverse events: The HRG costs of AEs range spanned from -20% to 20% resulting in an ICER between £ 35,091 and £ 47,148. A difference of £ 12,057 indicated that the progressive disease utility value is the first biggest factor influencing the ICER in this economic model.

Table 81 Deterministic Sensitivity Analysis - Scenario Results for Subgroup 1

Scenario results - ICER	*Low*	*Basecase*	*High*
*Scenario 1: Benefits discounting rate**	33,499	36,244	38,232
*Scenario 2: Costs discounting rate**	35,583	36,244	37,255
*Scenario 3: Costs and benefits discounting rates**	34,433	36,244	37,535
Scenario 4: Halaven price	32,095	36,244	40,394
Scenario 5: Comparator price	36,132	36,244	36,356
*Scenario 6: Administration costs**	34,879	36,244	37,610
*Scenario 7: Direct Healthcare costs**	35,622	36,244	36,866
*Scenario 8: Prevalence of Adverse events (G3/G4)**	36,098	36,244	36,390
*Scenario 9: Progressive disease utility**	35,091	36,244	47,148

**Scenario applied to both arms*

The results of the scenarios for subgroup 2 are discussed below and summarised in Table 82 overleaf.

1. Scenario 1: Benefits Discounting Rate: The benefits discounting rate range spanned from 0% to 6% resulting in an ICER range between £ 33,326 and £ 37,255.
2. Scenario 2: Costs Discounting Rate: The costs discounting rate range spanned from 0% to 6%, resulting in an ICER range between £ 35,037 and £ 36,518.
3. Scenario 3: Costs and Benefits Discounting Rates: The costs and benefits discounting rate range spanned from 0%-6% resulting in an ICER range between £ 34,162 and £ 36,641.
4. Scenario 4: Eribulin Price: The Eribulin price range spanned from -20% to 20% resulting in an ICER between £ 31,226 and £ 40,022. A difference of £ 8,796 indicated that the price of eribulin is the second biggest factor influencing the ICER in this economic model.
5. Scenario 5: Price of the comparator: The comparator price range spanned from -20% to 20% resulting in an ICER between £ 35,401 and £ 35,848.
6. Scenario 6: Administration Costs: The administration costs range spanned from -20% to 20 resulting in an ICER range between £ 34,930 and £ 36,319.
7. Scenario 7: Direct Healthcare costs: The direct healthcare costs range spanned from -20% to 20% resulting in an ICER between £ 34,947 and £ 36,302.
8. Scenario 8: Prevalence of AEs: The prevalence of AEs range spanned from -20% to 20% resulting in an ICER between £ 35,346 and £ 35,903.
9. Scenario 9: HRG costs of adverse events: The HRG costs of AEs range spanned from -20% to 20% resulting in an ICER between £ 34,447 and £ 46,912. A difference of £ 12,465 indicated that the progressive disease utility value is the first biggest factor influencing the ICER in this economic model.

Table 82 Deterministic Sensitivity Analysis - Scenario Results for Subgroup 2

Scenario results - ICER	*Low*	*Basecase*	*High*
*Scenario 1: Benefits discounting rate**	33,326	35,624	37,255
*Scenario 2: Costs discounting rate**	35,037	35,624	36,518
*Scenario 3: Costs and benefits discounting rates**	34,162	35,624	36,641
Scenario 4: Halaven price	31,226	35,624	40,022
Scenario 5: Comparator price	35,401	35,624	35,848
*Scenario 6: Administration costs**	34,930	35,624	36,319
*Scenario 7: Direct Healthcare costs**	34,947	35,624	36,302
*Scenario 8: Prevalence of Adverse events (G3/G4)**	35,346	35,624	35,903
*Scenario 9: Progressive disease utility**	34,447	35,624	46,912

These results are illustrated in the following tornado graphs for each of the subgroups.

Figure 47 Tornado graph for subgroup 1

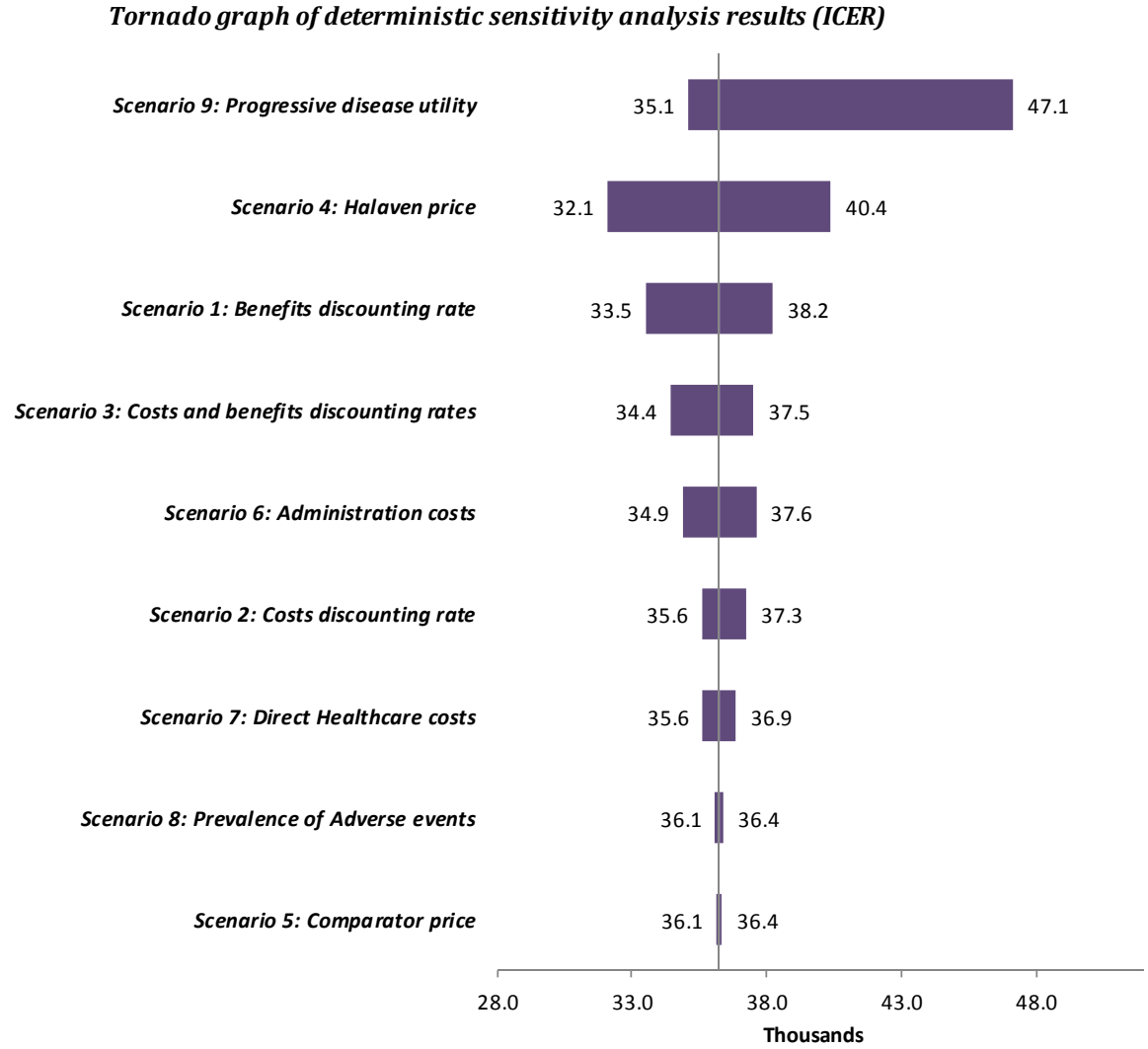
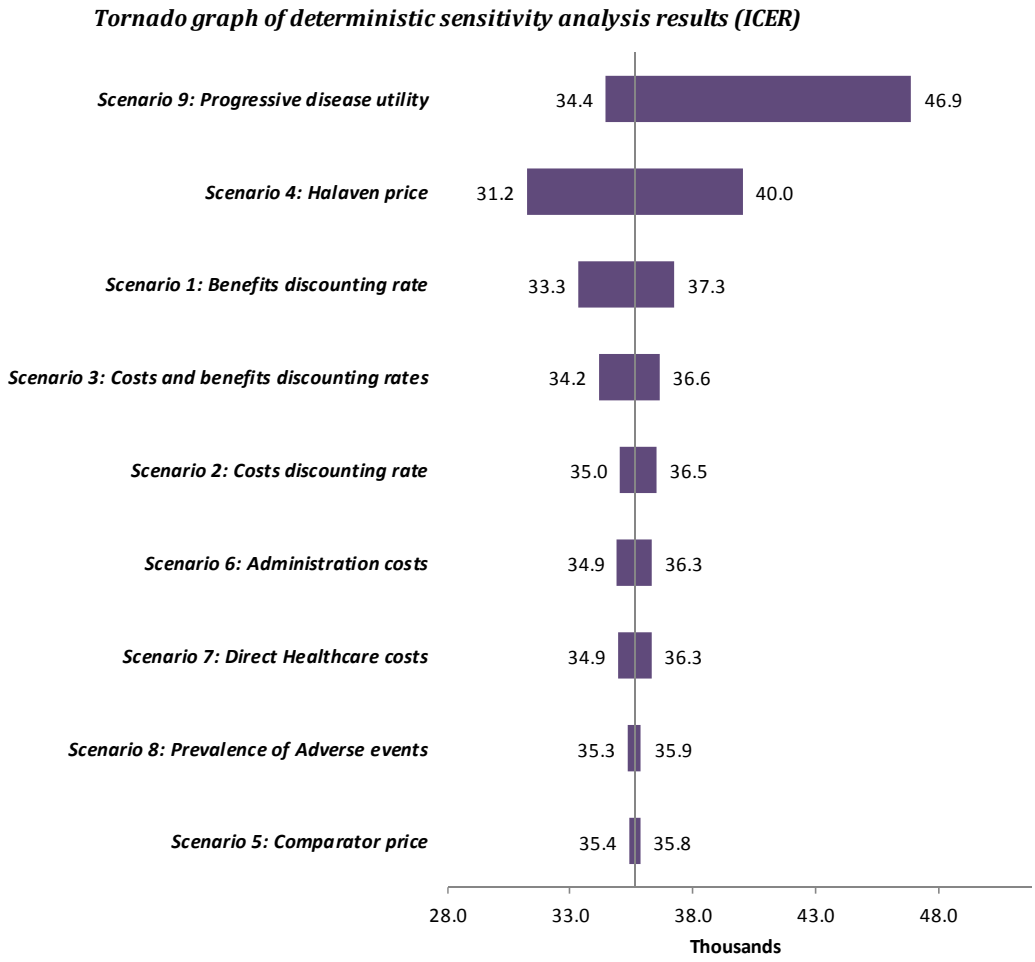


Figure 48 Tornado graph for subgroup 2



Scenario analysis

To address uncertainty, certain additional sensitivity scenarios have been assessed for both subgroups. Table 83 overleaf summarises the scenarios assessed and the justification for each of them.

Table 84 presents the results for each scenario.

Table 83 Additional Sensitivity Scenarios assessed for each Subgroup

Scenario	Justification
For both subgroups	
Secondary therapy duration of 12 months	Testing for a longer horizon reduces the uncertainty in this variable.
Excluding Wastage	Although the presentation of eribulin in 2ml and 3ml vials aims at the minimization of wastage, the exclusion of wastage was tested as an additional scenario to understand the impact of it.
Prevalence of AEs cost based on G3/4	An additional scenario was included considering the grade ¾ AEs with prevalence greater than 2% regardless of the proportion of patients that required treatment and or hospitalization. The aim of this scenario is to assess the impact of decision criterion considered to select for inclusion the prevalence related to treatment and/or hospitalization versus the overall prevalence of grade ¾ AEs.
Time horizon spanning to 10 and 20 years	According to Decision Problem meeting and inputs from the ERG group, 10-year and 20-year time horizons have been considered for both subgroups. The 20-year time horizon is assumed to approximate lifetime.
For Subgroup 1	
Using a mix of capecitabine and vinorelbine as a comparator	The mix of comparators was based on the feedback received by the Decision problem meeting and the current NICE clinical guidelines. Despite the efficacy and safety assumptions needed to be made for vinorelbine, this scenario aims at assessing the impact of including vinorelbine costs in the primary therapy over basecase.
For Subgroup 2	
Using a mix of vinorelbine and gemcitabine as a comparator	The mix of comparators was based on the feedback received by the Decision problem meeting and the current NICE clinical guidelines. This scenario aims at assessing the impact of considering vinorelbine and gemcitabine in terms of efficacy and costs in the primary therapy over basecase.

Table 84 Results of Additional Sensitivity Scenarios

	ΔLY	ΔQALY	ΔCost	ΔICER
Basecase scenario - Subgroup 1	**0.36**	**0.24**	**8,875**	**36,244**
Capecitabine+Vinorelbine as a comparator	0.36	0.24	8,241	33,654
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
Prevalence of AEs cost based on G3/4	0.36	0.24	8,869	36,221
Time Horizon				
5 years (basecase)	0.36	0.24	8,875	36,244
10 years	0.45	0.31	9,346	30,217
20 years	0.46	0.32	9,399	29,743
Basecase scenario - Subgroup 2	**0.24**	**0.16**	**5,804**	**35,624**
Maximum treatment duration threshold of 12 months	0.24	0.16	6,380	39,164
Excluding Wastage	0.24	0.16	2,615	16,053
Vinorelbine+Gemcitabine as a comparator	0.36	0.24	5,849	23,931
Prevalence of AEs cost based on G3/4	0.24	0.16	5,859	35,964
Scenario F: Time Horizon				
5 years (basecase)	0.24	0.16	5,804	35,624
10 years	0.27	0.19	6,021	32,362
20 years	0.27	0.19	6,028	32,282

Although the option for treatment duration being limited at progression is available in the model, it has not been reported as an additional sensitivity scenario since it was considered too optimistic.

Summary of sensitivity analyses results

Overall, both the probabilistic and deterministic sensitivity analyses and the additional scenarios provided indicate that the cost effectiveness analysis is relatively robust without substantial distances from the basecase results for two subgroups.

The planes of the probabilistic sensitivity analysis indicate that there is a greater variation in the QALY gain compared to the costs. However, the cost effectiveness acceptability curves indicate that the ICERs are very consistent. Although the cost effectiveness probability increases only by 12% and 13% for subgroup 1 and subgroup 2 from £25,000 to £30,000 per QALY, the increase is 50% from £30,000 to £50,000 as illustrated by the subgroups acceptability curves.

With regards to the deterministic probabilistic analysis, the utility value assigned to the progressive health state and the eribulin price are the most impactful factors on the ICER. This was consistent for both subgroups.

Finally, the additional scenarios provided for both subgroups that none of the variable variations affect the ICER negatively (i.e. increase) compared to the basecase results, except for the scenario considering extending the treatment duration to 12 months. In comparison, the ICER is positively impacted (i.e. decrease) by the extension of the time horizon – highlighting the impact of accumulating QALY benefits for eribulin – and by the exclusion of wastage.

5.9 Subgroup analysis

No further subgroups in addition to Subgroup 1 and 2 were assessed.

5.10 Validation

Validation of de novo cost-effectiveness analysis

Internal validation of the extrapolation: The patient-level data based Kaplan-Meier curves have been used for both subgroups until the trial cut-off point (5-year time horizon). The use of patient-level data is consistent with the study 301 and 305 results. For the tail extrapolation, the Tremblay et al (94) decision making criteria have been used, which led to the selection of piecewise models for OS (PFS was only based on KM data as the data was complete). The Tremblay et al, 2015 decision making criteria are based on the NICE DSU 14 on survival extrapolations (78). The extrapolation is only used for the 10-year and 20-year time horizons, and not for the basecase as the data is complete for the first 5 years. Therefore the internal consistency of the 5 years horizon is superior to the lifetime horizon. To our knowledge, no other economic evaluation was published for these specific subgroups, so an external validation was not performed.

External validation of the costs: Cost inputs were primarily based on the NICE advanced breast cancer guideline (17) and the most recent 2014-2015 NHS reference costs for this model. To our knowledge, no other economic evaluation was published for these specific subgroups, so an external validation based on published health economic evaluations was not performed.

External validation of the utility and disutility: While no other publication was readily available for these subgroups to our knowledge, the utility values were kept as conservative as possible. As an example, the post-progression utility values were assumed equal to avoid overestimating the QALY gain for eribulin. All the values included in the model derived from study 301 and have been published establishing transparency of the data.

External validation of the Adverse events prevalence and costs: The AE costs were based on a HRG/DRG approach. The HRG approach is in line with the NICE guidelines and the feedback received from TA250. The AEs with >2% prevalence for G3/4 were included in the analysis. The inclusion threshold was reduced from 5% to 2% compared to TA250 in order to ensure the inclusion of all important AEs and have consistency with the AEs considered in the estimation of the disutilities.

Quality control: The quality control was performed both by Eisai internal HEOR experts and an external health economist. The extrapolations were validated by an expert from Glasgow University.

5.11 Interpretation and conclusions of economic evidence

Overall, the economic evaluation of eribulin was conducted strictly according to all the NICE technical and clinical guidelines and it reflects the subgroup populations in which eribulin has

been shown to offer the greatest benefit and are characterised by unmet medical need based on current clinical practice.

The deterministic sensitivity analysis indicated that the progressive disease utility value is one of the most influential factors in the estimation of the ICER. This is primarily due to the fact that the main clinical benefit of eribulin is derived from the OS endpoint. In relation to this, it is worth mentioning that the OS results observed in the two subgroups across studies 301 and 305 were statistically significant while the subgroups were based on pre-specified variables. Moreover, the conservative (low) limit utility value of 0.500 considered in the Scenario 9 of the deterministic sensitivity analysis is derived by Lloyd et al (95), as sourced in the previous economic submissions. These utility values were elicited based on preferences from members of the general public through a vignette study. In contrast, utility values used within this economic evaluation have been estimated – through a mapping exercise - based on patient-level HRQoL data collected through the study 301 using QLQ-C30 instrument. The preference of using study 301 extracted utility values within the cost utility assessment was due to the fact that the aforementioned values are extracted through patient-reported outcomes rather than members of the public and thus are more robust.

Furthermore, QLQ-C30 is considered to be more sensitive in capturing the impact on Health-related Quality of life in cancer patients (i.e. by using a disease-specific measurement tool) compared to a generic measurement tool such as EQ-5D. This approach is in accordance with the NICE Decision Support Unit document 11 (96).

All the sensitivity analyses conducted strongly indicate that the evaluation is very robust with all the ICER derivatives being within a very narrow range from the basecase ICERs. The basecase ICERs for subgroup 1 and 2 are fairly close to the willingness to pay thresholds used for other treatments which have been recently approved by NICE. Considering the increased willingness to pay thresholds for treatments meeting the “end of life criteria”, both the observed basecase ICERs and sensitivity analysis ICERs fall below these thresholds given that eribulin meets the “end of life” criteria as mentioned in section 4.13.

In light of all of the above, the cost effectiveness analysis demonstrates that eribulin in the two specified subgroups has been robustly and conservatively demonstrated to meet all the accepted criteria for a cost-effective end of life treatment and could be considered good value for money for adoption by the NHS.

In further detail, the main strengths and limitations of the evaluation are presented below.

Strengths of the analysis

- **Clinical data:** the survival functions estimated in the model (basecase) for both subgroups have been based on patient-level data derived directly from the two studies. The key subgroup variables – HER2 status for subgroup 1 and prior capecitabine usage were pre-specified variables in the clinical trial protocols of the corresponding studies. Moreover, the completeness of the survival data across both studies allowed avoiding data extrapolation, which is one of the greatest sources of uncertainty in partition survival models.

- **Comparators:** The model is a within-trial model including direct comparison to the comparative treatments included in studies 301 and 305. Therefore, no indirect comparison was included in the model. The Kaplan-Meier Survivor Function was extracted in Stata and used as the partition to calculate the area under the curve. No adjustment or correction was conducted.

- **Model scope & NICE guidelines/ previous TAs:** The model was developed according to all the relevant NICE technical and clinical guidelines. It also aims at

reflecting to the greatest extent the NICE scope and the Decision Problem characteristics. Model scope and parameters were defined according to the feedback received by the ERG and NICE during the TA250 as well.

- **Utility and disutility:** Utility and disutility values are based on within-trial QOL data collection and analysis.

- **Sensitivity analysis:** The assessment and sensitivity analysis included as much options as possible, including time horizon variations, comparator variations, cost and utility values variations. The aim of this was to reduce uncertainty to the greatest possible extent. It is worth mentioning that the basecase scenario is one of the most conservative one for each subgroup as concluded by the probabilistic, deterministic and additional scenarios analyses.

Limitations

- **Utility and disutility:** While within trial QOL data was collected, no EQ-5D questionnaires or other preference based techniques were used. Therefore, a mapping technique was used to transform the QLQC-30 values into utility values. Lower post-progression utility was tested as a deterministic sensitivity analysis to address this limitation.

- **Duration of secondary therapy:** Secondary treatment duration is associated with difficulties in its estimation. Although real-world Kantar Health data were used for this purpose, this data is not specifically developed for the selected subgroups, but per line of therapy within MBC. This limitation was addressed by assessing in one of the additional sensitivity scenarios the extension of the overall treatment duration to 12 months allowing for longer secondary therapy period.

- **Subgroup 2 – utility and disutility:** The utility values are based on the 301 trial and applied to subgroup 2. No utility data was collected for the TPC comparator, so capecitabine utilities were used as a proxy.

In conclusion, all the sensitivity analyses conducted strongly indicate that the evaluation is very robust with all the ICER derivatives being a very narrow range from the basecase ICERs. The basecase ICERs for subgroup 1 and 2 are fairly close to the willingness to pay thresholds used for other treatments which have been recently approved by NICE. Considering the increased willingness to pay thresholds for treatments meeting the “end of life criteria”, both the observed basecase ICERs and sensitivity analysis ICERs fall below these thresholds given that eribulin meets the “end of life” criteria as mentioned in section 4.13.

Considering all of the above, the cost effectiveness analysis demonstrates that eribulin in the two specified subgroups has been robustly and conservatively demonstrated to meet all the accepted criteria for a cost-effective end of life treatment and could be considered good value for money for adoption by the NHS.

6 Assessment of factors relevant to the NHS and other parties

To assess the factors relevant to the NHS and other parties, a budget impact model (BIM) was developed in order to assess the impact of eribulin's introduction. As for the assessment of cost effectiveness of eribulin, the two subgroups mentioned in the decision problem (Table 1) were considered separately.

Epidemiology Inputs

As mentioned in section 5.2, subgroup 1 considers HER2-negative patients with LABC/MBC, whose disease has progressed after one prior chemotherapy regimen in the advanced setting. This population can also be described as second line only, HER2 negative.

Similarly for subgroup 2, the patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated) can be described as third line/post capecitabine population.

Given these definitions, the tables below illustrate the prevalence and the relevant estimations for each subgroup.

Table 85 Prevalence of Subgroup 1

Country	Input	Output	Source
Population of England & Wales		57,408,700	https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates#timeseries
PREVALENCE + INCIDENCE:			
Prevalence of Breast Cancer (BC)	0.14%	80,372	Cancer Mpact database, Kantar Health (97)
Prevalence of Metastatic Breast Cancer (MBC)	7.39%	5,940	Cancer Mpact database, Kantar Health (97)
Patients receiving Chemo	100.00%	5,940	Assumption
Patients on Second Line Chemo	65.37%	3,883	Cancer Mpact database, Kantar Health (97)
HER2 Negative Patients	68.50%	2,660	Study 301 (10)
SELECTED PATIENT POPULATION			
Model patient population		2,660	

Table 86 Prevalence of Subgroup 2

Country	Input	Output	Source
Population of England & Wales		57,408,700	https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates#timeseries
PREVALENCE + INCIDENCE:			
Prevalence of Breast Cancer (BC)	0.14%	80,372	Cancer Mpact database, Kantar Health (97)
Prevalence of Metastatic Breast Cancer (MBC)	7.39%	5,940	Cancer Mpact database, Kantar Health (97)
Patients receiving Chemo	100.00%	5,940	Assumption
Patients on Second Line Chemo	65.37%	3,883	Cancer Mpact database, Kantar Health (97)
Patients on Third Line Chemo	52.64%	2,044	Cancer Mpact database, Kantar Health (97)
Post Cape Patients	73.40%	1,500	Study 305 (EMBRACE) (6)
SELECTED PATIENT POPULATION			
Model patient population		1,500	

Due to the advanced stage of the disease, the poor prognosis and the setting of this analysis, the number of patients eligible for treatment with eribulin have been calculated based on prevalence and mortality-based incidence. Annual mortality rates have been estimated based on data observed in study 305 by inversing the one-year survival rate, which was equal to 0.461. Thus, the incidence numbers have been calculated based on the formula below:

Incidence= Prevalence – Prevalence from previous year

where

Prevalence from previous year = Prevalence – [Prevalence *(1- EMBRACE one-year survival rate)]

Market Shares

Two scenarios were assessed in the BIM for each subgroup. The Status Quo scenario aims at reflecting the current clinical practice whereas the eribulin adoption scenario aims at capturing the impact of introducing eribulin in the current clinical practice, with the exception of subgroup 2. The impact of the eribulin adoption on NHS relevant budget was studied over a 5-year period.

For subgroup 2, eribulin market share at baseline is assumed to be 20% given the usage that has been observed through the CDF.

With regards to the mix of treatments considered, only capecitabine and vinorelbine were considered for subgroup 1, reflecting the NICE clinical guidelines.

For subgroup 2, the treatments included in the TPC arm of study 305 were considered, excluding capecitabine. Market shares were derived from Kantar Health real world evidence. Table 87 below presents the market shares for each subgroup for the Status Quo scenario. These market shares remained constant over the period of 5 years in the Status Quo scenario.

Table 87 Market Shares per subgroup

Subgroup 1		Subgroup 2	
Drug Name	Market Share at Baseline	Drug Name	Market Share at Baseline
Capecitabine	74.40%	Eribulin	20.00%
Vinorelbine Oral	12.80%	Vinorelbine Oral	10.24%
Vinorelbine IV	12.80%	Vinorelbine IV	10.24%
		Gemcitabine	20.08%
		Doxorubicin	9.49%
		Docetaxel	15.89%
		Paclitaxel	14.07%
Total	100%	Total	100%

An annual increase of 2% is assumed for the market share of eribulin in the eribulin adoption scenario. Table 88 below presents the market shares of eribulin in each subgroup.

Table 88 Eribulin market shares in each subgroup

Subgroup 1						
Eribulin market shares	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Status Quo scenario	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Eribulin adoption scenario	0.00%	2.00%	4.00%	6.00%	8.00%	10.00%
Subgroup 2						
Eribulin market shares	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Status Quo scenario	20.00%	20.00%	20.00%	20.00%	20.00%	20.00%
Eribulin adoption scenario	20.00%	22.00%	24.00%	26.00%	28.00%	30.00%

The switching from each treatment to eribulin is based on the baseline market shares. Therefore, the uptake of eribulin will reduce the market share of the other therapies proportionally to their baseline market shares. The detailed calculation is explained as follows:

$Treatment_C^T$ represent any of the comparator treatments c at time t (year 1 to 5). ERI^T represent eribulin market share (uptake) at year 1 to 5 = Based on internal assumption

$$Treatment_C^T = Treatment_C^{T-1} * (1 - ERI^T)$$

As an example, the market share of Gemcitabine at baseline is 28.48% (TPC_{GEM}^{T-1}) and the uptake of Eribulin in year 1 is 10% (ERI^1). So the calculation for Gemcitabine market share in year one is:

$$Treatment_{GEM}^T = Treatment_{GEM}^{T-1} * (1 – ERI^1)$$

$$Treatment_{GEM}^T = 28.48\% * (100\% - 10\%)$$

$$Treatment_{GEM}^T = 25.63\%$$

Thus, the market shares of the treatment mix in the eribulin adoption scenario for years 1-5 are estimated as presented in the tables below.

Table 89 Eribulin adoption scenario market shares for Subgroup 1

Drug Name	Baseline Market Share, %	Year 1	Year 2	Year 3	Year 4	Year 5
Eribulin	0.00%	2.00%	4.00%	6.00%	8.00%	10.00%
Capecitabine	74.39%	72.91%	71.42%	69.93%	68.44%	66.95%
Vinorelbine Oral	12.80%	12.55%	12.29%	12.04%	11.78%	11.52%
Vinorelbine IV	12.80%	12.55%	12.29%	12.04%	11.78%	11.52%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 90 Eribulin adoption scenario market shares for Subgroup 2

Drug Name	Baseline Market Share, %	Year 1	Year 2	Year 3	Year 4	Year 5
Eribulin	20.00%	22.00%	24.00%	26.00%	28.00%	30.00%
Vinorelbine Oral	10.24%	9.98%	9.72%	9.47%	9.21%	8.96%
Vinorelbine IV	10.24%	9.98%	9.72%	9.47%	9.21%	8.96%
Gemcitabine	20.08%	19.58%	19.08%	18.58%	18.07%	17.57%
Doxorubicin	9.49%	9.25%	9.01%	8.78%	8.54%	8.30%
Docetaxel	15.89%	15.49%	15.09%	14.70%	14.30%	13.90%
Paclitaxel	14.07%	13.72%	13.37%	13.02%	12.66%	12.31%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Costs

For simplifications reasons, only drug and administration costs were included in the BIM.

Drug and administration costs were calculated as described in section 5.4. The annual costs per patient for each treatment were estimated based on the assumption that each patient received primary therapy until progression and then switched to secondary therapy (TPC) until the end of the year. Primary therapies assessed for each subgroup have been described in the tables above.

In detail, the monthly drug costs (equal to one Markov cycle) were multiplied by the number of PFS months for primary therapy and 12-PFS months for secondary therapy. Associated administration costs were added once for primary and secondary therapy.

For the treatment duration, mean PFS values were considered as estimated by the CEA model. For subgroup 1, capecitabine PFS duration was applied to all treatments other than eribulin. Accordingly, TPC PFS duration was applied to all treatments included in the treatment mix assessed for subgroup 2, except for eribulin.

Table 91 overleaf presents the treatment duration values considered for each subgroup.

Table 91 Treatment duration considered in BIM

Subgroup 1 Model results – mean (months)			Subgroup 2 Model results – mean (months)		
	Eribulin	**Capecitabine**		**Eribulin**	**TPC**
PFS	4.56	3.99	**PFS**	4.06	3.8
Year - PFS	7.44	8.01	**Year - PFS**	7.94	8.2

Results

The following tables display the number of patients estimated for each treatment across the two scenarios for each subgroup. Small differences in the total population across the 5 years are due to automatic round up.

Table 92 Patient number estimation for Subgroup 1 – Status Quo scenario

Drug Name	Baseline Market Share, %	Year 1	Year 2	Year 3	Year 4	Year 5
Eribulin	0	0	0	0	0	0
Capecitabine	1979	1979	1979	1979	1979	1979
Vinorelbine Oral	340	340	340	340	340	340
Vinorelbine IV	340	340	340	340	340	340
Total	2660	2660	2660	2660	2660	2660

Table 93 Patient number estimation for Subgroup 1 – Eribulin adoption scenario

Drug Name	Baseline Market Share, %	Year 1	Year 2	Year 3	Year 4	Year 5
Eribulin	0	53	106	160	213	266
Capecitabine	1979	1939	1899	1860	1820	1781
Vinorelbine Oral	340	334	327	320	313	306
Vinorelbine IV	340	334	327	320	313	306
Total	2660	2660	2660	2660	2660	2660

Table 94 Patient number estimation for Subgroup 2 – Status Quo scenario

Drug Name	Baseline Market Share, %	Year 1	Year 2	Year 3	Year 4	Year 5
Eribulin	300	300	300	300	300	300
Vinorelbine Oral	154	154	154	154	154	154
Vinorelbine IV	154	154	154	154	154	154
Gemcitabine	301	301	301	301	301	301
Doxorubicin	142	142	142	142	142	142
Docetaxel	238	238	238	238	238	238
Paclitaxel	211	211	211	211	211	211
Total	1500	1500	1500	1500	1500	1500

Table 95 Patient number estimation for Subgroup 2 – Eribulin adoption scenario

Drug Name	Baseline Market Share, %	Year 1	Year 2	Year 3	Year 4	Year 5
Eribulin	300	330	360	390	420	450
Vinorelbine Oral	154	150	146	142	138	134
Vinorelbine IV	154	150	146	142	138	134
Gemcitabine	301	294	286	279	271	264
Doxorubicin	142	139	135	132	128	125
Docetaxel	238	232	226	220	214	209
Paclitaxel	211	206	201	195	190	185
Total	1500	1500	1500	1500	1500	1500

Based on these patient numbers and the cost estimation mentioned above, the following tables present the annual and total costs across the two scenarios for each subgroup.

Table 96 Total annual treatment costs for Subgroup 1 – Status Quo scenario

Drug Name	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1-5
Eribulin						
Capecitabine	£2,591,679	£2,591,679	£2,591,679	£2,591,679	£2,591,679	£12,958,395
Vinorelbine Oral	£412,223	£412,223	£412,223	£412,223	£412,223	£2,061,116
Vinorelbine IV	£775,345	£775,345	£775,345	£775,345	£775,345	£3,876,723
Total	£3,779,247	£3,779,247	£3,779,247	£3,779,247	£3,779,247	£18,896,235

Table 97Total annual treatment costs for Subgroup 1 – Eribulin adoption

Drug Name	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1-5
Eribulin	£389,459	£778,919	£1,168,378	£1,557,838	£1,947,297	£5,841,891
Capecitabine	£2,539,776	£2,487,873	£2,435,969	£2,384,066	£2,332,511	£12,180,195
Vinorelbine Oral	£404,172	£395,799	£387,747	£379,374	£371,001	£1,938,093
Vinorelbine IV	£760,201	£744,452	£729,309	£713,559	£697,810	£3,645,331
Total	£4,093,608	£4,407,042	£4,721,403	£5,034,837	£5,348,619	£23,605,510

Table 98 Total annual treatment costs for Subgroup 2 – Status Quo scenario

Drug Name	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1-5
Eribulin	£2,225,921	£1,501,652	£1,501,652	£1,501,652	£1,501,652	£8,232,530
Vinorelbine Oral	£186,855	£186,855	£186,855	£186,855	£186,855	£934,276
Vinorelbine IV	£348,622	£348,622	£348,622	£348,622	£348,622	£1,743,108
Gemcitabine	£559,899	£559,899	£559,899	£559,899	£559,899	£2,799,496
Doxorubicin	£190,433	£190,433	£190,433	£190,433	£190,433	£952,163
Docetaxel	£349,945	£349,945	£349,945	£349,945	£349,945	£1,749,726
Paclitaxel	£340,392	£340,392	£340,392	£340,392	£340,392	£1,701,961
Total	£4,202,067	£3,477,798	£3,477,798	£3,477,798	£3,477,798	£18,113,261

Table 99 Total annual treatment costs for Subgroup 2 – Eribulin adoption

Drug Name	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1-5
Eribulin	£2,448,513	£2,671,105	£2,893,697	£3,116,289	£3,338,881	£14,468,486
Vinorelbine Oral	£182,184	£177,512	£172,841	£168,170	£163,498	£864,205
Vinorelbine IV	£339,906	£331,191	£322,475	£313,760	£305,044	£1,612,375
Gemcitabine	£545,902	£531,904	£517,907	£503,909	£489,912	£2,589,534
Doxorubicin	£185,672	£180,911	£176,150	£171,389	£166,629	£880,751
Docetaxel	£341,197	£332,448	£323,699	£314,951	£306,202	£1,618,497
Paclitaxel	£331,882	£323,373	£314,863	£306,353	£297,843	£1,574,314
Total	£4,375,255	£4,548,444	£4,721,632	£4,894,821	£5,068,009	£23,608,162

Finally, the tables below present the absolute and relative budget impact for each subgroup.

Table 100 Budget impact for Subgroup 1

Drug Name	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1-5
Budget impact	£314,361	£627,795	£942,157	£1,255,590	£1,569,372	£4,709,275
Budget impact %	8%	17%	25%	33%	42%	25%

Table 101 Budget impact for Subgroup 2

Drug Name	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1-5
Budget impact	£173,188	£1,070,645	£1,243,834	£1,417,022	£1,590,211	£5,494,901
Budget impact %	4%	31%	36%	41%	46%	30%

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8 Appendices

Appendix 1: Initial European public assessment report, published 11 04 2011; European public assessment report – variation, published 01 08 2014; Halaven SPC, May 2016

Appendix 2: Search Strategies for Section 4.1, 5.1 and 5.4 (Identification and selection of relevant studies)

Appendix 3: Quality assessment of RCT(s) (section 4.6)

Appendix 4: Sub-group analyses (Section 4.8)

Appendix 5: Quality assessment of cost effectiveness studies (section 5.1)

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Single Technology Appraisal (STA)

Eribulin for treating locally advanced or metastatic breast cancer after chemotherapy [ID964]

Dear company,

The Evidence Review Group, the Liverpool Reviews and Implementation Group, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 17th June 2016 by Eisai. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

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We would be grateful if you could provide a written response to this letter, particularly to the priority questions, if possible by **5:00 pm** on **Friday 29th July**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

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https://appraisals.nice.org.uk/request/15139

If you have any further queries on the technical issues raised in this letter then please contact XXXXXXXXXXXXXXX Technical Lead XXXXXXXXXXXXXXXXXX . Any procedural questions should be addressed to XXXXXXXXXX, XXXXXXXXXXXXXXXXXXXX Project Manager in the first instance.

Yours sincerely
Janet Robertson
Associate Director – Appraisals. Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

Study 305 (EMBRACE)

A1. **Priority Question**: Please provide participant flow for Study 305 specifically for patients included in Subgroup 2: Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease and includes capecitabine (if indicated).

A2. **Priority Question**: The statistical methods used to analyse overall survival (OS) and progression-free survival (PFS) for Study 305 require the assumption of proportional hazards (PH) between treatment arms within each of these studies to hold. Please clarify whether any formal testing of the assumption of PH between treatment arms has been undertaken for OS and PFS for:

a. Intention-to-treat (ITT) population

b. Subgroup 2

If formal testing for PH was conducted, please provide the results of such testing.

A3. **Priority Question**: In Study 305, the company has presented analysis of OS and PFS for the ITT population and Subgroup 2. However, the analyses are at different data-cuts, the OS and PFS analyses in the ITT population are after 55% of patients had died (with an updated OS analysis after 77% of patients had died) whereas for Subgroup 2, the OS and PFS analyses are after 95% of patients had died. To enable a direct comparison with the ITT population, please provide the OS and PFS analyses for the ITT population at the 95% OS cut off and additional missing data (i.e. confidence intervals) for the subgroup for patients previously treated with capecitabine in Table A1 of this clarification letter.

A4. For Study 305, please provide a table with study drug exposure for Subgroup 2 (in a format similar to Table 16 of the Company Submission (CS). Please also update the data for Table 16 if this differs at the 95% OS cut off.

A5. Please clarify whether all patients discontinued treatment at the time of the final data-cut in Study 305.

A6. Please provide further details about the sample size calculation for Study 305. Specifically, please provide the significance level used, the power, the assumed hazard ratio and the length of follow-up.

A7. For Study 305, in order to fully compare the baseline characteristics of Subgroup 2 with the ITT trial population, please provide the missing baseline characteristics by trial arm for the ITT population and Subgroup 2 in Table A2 of this clarification letter.

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A8. Please provide in Table A3 of this clarification letter the number and proportion of patients who received subsequent treatment (including any crossover to eribulin, if this occurred) on disease progression with details about the subsequent treatment, for both the complete ITT population and Subgroup 2.

A9. Please clarify whether any adverse event data has been collected specifically for Subgroup 2 in Study 305 and if so, whether there are any notable differences in the types of any adverse events experienced in this subgroup compared with the overall safety population.

Study 301

A10. For health-related quality of life (HRQoL) data, please provide the following information:

a. The number of patients for which data were available for Subgroup 2.

b. The numbers of patients represented in each bar of Figure 18 of the CS.

Pooled analysis

A11. Please clarify why the published paper of the pooled analysis of Study 301 and Study 305 was not considered eligible for inclusion in the systematic review for Subgroup 2 (Section 4.1; page 46 of the CS)?

A12. Please clarify whether the results from the pooled analysis of Study 301 and Study 305 provide evidence for the use of eribulin specifically for Subgroup 2 or for a different patient population?

A13. Please describe in more detail how data were pooled from Study 301 and Study 305 for the pooled analysis. Specifically, please provide:

a. The data inputs from Study 301 and Study 305.

b. The methodology, statistical program and code used to perform this analysis.

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Section B: Clarification on cost-effectiveness data

B1. **Priority Question**: Please provide the following Kaplan-Meier analyses (listed in a to d below) to the following specification:

Population: Use subset of Study 305 patients who have progressed after two chemotherapeutic regimens and had received capecitabine previously, including all patients lost to follow-up or withdrawing from trial.

Trial data set: Study 305 latest data cut.

Format: Please present analysis outputs using the format of the sample table (B1) in this clarification.

a. Time to death from any cause (OS) Kaplan-Meier analysis stratified by treatment arm (eribulin vs Treatment of Physician's Choice [TPC]).

b. Time to disease progression or death (PFS) Kaplan-Meier analysis based on investigator assessment, stratified by treatment arm (eribulin vs TPC).

c. Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis stratified by treatment arm (eribulin vs TPC).

d. Time to treatment discontinuation Kaplan-Meier analysis stratified by treatment arm (eribulin vs TPC).

Rationale for clarification requests:

- B1: All Kaplan-Meier analyses with alternative censoring rule – when trials are stopped early or subject to early analysis the conventional censoring rule (censor when last contacted/reviewed) always understates the time exposed to risk but is much less likely to understate events, especially deaths. The result is that the hazard rate calculated by Kaplan-Meier algorithm are exaggerated when multiple patients are censored in any period. The resulting Kaplan-Meier estimated time-to-event trends may therefore be distorted by 'informative censoring' and poorly reflect the true profile of time-to-event. In some of the specified analyses there are suggestive indications that such effects are present, but it is not possible to confirm or refute this possibility without having access to re-analysis using the alternative censoring rule.

- B1 (a, b & c): Survival gain for eribulin versus comparator is the most important parameter governing cost-effectiveness. Careful analysis of OS and its components (PFS and PPS) is essential to validation of the survival gains estimated by the decision model.

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- B1 (d): Time to treatment discontinuation offers an alternative to PFS as a basis for estimating treatment costs in both trial arms. This analysis will allow the sensitivity of incremental costs to the method of estimation to be assessed.

B2. **Priority Question**: For Subgroup 2 of study 305, please provide the analysis of baseline characteristics as shown in Table 31 of the CS for:

a. Patients still alive and uncensored 12 months after randomisation.

b. Patients still alive and uncensored 24 months after randomisation.

Section C: Textual clarifications and additional points

C1. **Priority Question**: Please provide the Statistical Analysis Plans for Study 305.

C2. **Priority Question**: Please provide the trial protocol for Study 305.

C3. Table 40, appears to be missing text as the following appears to be an incomplete sentence: “the adverse events prevalence will depend on the MS in the trial, but” Please clarify.

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Table A1 Overall survival and progression-free survival in Study 305 – ITT population and Subgroup 2

	ITT population		Subgroup 2	
Parameter	**Treatment Group**		**Treatment Group**	
	Eribulin (N = 508)	**TPC (N = 254)**	**Eribulin (N = 370)**	**TPC (N = 189)**
Overall survival (OS)				
Number of patients who died, n (%)			356 (96.2)	183 (96.8)
OS, months				
Median (95% CI)			13.0	10.1
Difference in Medians (95% CI)			2.9	
Stratified log-rank test:			p = 0.008	
Hazard ratio (95% CI)			0.78 (0.65 to 0.94)	
Progression-free survival (PFS) - investigator review				
Number of patients who progressed or died, n (%)			334 (90.2)	161 (85.1)
PFS, months				
Median (95% CI)			3.6	2.1
Difference in Medians (95% CI)			1.5	
Stratified log-rank test:			P < 0.001	
Hazard ratio (95% CI)			0.68 (0.56 to 0.83)	

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Table A2 Baseline characteristics in Study 305– ITT population and Subgroup 2

Characteristic	ITT population			Subgroup 2		
	Eribulin (n = 508)	TPC (n = 254)	Total (n = 762)	Eribulin (n = 370)	TPC (n = 189)	Total (n =559)
Median Age (range)	55.0 years (28–85)	55.0 years (27–81)	55.0 years (27–85)			
Age distribution, n (%)						
< 40 yrs	34 (6.7)	17 (6.7)	51 (6.7)	24 (6.5)	15 (7.9)	39 (7.0)
≥ 40 – < 65 yrs	380 (74.8)	180 (70.9)	560 (73.5)	280 (75.7)	133 (70.4)	413 (73.9)
≥ 65 yrs	94 (18.5)	57 (22.4)	151 (19.8)	66 (17.8)	41 (21.7)	107 (19.1)
Race, n (%)						
Caucasian	470 (92.5)	233 (91.7)	703 (92.3)	346 (93.5)	174 (92.1)	520 (93.0)
Black	20 (3.9)	14 (5.5)	34 (4.5)	13 (3.5)	10 (5.3)	23 (4.1)
Asian/Pacific Islander	3 (0.6)	2 (0.8)	5 (0.7)	1 (0.3)	2 (1.1)	3 (0.5)
Other	15 (3.0)	5 (2.0)	20 (2.6)	10 (2.7)	3 (1.6)	13 (2.3)
Geographic region, n (%)						
North America, Western Europe, Australia	325 (64.0)	163 (64.2)	488 (64.0)			
Eastern Europe	129 (25.4)	64 (25.2)	193 (25.3)			
Latin America, South Africa	54 (10.6)	27 (10.6)	81 (10.6)			
Reproductive status, n (%)						
Fertile	46 (9.1)	20 (7.9)	66 (8.7)			
Post-menopausal	379 (74.6)	199 (78.3)	578 (75.9)			
Surgically sterile	78 (15.4)	35 (13.8)	113 (14.8)			
Infertile	5 (1.0)	0	5 (0.7)			
Median time since original diagnosis (range)	5.4 years (0.1, 37.4)	5.1 years (0.6, 22.9)	5.2 years (0.1, 37.4)			

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Characteristic	ITT population			Subgroup 2		
	Eribulin (n = 508)	TPC (n = 254)	Total (n = 762)	Eribulin (n = 370)	TPC (n = 189)	Total (n =559)
ER Status, n (%)†						
+	336 (70.0)	171 (70.4)	507 (70.1)	257 (69.5)	130 (68.8)	387 (69.2)
–	143 (29.8)	72 (29.6)	215 (29.7)	99 (26.8)	54 (28.6)	153 (27.3)
Not done				13 (3.5)	5 (2.6)	18 (3.2)
Unknown	1 (0.2)	0	1 (0.1)	1 (0.3)	0	1 (0.2)
PR Status, n (%)†						
+	254 (56.2)	123 (54.7)	377 (55.7)	195 (52.7)	93 (49.2)	
–	197 (43.6)	102 (45.3)	299 (44.2)	141 (38.1)	78 (41.3)	
Not done				33 (8.9)	18 (9.5)	
Unknown	1 (0.2)	0	1 (0.1)	1 (0.3)	0	
HER2 status, n (%)†						
+	83 (18.0)	40 (17.2)	123 (17.8)			
–	373 (81.1)	192 (82.8)	565 (81.6)			
Unknown	4 (0.9)	0	4 (0.6)			
Triple negative (ER/PR/HER2-negative), n (%)†	93 (18.3)	51 (20.9)	144 (19.8)	68 (18.4)	38 (20.1)	106 (19.0)
No. of organs involved‡, n (%)						
1	85 (16.7)	35 (13.8)	120 (15.7)	61 (16.5)	25 (13.2)	86 (15.3)
2	172 (33.9)	82 (32.3)	254 (33.3)	128 (34.6)	59 (31.2)	187 (33.4)
3	145 (28.5)	77 (30.3)	222 (29.1)	≥3 = 179 (48.4)	≥3 = 105 (55.6)	≥3 = 284 (50.8)
4	71 (14.0)	37 (14.6)	108 (14.2)			
5	24 (4.7)	16 (6.3)	40 (5.2)			
≥ 6	9 (1.8)	7 (2.8)	16 (2.1)			
Tumour sites in > 10% patients						

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Characteristic	ITT population			Subgroup 2		
	Eribulin (n = 508)	TPC (n = 254)	Total (n = 762)	Eribulin (n = 370)	TPC (n = 189)	Total (n =559)
overall, n (%)						
Bone	306 (60.2)	158 (62.2)	464 (60.9)			
Liver	296 (58.3)	159 (62.6)	455 (59.7)			
Lymph nodes	220 (43.3)	118 (46.5)	338 (44.4)			
Lung	197 (38.8)	95 (37.4)	292 (38.3)			
Pleura	87 (17.1)	42 (16.5)	129 (16.9)			
Breast	54 (10.6)	24 (9.4)	78 (10.2)			
ECOG performance status, n (%)						
0						
1	217 (42.7)	103 (40.6)	320 (42.0)	154 (41.6)	80 (42.3)	234 (41.9)
2	244 (48.0)	126 (49.6)	370 (48.6)	179 (48.4)	90 (47.6)	269 (44.9)
	39 (7.7)	22 (8.7)	61 (8.0)	30 (8.1)	16 (8.5)	46 (8.2)
No. of prior chemotherapy regimens (adjuvant and LABC/MBC setting), n (%)						
1	1 (0.2)	0	1 (0.1)			
2	65 (12.8)	31 (12.2)	96 (12.6)			
3	176 (34.6)	83 (32.7)	259 (34.0)			
4	166 (32.7)	79 (31.1)	245 (32.2)			
5	85 (16.7)	51 (20.1)	136 (17.8)			
≥ 6	13 (2.6)	9 (3.5)	22 (2.9)			

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Characteristic	ITT population			Subgroup 2		
	Eribulin (n = 508)	**TPC (n = 254)**	**Total (n = 762)**	**Eribulin (n = 370)**	**TPC (n = 189)**	**Total (n =559)**
No. of prior regimens in LABC/MBC setting, n (%) 0 1 2 3 4 5 ≥ 6						
Duration of last chemotherapy (months), Median (min, max)†	3.57 (0.0, 32.0)	3.50 (0.1, 25.3)	3.53 (0.0, 32.0)			
No. of patients who previously (adjuvant and LABC/MBC setting) received: n (%) Taxanes Anthracyclines Capecitabine	 503 (99.0) 502 (98.8) 370 (72.8)	 251 (98.8) 250 (98.4) 189 (74.4)	 754 (99.0) 752 (98.7) 559 (73.4)			

†For the ER, PR, HER2 and triple negative status, the percentages are calculated from the total number of patients tested

‡The number of organs involved was based on the investigator review data

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Table A3 Subsequent treatment received on disease progression in Study 305

	ITT population		Subgroup 2	
Treatment on disease progression	**Number**	**%**	**Number**	**%**
Any				
Treatment A				
Treatment B				
Treatment C				
Treatment D				
Etc				

Table B1 Example of output (SAS) required from specified Kaplan-Meier analyses

The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP...		...	...	...	...	...
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

Single Technology Appraisal (STA)

Eribulin for treating locally advanced or metastatic breast cancer after chemotherapy [ID964]

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If you have any further queries on the technical issues raised in this letter then please contact Boglarka Mikudina,Technical Lead Boglarka.mikudina@nice.org.uk . Any procedural questions should be addressed to Liv Gualda, Project Manager liv.gualda@nice.org.uk in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals. Centre for Health Technology Evaluation

Section A: Clarification on effectiveness data

Study 305 (EMBRACE)

A1. **Priority Question**: Please provide participant flow for Study 305 specifically for patients included in Subgroup 2: Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease and includes capecitabine (if indicated).

The following table presents the patient withdrawals for subgroup 2 following screening and randomisation for patients included in Subgroup 2, as requested.

	Treatment Group	
	Eribulin	TPC
Screening	370	189
Randomised	370	189
Discontinued: ADVERSE EVENT	1	
Discontinued: CLINICAL PROGRESSION	1	
Discontinued: PHYSICIAN DECISION	1	1
Discontinued: PROGRESSIVE DISEASE	1	
Discontinued: WITHDRAWAL BY SUBJECT		2
Discontinued: OTHER		1
Discontinued: Missing		1
Discontinued treatment: ADVERSE EVENT	34	21
Discontinued treatment: CLINICAL PROGRESSION	46	23
Discontinued treatment: PHYSICIAN DECISION	14	9
Discontinued treatment: PROGRESSIVE DISEASE	263	118
Discontinued treatment: WITHDRAWAL BY SUBJECT	5	5
Discontinued treatment: OTHER	3	5
Discontinued treatment: DEATH	2	2
On Treatment	0	0

Note: Post-Capecitabine patients include all patients who previously received Capecitabine as anti-cancer therapy before study. Safety population uses actual treatment.

Source: Eisai Ltd data on file 95% OS data additional info for ERG

A2. **Priority Question**: The statistical methods used to analyse overall survival (OS) and progression-free survival (PFS) for Study 305 require the assumption of proportional hazards (PH) between treatment arms within each of these studies to hold. Please clarify whether any formal testing of the assumption of PH between treatment arms has been undertaken for OS and PFS for:

a. Intention-to-treat (ITT) population

No formal test was used for testing proportionality of HR.

b. Subgroup 2

No formal test was used for testing proportionality of HR.

If formal testing for PH was conducted, please provide the results of such testing.

A3. **Priority Question**: In Study 305, the company has presented analysis of OS and PFS for the ITT population and Subgroup 2. However, the analyses are at different data-cuts, the OS and PFS analyses in the ITT population are after 55% of patients had died (with an updated OS analysis after 77% of patients had died) whereas for Subgroup 2, the OS and PFS analyses are after 95% of patients had died. To enable a direct comparison with the ITT population, please provide the OS and PFS analyses for the ITT population at the 95% OS cut off and additional missing data (i.e. confidence intervals) for the subgroup for patients previously treated with capecitabine in Table A1 of this clarification letter.

Please see overleaf Table A1 completed with the OS and PFS analyses for the ITT population at the 95% OS cut off, as requested.

Table A1 Overall survival and progression-free survival in Study 305 – ITT population and Subgroup 2

Parameter	ITT population		Subgroup 2	
	Treatment Group		Treatment Group	
	Eribulin (N = 508)	TPC (N = 254)	Eribulin (N = 370)	TPC (N = 189)
Overall survival (OS)				
Number of patients who died, n (%)	485 (95.5)	242 (95.3)	356 (96.2)	183 (96.8)
OS, months				
Median (95% CI)	13.24 (12.06, 14.4)	10.55 (9.23, 12)	13.0 (11.7, 13.8)	10.1 (7.7, 11.4)
Difference in Medians (95% CI)	2.7 (1, 4.4)		2.9 (CIs N/A)	
Stratified log-rank test:	p = 0.011		p = 0.008	
Hazard ratio (95% CI)	0.815 (0.696, 0.955)		0.78 (0.65, 0.94)	
Progression-free survival (PFS) - investigator review				
Number of patients who progressed or died, n (%)	453 (89.2)	217 (85.4)	334 (90.2)	161 (85.1)
PFS, months				
Median (95% CI)	3.61 (3.29, 3.75)	2.17 (1.97, 2.76)	3.6 (3.3, 3.8)	2.1 (1.9, 2.2)
Difference in Medians (95% CI)	1.4 (CIs N/A)		1.5 (CIs N/A)	
Stratified log-rank test:	p = 0.002		p < 0.001	
Hazard ratio (95% CI)	0.771 (0.651, 0.913)		0.68 (0.56, 0.83)	

Source: Eisai Ltd data on file 95% OS data additional info for ERG

A4. For Study 305, please provide a table with study drug exposure for Subgroup 2 (in a format similar to Table 16 of the Company Submission (CS). Please also update the data for Table 16 if this differs at the 95% OS cut off.

As requested, please see below a table with updated data for study drug exposure for the ITT population at the 95% OS cut off and overleaf a table with study drug exposure for Subgroup 2.

Exposure to eribulin: Study 305 (EMBRACE) (Safety population) 95% data cut ITT

	Eribulin (N=503)	**TPC (Chemotherapy) (N=238)**	**TPC (Hormonal) (N=9)**
Duration of exposure, median days (min, max)	118 (21–1241)	70.0 (1, 1578)	30.0 (25–188)
Number of cycles completed on study, n (%) 1–2 3–4 5–6 > 6 Range	 81 (16.1%) 127 (25.2%) 110 (21.9%) 185 (36.8%) 1–55 cycles	NA	NA
Dose intensity, median mg/m^2/week (min, max)	0.84 (0.2, 1.0)	NA	NA
Relative dose intensity, % (min, max)	91% (30, 110)	NA	NA
Patients with dose interruption, n (%)	29 (5.8%)	22 (9.2%)	2 (22.2%)
Patients with dose delay, n (%)	253 (50.3%)	100 (42.0%)	0 (0.0%)
Patients with dose reduction, n (%)	146 (29%)	63 (26.5%)	0 (0.0%)

Source: Eisai Ltd data on file 95% OS data additional info for ERG

Exposure to eribulin: Study 305 (EMBRACE) (Safety population) 95% data cut Subgroup 2 (post capecitabine)

	Eribulin (N=367)	**TPC (N=183)**
Duration of exposure, median days (min, max)	119 (21, 1241)	55 (1, 1578)
Number of cycles completed on study, n (%) 1–2 3–4 5–6 > 6 Range	 57 (15.5%) 91 (24.8%) 86 (23.4%) 133 (36.2%) 1–55 cycles	 NA
Dose intensity, median mg/m^2/week (min, max)	0.84 (0.2, 1.0)	NA
Relative dose intensity, % (min, max)	90% (30, 110)	NA
Patients with dose interruption, n (%)	26 (7.1 %)	14 (7.7%)
Patients with dose delay, n (%)	188 (51.2%)	75 (41.0%)
Patients with dose reduction, n (%)	109 (29.7%)	46 (25.1%)

Source: Eisai Ltd data on file 95% OS data additional info for ERG

A5. Please clarify whether all patients discontinued treatment at the time of the final data-cut in Study 305.

Yes, all patients discontinued treatment at the time of the final data-cut.

A6. Please provide further details about the sample size calculation for Study 305. Specifically, please provide the significance level used, the power, the assumed hazard ratio and the length of follow-up.

East 4 software was used to calculate the sample size required for this trial. The following assumptions were made in the estimation of the required sample size:

- Exponential distributions of overall survival.

- Median overall survival of 9 months and 12 months in the TPC and eribulin arms, respectively, i.e. a hazard ratio of 0.75.
- 2:1 randomisation scheme.
- An overall 5% risk of erroneously claiming superiority of eribulin or TPC in the presence of no true underlying difference (two-sided Type I error).
- An 80% probability of successfully detecting a difference if there was a 3 month increase in overall survival in subjects who receive eribulin over the 9 month survival in the TPC group (power).
- An average accrual rate of 35 patients per month and an accrual period of 18 months (study duration (follow-up) of 26.5 months).

A7. For Study 305, in order to fully compare the baseline characteristics of Subgroup 2 with the ITT trial population, please provide the missing baseline characteristics by trial arm for the ITT population and Subgroup 2 in Table A2 of this clarification letter.

Please see below and overleaf Table A2 completed with the missing baseline characteristics, as requested.

Table A2 Baseline characteristics in Study 305– ITT population and Subgroup 2

Characteristic	**ITT population**			**Subgroup 2**		
	Eribulin (n = 508)	**TPC (n = 254)**	**Total (n = 762)**	**Eribulin (n = 370)**	**TPC (n = 189)**	**Total (n =559)**
Median Age (range)	55.0 years (28–85)	55.0 years (27–81)	55.0 years (27–85)	55.0 years (28-80)	56.0 years (27-78)	55.0 years (28-80)
Age distribution, n (%)						
< 40 yrs	34 (6.7)	17 (6.7)	51 (6.7)	24 (6.5)	15 (7.9)	39 (7.0)
≥ 40 – < 65 yrs	380 (74.8)	180 (70.9)	560 (73.5)	280 (75.7)	133 (70.4)	413 (73.9)
≥ 65 yrs	94 (18.5)	57 (22.4)	151 (19.8)	66 (17.8)	41 (21.7)	107 (19.1)
Race, n (%)						
Caucasian	470 (92.5)	233 (91.7)	703 (92.3)	346 (93.5)	174 (92.1)	520 (93.0)
Black	20 (3.9)	14 (5.5)	34 (4.5)	13 (3.5)	10 (5.3)	23 (4.1)
Asian/Pacific Islander	3 (0.6)	2 (0.8)	5 (0.7)	1 (0.3)	2 (1.1)	3 (0.5)
Other	15 (3.0)	5 (2.0)	20 (2.6)	10 (2.7)	3 (1.6)	13 (2.3)

Characteristic	ITT population			Subgroup 2		
	Eribulin (n = 508)	**TPC (n = 254)**	**Total (n = 762)**	**Eribulin (n = 370)**	**TPC (n = 189)**	**Total (n =559)**
Geographic region, n (%)						
North America, Western Europe, Australia	325 (64.0)	163 (64.2)	488 (64.0)	258 (69.7)	131 (69.3)	389 (69.6)
Eastern Europe	129 (25.4)	64 (25.2)	193 (25.3)	77 (20.8)	40 (21.2)	117 (20.9)
Latin America, South Africa	54 (10.6)	27 (10.6)	81 (10.6)	35 (9.5)	18 (9.5)	53 (9.5)
Reproductive status, n (%)						
Fertile	46 (9.1)	20 (7.9)	66 (8.7)	33 (8.9)	14 (7.4)	47 (8.4)
Post-menopausal	379 (74.6)	199 (78.3)	578 (75.9)	280 (75.7)	150 (79.4)	430 (76.9)
Surgically sterile	78 (15.4)	35 (13.8)	113 (14.8)	53 (14.3)	25 (13.2)	78 (14.0)
Infertile	5 (1.0)	0	5 (0.7)	4 (1.1)	0 (0.0)	4 (0.7)
Median time since original diagnosis (range)	5.4 years (0.1, 37.4)	5.1 years (0.6, 22.9)	5.2 years (0.1, 37.4)	5.7 years (0.1, 37.4)	5.3 years (0.6, 22.9)	5.6 years (0.1, 37.4)
ER Status, n (%)†						
+	336 (70.0)	171 (70.4)	507 (70.1)	257 (69.5)	130 (68.8)	387 (69.2)
–	143 (29.8)	72 (29.6)	215 (29.7)	99 (26.8)	54 (28.6)	153 (27.3)
Not done				13 (3.5)	5 (2.6)	18 (3.2)
Unknown	1 (0.2)	0	1 (0.1)	1 (0.3)	0	1 (0.2)
PR Status, n (%)†						
+	254 (56.2)	123 (54.7)	377 (55.7)	195 (52.7)	93 (49.2)	288 (51.5)
–	197 (43.6)	102 (45.3)	299 (44.2)	141 (38.1)	78 (41.3)	219 (39.2)
Not done				33 (8.9)	18 (9.5)	51 (9.1)
Unknown	1 (0.2)	0	1 (0.1)	1 (0.3)	0	1 (0.2)
HER2 status, n (%)†						
+	83 (18.0)	40 (17.2)	123 (17.8)	60 (16.2)	29 (15.3)	89 (15.9)
–	373 (81.1)	192 (82.8)	565 (81.6)	285 (77.0)	149 (78.8)	434 (77.6)
Unknown	4 (0.9)	0	4 (0.6)	25 (6.8)	11 (5.8)	36 (6.4)
Triple negative (ER/PR/HER2-negative), n (%)†	93 (18.3)	51 (20.9)	144 (19.8)	68 (18.4)	38 (20.1)	106 (19.0)

Characteristic	ITT population			Subgroup 2		
	Eribulin (n = 508)	**TPC (n = 254)**	**Total (n = 762)**	**Eribulin (n = 370)**	**TPC (n = 189)**	**Total (n =559)**
No. of organs involved‡, n (%)						
1	85 (16.7)	35 (13.8)	120 (15.7)	61 (16.5)	25 (13.2)	86 (15.3)
2	172 (33.9)	82 (32.3)	254 (33.3)	128 (34.6)	59 (31.2)	187 (33.4)
3	145 (28.5)	77 (30.3)	222 (29.1)	106 (28.6)	60 (31.7)	166 (29.7)
4	71 (14.0)	37 (14.6)	108 (14.2)	49 (13.2)	29 (15.3)	78 (14.0)
5	24 (4.7)	16 (6.3)	40 (5.2)	18 (4.9)	10 (5.3)	28 (5.0)
≥ 6	9 (1.8)	7 (2.8)	16 (2.1)	6 (1.6)	6 (3.2)	12 (2.1)
Tumour sites in > 10% patients overall, n (%)						
Bone	306 (60.2)	158 (62.2)	464 (60.9)	234 (63.2)	120 (63.5)	354 (63.3)
Liver	296 (58.3)	159 (62.6)	455 (59.7)	225 (60.8)	127 (67.2)	352 (63.0)
Lymph nodes	220 (43.3)	118 (46.5)	338 (44.4)	150 (40.5)	87 (46.0)	237 (42.4)
Lung	197 (38.8)	95 (37.4)	292 (38.3)	138 (37.3)	67 (35.4)	205 (36.7)
Pleura	87 (17.1)	42 (16.5)	129 (16.9)	62 (16.8)	34 (18.0)	96 (17.2)
Breast	54 (10.6)	24 (9.4)	78 (10.2)	30 (8.1)	13 (6.9)	43 (7.7)
ECOG performance status, n (%)						
0	217 (42.7)	103 (40.6)	320 (42.0)	154 (41.6)	80 (42.3)	234 (41.9)
1	244 (48.0)	126 (49.6)	370 (48.6)	179 (48.4)	90 (47.6)	269 (44.9)
2	39 (7.7)	22 (8.7)	61 (8.0)	30 (8.1)	16 (8.5)	46 (8.2)
No. of prior chemotherapy regimens (adjuvant and LABC/MBC setting), n (%)						
1	1 (0.2)	0	1 (0.1)	1 (0.3)	0 (0.0)	1 (0.2)
2	65 (12.8)	31 (12.2)	96 (12.6)	17 (4.6)	11 (5.8)	28 (5.0)
3	176 (34.6)	83 (32.7)	259 (34.0)	122 (33.0)	51 (27.0)	173 (30.9)
4	166 (32.7)	79 (31.1)	245 (32.2)	142 (38.4)	69 (36.5)	211 (37.7)
5	85 (16.7)	51 (20.1)	136 (17.8)	74 (20.0)	48 (25.4)	122 (21.8)
≥ 6	13 (2.6)	9 (3.5)	22 (2.9)	13 (3.5)	9 (4.8)	22 (3.9)

Characteristic	ITT population			Subgroup 2		
	Eribulin (n = 508)	**TPC (n = 254)**	**Total (n = 762)**	**Eribulin (n = 370)**	**TPC (n = 189)**	**Total (n =559)**
No. of prior regimens in LABC/MBC setting, n (%)						
0	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	8 (1.6)	7 (2.8)	15 (2.0)	2 (0.5)	2 (1.1)	4 (0.7)
2	219 (43.1)	90 (35.4)	309 (40.6)	130 (35.1)	53 (28.0)	183 (32.7)
3	163 (32.1)	83 (32.7)	246 (32.3)	132 (35.7)	67 (35.4)	199 (35.6)
4	92 (18.1)	55 (21.7)	147 (19.3)	81 (21.9)	48 (25.4)	129 (23.1)
5	21 (4.1)	13 (5.1)	34 (4.5)	21 (5.7)	13 (6.9)	24 (6.1)
≥ 6	4 (0.8)	5 (2.0)	9 (1.2)	4 (1.1)	5 (2.6)	9 (1.6)
Duration of last chemotherapy (months), Median (min, max)[‡]	3.57 (0.0, 32.0)	3.50 (0.1, 25.3)	3.53 (0.0, 32.0)	3.8 (0.0, 32.0)	3.7 (0.1, 25.3)	3.7 (0.0, 32.0)
No. of patients who previously (adjuvant and LABC/MBC setting) received: n (%)						
Taxanes	503 (99.0)	251 (98.8)	754 (99.0)	365 (98.6)	186 (98.4)	551 (98.6)
Anthracyclines	502 (98.8)	250 (98.4)	752 (98.7)	365 (98.6)	185 (97.9)	550 (98.4)
Capecitabine	370 (72.8)	189 (74.4)	559 (73.4)	370 (100.0)	189 (100.0)	559 (100.0)

†For the ER, PR, HER2 and triple negative status, the percentages are calculated from the total number of patients tested
‡The number of organs involved was based on the investigator review data
Source: Eisai Ltd data on file 95% OS data additional info for ERG

A8. Please provide in Table A3 of this clarification letter the number and proportion of patients who received subsequent treatment (including any crossover to eribulin, if this occurred) on disease progression with details about the subsequent treatment, for both the complete ITT population and Subgroup 2.

As requested, please see below and overleaf a table with the number and proportion of patients who received subsequent treatment on disease progression with details about the subsequent treatment for both the complete ITT population and Subgroup 2.

Subsequent Treatment Received after Discontinuation of Study Treatment
ITT Population and Post-Capecitabine patients (95% OS cutoff)

	ITT population			Post-Capecitabine Patients		
Preferred Term/Drug Name	Eribulin (N=508) n (%)	TPC (N=254) n (%)	Total (N=762) n (%)	Eribulin (N=370) n (%)	TPC (N=189) n (%)	Total (N=559) n (%)
Overall	394(77.56)	164(64.57)	558(73.23)	290(78.38)	123(65.08)	413(73.88)
ANASTROZOLE	6(1.18)	3(1.18)	9(1.18)	4(1.08)	1(0.53)	5(0.89)
BEVACIZUMAB	16(3.15)	3(1.18)	19(2.49)	14(3.78)	2(1.06)	16(2.86)
BIOFLAVONOIDS	1(0.20)	0(0.00)	1(0.13)	1(0.27)	0(0.00)	1(0.18)
CAPECITABINE	58(11.42)	6(2.36)	64(8.40)	8(2.16)	0(0.00)	8(1.43)
CARBOPLATIN	20(3.94)	12(4.72)	32(4.20)	17(4.59)	10(5.29)	27(4.83)
CARBOPLATIN W/GEMCITABINE HYDROCHLORIDE	2(0.39)	1(0.39)	3(0.39)	2(0.54)	1(0.53)	3(0.54)
CETUXIMAB	1(0.20)	0(0.00)	1(0.13)	1(0.27)	0(0.00)	1(0.18)
CHEMOTHERAPEUTICS NOS	0(0.00)	1(0.39)	1(0.13)	0(0.00)	0(0.00)	0(0.00)
CHEMOTHERAPY	1(0.20)	0(0.00)	1(0.13)	1(0.27)	0(0.00)	1(0.18)
CISPLATIN	11(2.17)	7(2.76)	18(2.36)	9(2.43)	6(3.17)	15(2.68)
CYCLOPHOSPHAMID W/DOXORUBICIN	1(0.20)	0(0.00)	1(0.13)	1(0.27)	0(0.00)	1(0.18)
CYCLOPHOSPHAMIDE	22(4.33)	10(3.94)	32(4.20)	21(5.68)	9(4.76)	30(5.37)
DOCETAXEL	20(3.94)	9(3.54)	29(3.81)	14(3.78)	7(3.70)	21(3.76)
DOXORUBICIN	40(7.87)	7(2.76)	47(6.17)	31(8.38)	4(2.12)	35(6.26)
EPIRUBICIN	3(0.59)	4(1.57)	7(0.92)	3(0.81)	4(2.12)	7(1.25)
ETOPOSIDE	3(0.59)	3(1.18)	6(0.79)	3(0.81)	3(1.59)	6(1.07)
EXEMESTANE	16(3.15)	6(2.36)	22(2.89)	15(4.05)	4(2.12)	19(3.40)
FLUOROURACIL	14(2.76)	5(1.97)	19(2.49)	12(3.24)	4(2.12)	16(2.86)
FOLINIC ACID	1(0.20)	0(0.00)	1(0.13)	0(0.00)	0(0.00)	0(0.00)

Note: Post-Capecitabine patients include all patients who previously received Capecitabine as anti-cancer therapy before study.

Subsequent Treatment Received after Discontinuation of Study Treatment
ITT Population and Post-Capecitabine patients (95% OS cutoff)

	ITT Population			Post-Capecitabine Patients		
Preferred Term/Drug Name	Eribulin (N=508) n (%)	TPC (N=254) n (%)	Total (N=762) n (%)	Eribulin (N=370) n (%)	TPC (N=189) n (%)	Total (N=559) n (%)
FULVESTRANT	16(3.15)	4(1.57)	20(2.62)	15(4.05)	3(1.59)	18(3.22)
GALENIC /CISPLATIN/FLUOROURACIL/	0(0.00)	1(0.39)	1(0.13)	0(0.00)	1(0.53)	1(0.18)
GEMCITABINE	34(6.69)	24(9.45)	58(7.61)	29(7.84)	17(8.99)	46(8.23)
GOSERELIN	0(0.00)	1(0.39)	1(0.13)	0(0.00)	1(0.53)	1(0.18)
HORMONE THERAPY	0(0.00)	1(0.39)	1(0.13)	0(0.00)	0(0.00)	0(0.00)
INVESTIGATIONAL DRUG	2(0.39)	0(0.00)	2(0.26)	2(0.54)	0(0.00)	2(0.36)
IXABEPILONE	14(2.76)	16(6.30)	30(3.94)	11(2.97)	15(7.94)	26(4.65)
LAPATINIB	6(1.18)	1(0.39)	7(0.92)	3(0.81)	1(0.53)	4(0.72)
LETROZOLE	9(1.77)	6(2.36)	15(1.97)	5(1.35)	5(2.65)	10(1.79)
MASTECTOMY	0(0.00)	1(0.39)	1(0.13)	0(0.00)	1(0.53)	1(0.18)
MEDROXYPROGESTERONE	0(0.00)	1(0.39)	1(0.13)	0(0.00)	0(0.00)	0(0.00)
MEGESTROL	5(0.98)	4(1.57)	9(1.18)	2(0.54)	4(2.12)	6(1.07)
MELPHALAN	0(0.00)	1(0.39)	1(0.13)	0(0.00)	0(0.00)	0(0.00)
METHOTREXATE	16(3.15)	6(2.36)	22(2.89)	15(4.05)	6(3.17)	21(3.76)
MILTEFOSINE	1(0.20)	0(0.00)	1(0.13)	1(0.27)	0(0.00)	1(0.18)
MITOMYCIN	9(1.77)	0(0.00)	9(1.18)	7(1.89)	0(0.00)	7(1.25)
MITOXANTRONE	1(0.20)	0(0.00)	1(0.13)	0(0.00)	0(0.00)	0(0.00)
OXALIPLATIN	0(0.00)	5(1.97)	5(0.66)	0(0.00)	5(2.65)	5(0.89)
PACLITAXEL	42(8.27)	15(5.91)	57(7.48)	39(10.54)	12(6.35)	51(9.12)
PAMIDRONIC ACID	2(0.39)	2(0.79)	4(0.52)	2(0.54)	2(1.06)	4(0.72)
PREDNISOLONE	1(0.20)	2(0.79)	3(0.39)	0(0.00)	2(1.06)	2(0.36)

Note: Post-Capecitabine patients include all patients who previously received Capecitabine as anti-cancer therapy before study.

Subsequent Treatment Received after Discontinuation of Study Treatment
ITT Population and Post-Capecitabine patients (95% OS cutoff)

	ITT Population			Post-Capecitabine Patients		
Preferred Term/Drug Name	Eribulin (N=508) n (%)	TPC (N=254) n (%)	Total (N=762) n (%)	Eribulin (N=370) n (%)	TPC (N=189) n (%)	Total (N=559) n (%)
RADIOTHERAPY	14(2.76)	4(1.57)	18(2.36)	12(3.24)	3(1.59)	15(2.68)
RADIOTHERAPY TO BONE	4(0.79)	0(0.00)	4(0.52)	3(0.81)	0(0.00)	3(0.54)
RADIOTHERAPY TO BRAIN	16(3.15)	4(1.57)	20(2.62)	14(3.78)	4(2.12)	18(3.22)
RADIOTHERAPY TO BREAST	2(0.39)	0(0.00)	2(0.26)	1(0.27)	0(0.00)	1(0.18)
TAMOXIFEN	7(1.38)	5(1.97)	12(1.57)	5(1.35)	5(2.65)	10(1.79)
TAXOL W/CARBOPLATIN	0(0.00)	2(0.79)	2(0.26)	0(0.00)	1(0.53)	1(0.18)
TEGAFUR	2(0.39)	0(0.00)	2(0.26)	1(0.27)	0(0.00)	1(0.18)
TEMOZOLOMIDE	2(0.39)	0(0.00)	2(0.26)	1(0.27)	0(0.00)	1(0.18)
THIOTEPA	0(0.00)	1(0.39)	1(0.13)	0(0.00)	1(0.53)	1(0.18)
TRABECTEDIN	1(0.20)	2(0.79)	3(0.39)	1(0.27)	2(1.06)	3(0.54)
TRASTUZUMAB	11(2.17)	6(2.36)	17(2.23)	7(1.89)	5(2.65)	12(2.15)
TRIPTORELIN	1(0.20)	0(0.00)	1(0.13)	1(0.27)	0(0.00)	1(0.18)
VINBLASTINE	2(0.39)	0(0.00)	2(0.26)	1(0.27)	0(0.00)	1(0.18)
VINDESINE	5(0.98)	2(0.79)	7(0.92)	5(1.35)	2(1.06)	7(1.25)
VINORELBINE	49(9.65)	17(6.69)	66(8.66)	41(11.08)	9(4.76)	50(8.94)
ZOLEDRONIC ACID	2(0.39)	2(0.79)	4(0.52)	1(0.27)	2(1.06)	3(0.54)

Note: Post-Capecitabine patients include all patients who previously received Capecitabine as anti-cancer therapy before study.

Source: Eisai Ltd data on file 95% OS data additional info for ERG

A9. Please clarify whether any adverse event data has been collected specifically for Subgroup 2 in Study 305 and if so, whether there are any notable differences in the types of any adverse events experienced in this subgroup compared with the overall safety population.

The adverse event data available for Subgroup 2 indicates that there are no notable differences experienced in this subgroup compared with the overall population.

Please see the table overleaf which compares the incidences of the most common adverse events in the ITT population from Study 305 (Table 34 in the CS) versus the incidence of the same adverse events in Subgroup 2.

Most commonly reported adverse events by treatment group: Study 305 (EMBRACE) ITT Population and Study 305 (EMBRACE) Subgroup 2; > 10% of patients in either study arm, all CTCAE grades)

	Study 305 (EMBRACE) ITT Population					Study 305 (EMBRACE) Subgroup 2	
System organ class AEs	**Eribulin N=503 n (%)**	**TPC N=247 n (%)**	**Vin. N=61 n (%)**	**Gem. N=46 n (%)**	**Cape. N=44 n (%)**	**Eribulin N=367 n (%)**	**TPC N=183 n (%)**
Blood and Lymphatic							
Neutropenia	260 (51.7%)	73 (29.6 %)	30 (49.2%)	17 (37.0%)	2 (4.5%)	201 (54.8%)	62 (33.9%)
Anaemia	94 (18.7%)	56 (22.7%)	13 (21.3%)	9 (19.6%)	10 (22.7%)	69 (18.8%)	44 (24.0%)
Leucopoenia	116 (23.1%)	28 (11.3%)	10 (16.4%)	8 (17.4%)	1 (2.3%)	85 (23.2%)	23 (12.6%)
Gastrointestinal							
Nausea	174 (34.6%)	70 (28.3%)	19 (31.1%)	18 (39.1%	9 (20.5%)	143 (39.0%)	52 (28.4%)
Constipation	124 (24.7%)	51 (20.6%)	24 (39.3%)	9 (19.6%)	6 (13.6%)	91 (24.8%)	41 (22.4%)
Diarrhoea	92 (18.3%)	45 (18.2%)	14 (23.0%)	9 (19.6%)	12 (27.3%)	66 (18.0%)	30 (16.4%)
Vomiting	91 (18.1%)	44 (17.8%)	13 (21.3%)	10 (21.7%)	10 (22.7%)	79 (21.5%)	29 (15.8%)
General disorders and administration site							
Asthenia/fatigue	270 (53.7%)	98 (39.7%)	31 (50.8%)	17 (37.0%)	17 (38.6%)	209 (56.9%)	75 (41%)
Pyrexia	105 (20.9%)	31 (12.6%)	6 (9.8%)	8 (17.4%)	6 (13.6%)	81 (22.1%)	19 (10.4%)
Mucosal inflammation	43 (8.5%)	25 (10.1%)	3 (4.9%)	3 (6.5%)	7 (15.9%)	<10%	<10%
Investigations							
Weight decreased	107 (21.3%)	35 (14.2%)	10 (16.4%)	5 (10.9%)	6 (13.6%)	83 (22.6%)	26 (14.2%)
Metabolism and nutrition							
Anorexia	98 (19.5%)	32 (13.0%)	11 (18.0%)	6 (13.0%)	6 (13.6%)	80 (21.8%)	23 (12.6%)
Musculoskeletal and connective tissue							
Arthralgia/ myalgia	109 (21.7%)	29 (11.7%)	7 (11.5%)	3 (6.5%)	8 (18.2%)	95 (25.9%)	19 (10.4%)
Back pain	79 (15.7%)	18 (7.3%)	7 (11.5%)	2 (4.3%)	4 (9.1%)	63 (17.2%)	14 (7.7%)
Bone pain	60 (11.9%)	23 (9.3%)	5 (8.2%)	4 (8.7%)	2 (4.5%)	49 (13.4%)	15 (8.2%)
Pain in extremity	57 (11.3%)	25 (10.1%)	11 (18.0%)	2 (4.3%)	8 (18.2%)	45 (12.3%)	16 (8.7%)
Nervous system							
Headache	97 (19.3%)	29 (11.7%)	9 (14.8%)	6 (13.0%)	8 (18.2%)	74 (20.2%)	18 (9.8%)
Peripheral neuropathy[†]	174 (34.6%)	40 (16.2%)	12 (19.7%)	2 (4.3%)	5 (11.4%)	142 (38.7%)	36 (19.7%)
Respiratory, thoracic and mediastinal							
Dyspnoea	79 (15.7%)	31 (12.6%)	7 (11.5%)	6 (13.0%)	3 (6.8%)	65 (17.7%)	27 (14.8%)
Cough	72 (14.3%)	21 (8.5%)	4 (6.6%)	7 (15.2%)	3 (6.8%)	52 (14.2%)	15 (8.2%)
Skin and subcutaneous tissue							
Alopecia	224 (44.5%)	24 (9.7%)	2 (3.3%)	3 (6.5%)	3 (6.8%)	181 (49.3%)	20 (10.9%)
Palmar-plantar erythrodysaesthesia syndrome	7 (1.4%)	34 (13.8%)	0	0	19 (43.2%)	4 (1.1%)	14 (7.7%)

Source: Eisai Ltd data on file 95% OS data additional info for ERG

Study 301

A10. For health-related quality of life (HRQoL) data, please provide the following information:

a. The number of patients for which data were available for Subgroup 2.

As mentioned in Figure 18 of the CS, the number of patients on eribulin is 158 and the number of patients on capecitabine is 151 for Subgroup 2. The number of patients constitutes the patients alive at baseline. The table below presents the proportion of patients that completed the questionnaire at the scheduled visits.

b. The numbers of patients represented in each bar of Figure 18 of the CS.

The table below presents the number of patients for each bar in the Figure 18 bar chart:

	Baseline	6 weeks	3 months	6 months	12 months	18 months	24 months
Eribulin ITT	536	(450	329	167	56	22	13
Eribulin 3rd line plus	148	118	86	46	17	6	5
Capecitabine ITT	526	419	299	170	63	24	15
Capecitabine 3rd line plus	147	122	75	44	17	9	6

Pooled analysis

A11. Please clarify why the published paper of the pooled analysis of Study 301 and Study 305 was not considered eligible for inclusion in the systematic review for Subgroup 2 (Section 4.1; page 46 of the CS)?

The published paper of the pooled analysis was considered out of scope in the systematic review for Subgroup 2 due to the inclusion of patient data from earlier lines of therapy. In other words, a proportion of patients included in the pooled analysis had received less than two prior treatments.

A12. Please clarify whether the results from the pooled analysis of Study 301 and Study 305 provide evidence for the use of eribulin specifically for Subgroup 2 or for a different patient population?

The pooled analysis results included in the CS have been estimated based on the ITT population of both studies 301 and 305.

Subgroup 2 is a subgroup of study 305. Subgroup 2 patients have been included in the pool of patients mentioned above.

A pooled analysis of patients enrolled in Study 301 and Study 305 for the patient population described under Subgroup 2 would not be meaningful since it would include:

- Study 305 patients as described by subgroup 2
- Study 301 patients on eribulin that had received two prior therapies including capecitabine. All capecitabine patients would need to be excluded due to the prior capecitabine usage inclusion criterion.

A13. Please describe in more detail how data were pooled from Study 301 and Study 305 for the pooled analysis. Specifically, please provide:

a. The data inputs from Study 301 and Study 305.

Individual patient data from Study 301 and Study 305 are used as data inputs for stratified log-rank tests and Cox regression models.

b. The methodology, statistical program and code used to perform this analysis.

In the pooled analysis, adjustment for study was necessary due to the 2:1 randomisation in Study 305. The median OS and PFS were derived from survival curves adjusted by study using methodology outlined by Chang et al. and Makuch [1, 2].

Stratified Cox regression analysis was used to calculate hazard ratios (HRs) for OS and PFS and p values for HRs were generated based on two-sided stratified log-rank tests. The stratification factors were geographical region, previous capecitabine use, HER2 status and study for analyses of the overall population. The stratification factors for analyses in patients with HER2 negative disease, the stratification factors are geographical region, previous capecitabine use, triple-negative status and study. The triple-negative status is defined as negative for HER2, estrogen receptors (ER), and progesterone receptors (PR).

The geographical regions are defined as:

Region 1: North America, Western Europe, Australia;
Region 2: Latin and South America;
Region 3: Eastern Europe;
Region 4: Asia,

1. Change IM, et al (1982) Corrected group prognostic curves and summary statistics. J. Chronic Dis 35: 669-674

2. Makuch RW (1982) Adjusted survival curve estimation using covariates. J Chronic Dis 35: 437-443

For overall population:

SAS program code for stratified Cox regression analysis:

```
proc phreg data=getdata ;
   strata  region priorcap her2 study;
   model   time*censor(1) = treat/ties=exact risklimits;
   test    treat;
run ;
```

SAS program code for stratified log-rank test:

```
proc lifetest data=getdata;
 strata region priorcap her2 study;
 time time*censor(1);
 test treat;
run;
```

For patients with HER2-negative disease:

SAS program code for stratified Cox regression analysis:

```
proc phreg data=getdata ;
strata  region priorcap tripneg study;
model   time*censor(1) = treat/ties=exact risklimits;
test    treat;
run ;
```

SAS program code for stratified log-rank test:

```
proc lifetest data=getdata;
 strata region priorcap tripneg study;
 time time*censor(1);
 test treat;
run;
```

(The variable names shown in SAS program code are for illustration purpose and may not be the same exact names of the actual variables in database.)

Section B: Clarification on cost-effectiveness data

B1. **Priority Question**: Please provide the following Kaplan-Meier analyses (listed in a to d below) to the following specification:

Population: Use subset of Study 305 patients who have progressed after two chemotherapeutic regimens and had received capecitabine previously, including all patients lost to follow-up or withdrawing from trial.

Trial data set: Study 305 latest data cut.

Format: Please present analysis outputs using the format of the sample table (B1) in this clarification.

a. Time to death from any cause (OS) Kaplan-Meier analysis stratified by treatment arm (eribulin vs Treatment of Physician's Choice [TPC]).

Interval		Total	Deaths	Lost	Survival	Error	[95% Conf. Int.]	
TPC								
10	11	126	0	1	1	0	.	.
22	23	125	2	0	0.984	0.0112	0.9375	0.996
25	26	123	1	0	0.976	0.0137	0.9274	0.9922
29	30	122	1	0	0.968	0.0157	0.917	0.9879
31	32	121	1	0	0.96	0.0175	0.9066	0.9832
35	36	120	0	1	0.96	0.0175	0.9066	0.9832
36	37	119	2	0	0.9439	0.0206	0.8859	0.9728
37	38	117	2	0	0.9277	0.0232	0.8657	0.9617
42	43	115	1	0	0.9197	0.0244	0.8558	0.956
44	45	114	2	0	0.9035	0.0265	0.8364	0.944
49	50	112	2	0	0.8874	0.0284	0.8173	0.9317
57	58	110	1	0	0.8793	0.0292	0.8078	0.9254
70	71	109	1	0	0.8713	0.03	0.7985	0.9191
73	74	108	1	0	0.8632	0.0308	0.7892	0.9126

88	89	107	1	0	0.8551	0.0316	0.7799	0.9061
89	90	106	2	0	0.839	0.033	0.7616	0.893
91	92	104	2	1	0.8228	0.0343	0.7434	0.8795
100	101	101	2	0	0.8065	0.0355	0.7253	0.8659
104	105	99	1	0	0.7983	0.036	0.7163	0.859
108	109	98	1	0	0.7902	0.0366	0.7074	0.852
110	111	97	1	0	0.782	0.0371	0.6985	0.845
111	112	96	1	0	0.7739	0.0376	0.6896	0.838
116	117	95	1	0	0.7658	0.0381	0.6808	0.8309
120	121	94	1	0	0.7576	0.0385	0.672	0.8238
127	128	93	1	0	0.7495	0.039	0.6632	0.8167
141	142	92	1	0	0.7413	0.0394	0.6545	0.8095
143	144	91	1	0	0.7332	0.0398	0.6458	0.8023
144	145	90	1	0	0.725	0.0402	0.6371	0.795
149	150	89	2	0	0.7087	0.0409	0.6199	0.7804
156	157	87	1	0	0.7006	0.0412	0.6114	0.7731
157	158	86	1	0	0.6924	0.0415	0.6028	0.7657
161	162	85	1	0	0.6843	0.0418	0.5943	0.7584
162	163	84	1	0	0.6761	0.0421	0.5859	0.7509
165	166	83	1	0	0.668	0.0424	0.5774	0.7435
171	172	82	1	0	0.6599	0.0427	0.569	0.736
175	176	81	1	0	0.6517	0.0429	0.5606	0.7285
180	181	80	2	0	0.6354	0.0434	0.5439	0.7134
182	183	78	1	0	0.6273	0.0436	0.5356	0.7059
190	191	77	1	0	0.6191	0.0437	0.5273	0.6983
191	192	76	3	0	0.5947	0.0442	0.5026	0.6753
193	194	73	1	0	0.5865	0.0444	0.4944	0.6676
201	202	72	1	0	0.5784	0.0445	0.4862	0.6599
215	216	71	1	0	0.5702	0.0446	0.4781	0.6521
218	219	70	1	0	0.5621	0.0447	0.47	0.6444
219	220	69	1	0	0.554	0.0448	0.4619	0.6366
243	244	68	1	0	0.5458	0.0449	0.4538	0.6288

256	257	67	1	0	0.5377	0.0449	0.4457	0.6209
257	258	66	1	0	0.5295	0.045	0.4377	0.6131
265	266	65	1	0	0.5214	0.045	0.4297	0.6052
266	267	64	1	0	0.5132	0.0451	0.4217	0.5973
272	273	63	1	0	0.5051	0.0451	0.4138	0.5893
281	282	62	1	0	0.4969	0.0451	0.4059	0.5814
286	287	61	1	0	0.4888	0.0451	0.398	0.5734
306	307	60	1	0	0.4806	0.045	0.3901	0.5654
308	309	59	1	0	0.4725	0.045	0.3822	0.5574
309	310	58	1	0	0.4643	0.045	0.3744	0.5494
316	317	57	1	0	0.4562	0.0449	0.3666	0.5413
319	320	56	1	0	0.448	0.0448	0.3588	0.5332
321	322	55	1	0	0.4399	0.0448	0.351	0.5251
324	325	54	1	0	0.4318	0.0447	0.3433	0.517
326	327	53	2	0	0.4155	0.0444	0.3279	0.5006
332	333	51	1	0	0.4073	0.0443	0.3202	0.4924
344	345	50	1	0	0.3992	0.0442	0.3126	0.4842
348	349	49	1	0	0.391	0.044	0.3049	0.476
365	366	48	1	0	0.3829	0.0438	0.2973	0.4677
385	386	47	1	0	0.3747	0.0437	0.2898	0.4594
390	391	46	1	0	0.3666	0.0435	0.2822	0.4511
396	397	45	2	0	0.3503	0.043	0.2672	0.4344
400	401	43	1	0	0.3421	0.0428	0.2598	0.426
405	406	42	1	0	0.334	0.0425	0.2523	0.4176
411	412	41	1	0	0.3259	0.0423	0.2449	0.4091
433	434	40	1	0	0.3177	0.042	0.2376	0.4006
446	447	39	1	0	0.3096	0.0417	0.2302	0.3921
448	449	38	1	0	0.3014	0.0414	0.2229	0.3836
473	474	37	1	0	0.2933	0.0411	0.2156	0.375
488	489	36	1	0	0.2851	0.0407	0.2084	0.3664
495	496	35	1	0	0.277	0.0404	0.2011	0.3578
506	507	34	1	0	0.2688	0.04	0.1939	0.3492

551	552	33	1	0	0.2607	0.0396	0.1868	0.3405
566	567	32	1	0	0.2525	0.0392	0.1797	0.3318
571	572	31	1	0	0.2444	0.0388	0.1726	0.323
586	587	30	1	0	0.2362	0.0383	0.1655	0.3143
592	593	29	1	0	0.2281	0.0379	0.1585	0.3054
642	643	28	1	0	0.22	0.0374	0.1515	0.2966
650	651	27	1	0	0.2118	0.0369	0.1446	0.2877
661	662	26	1	0	0.2037	0.0363	0.1377	0.2788
668	669	25	1	0	0.1955	0.0358	0.1309	0.2698
680	681	24	1	0	0.1874	0.0352	0.1241	0.2608
703	704	23	1	0	0.1792	0.0346	0.1174	0.2517
717	718	22	1	0	0.1711	0.034	0.1107	0.2426
731	732	21	1	0	0.1629	0.0333	0.104	0.2335
754	755	20	1	0	0.1548	0.0326	0.0975	0.2242
761	762	19	1	0	0.1466	0.0319	0.0909	0.215
833	834	18	0	1	0.1466	0.0319	0.0909	0.215
839	840	17	1	0	0.138	0.0312	0.084	0.2052
851	852	16	1	0	0.1294	0.0304	0.0772	0.1954
857	858	15	1	0	0.1208	0.0296	0.0704	0.1855
869	870	14	1	0	0.1121	0.0287	0.0638	0.1755
895	896	13	1	0	0.1035	0.0278	0.0573	0.1655
896	897	12	1	0	0.0949	0.0267	0.0509	0.1553
945	946	11	1	0	0.0863	0.0257	0.0446	0.1449
996	997	10	1	0	0.0776	0.0245	0.0385	0.1345
1008	1009	9	1	0	0.069	0.0233	0.0326	0.1239
1010	1011	8	1	0	0.0604	0.0219	0.0269	0.1131
1076	1077	7	1	0	0.0518	0.0204	0.0214	0.1021
1089	1090	6	1	0	0.0431	0.0187	0.0162	0.0909
1244	1245	5	1	0	0.0345	0.0169	0.0114	0.0794
1421	1422	4	1	0	0.0259	0.0147	0.0071	0.0675
1443	1444	3	1	0	0.0173	0.0121	0.0034	0.0552
1515	1516	2	1	0	0.0086	0.0086	0.0008	0.0427

1716	1717	1	0	1	0.0086	0.0086	0.0008	0.0427
Interval eribulin		Total	Deaths	Lost	Survival	Error	[95% Conf. Int.]	
12	13	219	1	0	0.9954	0.0046	0.968	0.9994
18	19	218	1	0	0.9909	0.0064	0.964	0.9977
26	27	217	1	0	0.9863	0.0079	0.9581	0.9956
47	48	216	1	0	0.9817	0.009	0.9521	0.9931
48	49	215	1	0	0.9772	0.0101	0.946	0.9904
50	51	214	1	0	0.9726	0.011	0.94	0.9876
58	59	213	1	0	0.968	0.0119	0.9341	0.9846
61	62	212	1	0	0.9635	0.0127	0.9283	0.9816
62	63	211	2	0	0.9543	0.0141	0.9168	0.9752
81	82	209	1	0	0.9498	0.0148	0.9111	0.9719
83	84	208	1	0	0.9452	0.0154	0.9055	0.9685
89	90	207	1	0	0.9406	0.016	0.9	0.9651
91	92	206	1	0	0.9361	0.0165	0.8944	0.9616
93	94	205	1	0	0.9315	0.0171	0.889	0.9581
102	103	204	1	0	0.9269	0.0176	0.8835	0.9546
103	104	203	1	0	0.9224	0.0181	0.8781	0.951
104	105	202	1	0	0.9178	0.0186	0.8727	0.9474
109	110	201	1	0	0.9132	0.019	0.8674	0.9438
115	116	200	2	0	0.9041	0.0199	0.8567	0.9364
116	117	198	1	0	0.8995	0.0203	0.8514	0.9327
118	119	197	1	0	0.895	0.0207	0.8462	0.9289
119	120	196	1	0	0.8904	0.0211	0.841	0.9252
126	127	195	1	0	0.8858	0.0215	0.8357	0.9214
127	128	194	1	0	0.8813	0.0219	0.8306	0.9176
129	130	193	0	1	0.8813	0.0219	0.8306	0.9176
130	131	192	1	0	0.8767	0.0222	0.8253	0.9137
131	132	191	1	0	0.8721	0.0226	0.8202	0.9099
133	134	190	1	0	0.8675	0.0229	0.815	0.906
134	135	189	1	0	0.8629	0.0233	0.8098	0.9021

135	136	188	1	0	0.8583	0.0236	0.8047	0.8982
136	137	187	1	0	0.8537	0.0239	0.7996	0.8942
137	138	186	1	0	0.8491	0.0242	0.7945	0.8903
138	139	185	2	0	0.84	0.0248	0.7843	0.8824
139	140	183	1	0	0.8354	0.0251	0.7792	0.8784
147	148	182	1	0	0.8308	0.0254	0.7742	0.8744
161	162	181	1	0	0.8262	0.0256	0.7691	0.8704
162	163	180	1	0	0.8216	0.0259	0.7641	0.8663
180	181	179	1	0	0.817	0.0262	0.7591	0.8623
181	182	178	1	0	0.8124	0.0264	0.7541	0.8582
182	183	177	1	0	0.8078	0.0267	0.7491	0.8542
184	185	176	1	0	0.8032	0.0269	0.7441	0.8501
186	187	175	1	0	0.7987	0.0271	0.7391	0.846
188	189	174	1	0	0.7941	0.0274	0.7341	0.8419
192	193	173	1	0	0.7895	0.0276	0.7292	0.8378
193	194	172	1	0	0.7849	0.0278	0.7243	0.8337
196	197	171	2	0	0.7757	0.0282	0.7144	0.8255
203	204	169	1	0	0.7711	0.0284	0.7095	0.8213
204	205	168	2	0	0.7619	0.0288	0.6997	0.813
209	210	166	1	0	0.7573	0.029	0.6948	0.8089
213	214	165	1	0	0.7528	0.0292	0.6899	0.8047
217	218	164	1	0	0.7482	0.0294	0.6851	0.8005
218	219	163	1	0	0.7436	0.0296	0.6802	0.7963
225	226	162	1	0	0.739	0.0297	0.6753	0.7921
227	228	161	1	0	0.7344	0.0299	0.6705	0.7879
244	245	160	1	0	0.7298	0.0301	0.6657	0.7837
245	246	159	1	0	0.7252	0.0302	0.6608	0.7794
246	247	158	1	0	0.7206	0.0304	0.656	0.7752
247	248	157	1	0	0.716	0.0305	0.6512	0.771
248	249	156	1	0	0.7114	0.0307	0.6464	0.7667
253	254	155	1	0	0.7069	0.0308	0.6416	0.7625
256	257	154	1	0	0.7023	0.031	0.6368	0.7582

260	261	153	1	0	0.6977	0.0311	0.632	0.7539
264	265	152	1	0	0.6931	0.0312	0.6272	0.7497
268	269	151	2	0	0.6839	0.0315	0.6177	0.7411
269	270	149	1	0	0.6793	0.0316	0.6129	0.7368
270	271	148	1	0	0.6747	0.0317	0.6082	0.7325
271	272	147	2	0	0.6655	0.0319	0.5987	0.7239
272	273	145	1	0	0.661	0.032	0.594	0.7195
275	276	144	1	0	0.6564	0.0322	0.5893	0.7152
278	279	143	1	0	0.6518	0.0323	0.5845	0.7109
280	281	142	1	0	0.6472	0.0324	0.5798	0.7065
281	282	141	1	0	0.6426	0.0324	0.5751	0.7022
282	283	140	1	0	0.638	0.0325	0.5704	0.6978
283	284	139	1	0	0.6334	0.0326	0.5657	0.6935
286	287	138	1	0	0.6288	0.0327	0.5611	0.6891
287	288	137	1	0	0.6242	0.0328	0.5564	0.6847
288	289	136	1	0	0.6196	0.0329	0.5517	0.6804
292	293	135	1	0	0.6151	0.0329	0.547	0.676
300	301	134	1	0	0.6105	0.033	0.5424	0.6716
301	302	133	1	0	0.6059	0.0331	0.5377	0.6672
304	305	132	1	0	0.6013	0.0332	0.5331	0.6628
311	312	131	1	0	0.5967	0.0332	0.5284	0.6584
314	315	130	1	0	0.5921	0.0333	0.5238	0.654
326	327	129	2	0	0.5829	0.0334	0.5145	0.6451
327	328	127	1	0	0.5783	0.0334	0.5099	0.6407
330	331	126	1	0	0.5737	0.0335	0.5053	0.6362
335	336	125	1	0	0.5692	0.0335	0.5007	0.6318
339	340	124	2	0	0.56	0.0336	0.4915	0.6229
344	345	122	1	0	0.5554	0.0337	0.4869	0.6184
351	352	121	1	0	0.5508	0.0337	0.4823	0.614
355	356	120	1	0	0.5462	0.0337	0.4777	0.6095
365	366	119	1	0	0.5416	0.0337	0.4732	0.605
367	368	118	1	0	0.537	0.0338	0.4686	0.6006

373	374	117	2	0	0.5278	0.0338	0.4595	0.5916
379	380	115	3	0	0.5141	0.0338	0.4458	0.5781
382	383	112	1	0	0.5095	0.0339	0.4413	0.5736
384	385	111	1	0	0.5049	0.0339	0.4368	0.569
390	391	110	1	0	0.5003	0.0339	0.4323	0.5645
394	395	109	1	0	0.4957	0.0339	0.4277	0.56
395	396	108	1	0	0.4911	0.0339	0.4232	0.5554
399	400	107	1	0	0.4865	0.0339	0.4187	0.5509
401	402	106	1	0	0.4819	0.0338	0.4142	0.5464
403	404	105	1	0	0.4774	0.0338	0.4097	0.5418
404	405	104	1	0	0.4728	0.0338	0.4052	0.5372
407	408	103	1	0	0.4682	0.0338	0.4007	0.5327
410	411	102	1	0	0.4636	0.0338	0.3963	0.5281
412	413	101	1	0	0.459	0.0338	0.3918	0.5235
413	414	100	1	0	0.4544	0.0337	0.3873	0.519
414	415	99	1	0	0.4498	0.0337	0.3829	0.5144
419	420	98	1	0	0.4452	0.0337	0.3784	0.5098
420	421	97	1	0	0.4406	0.0336	0.374	0.5052
421	422	96	1	0	0.436	0.0336	0.3695	0.5006
430	431	95	1	0	0.4315	0.0335	0.3651	0.496
434	435	94	1	0	0.4269	0.0335	0.3606	0.4914
435	436	93	1	0	0.4223	0.0335	0.3562	0.4868
438	439	92	1	0	0.4177	0.0334	0.3518	0.4821
444	445	91	1	0	0.4131	0.0334	0.3474	0.4775
448	449	90	1	0	0.4085	0.0333	0.343	0.4729
449	450	89	0	1	0.4085	0.0333	0.343	0.4729
451	452	88	1	0	0.4039	0.0332	0.3385	0.4682
453	454	87	1	0	0.3992	0.0332	0.3341	0.4635
465	466	86	1	0	0.3946	0.0331	0.3296	0.4588
467	468	85	2	0	0.3853	0.033	0.3207	0.4494
470	471	83	1	0	0.3807	0.0329	0.3163	0.4447
478	479	82	2	0	0.3714	0.0328	0.3075	0.4352

480	481	80	1	0	0.3667	0.0327	0.303	0.4305
484	485	79	1	0	0.3621	0.0326	0.2986	0.4257
489	490	78	1	0	0.3574	0.0325	0.2942	0.421
491	492	77	1	0	0.3528	0.0324	0.2899	0.4162
492	493	76	1	0	0.3482	0.0323	0.2855	0.4115
506	507	75	1	0	0.3435	0.0322	0.2811	0.4067
514	515	74	1	0	0.3389	0.0321	0.2767	0.4019
515	516	73	1	0	0.3342	0.032	0.2724	0.3972
526	527	72	2	0	0.325	0.0318	0.2637	0.3876
527	528	70	1	0	0.3203	0.0317	0.2593	0.3828
529	530	69	1	0	0.3157	0.0315	0.255	0.378
537	538	68	1	0	0.311	0.0314	0.2507	0.3732
570	571	67	1	0	0.3064	0.0313	0.2463	0.3683
589	590	66	1	0	0.3017	0.0312	0.242	0.3635
591	592	65	1	0	0.2971	0.031	0.2377	0.3587
605	606	64	1	0	0.2925	0.0309	0.2334	0.3538
608	609	63	1	0	0.2878	0.0307	0.2291	0.349
622	623	62	1	0	0.2832	0.0306	0.2249	0.3441
643	644	61	1	0	0.2785	0.0304	0.2206	0.3393
650	651	60	1	0	0.2739	0.0303	0.2163	0.3344
651	652	59	1	0	0.2692	0.0301	0.2121	0.3295
661	662	58	1	0	0.2646	0.03	0.2078	0.3246
670	671	57	1	0	0.26	0.0298	0.2036	0.3197
671	672	56	1	0	0.2553	0.0296	0.1994	0.3148
677	678	55	1	0	0.2507	0.0294	0.1951	0.3099
690	691	54	1	0	0.246	0.0293	0.1909	0.305
693	694	53	1	0	0.2414	0.0291	0.1867	0.3
696	697	52	1	0	0.2367	0.0289	0.1825	0.2951
701	702	51	1	0	0.2321	0.0287	0.1783	0.2902
717	718	50	2	0	0.2228	0.0283	0.17	0.2802
719	720	48	1	0	0.2182	0.0281	0.1658	0.2753
736	737	47	1	0	0.2135	0.0279	0.1617	0.2703

747	748	46	1	0	0.2089	0.0276	0.1576	0.2653
763	764	45	1	0	0.2043	0.0274	0.1534	0.2603
776	777	44	1	0	0.1996	0.0272	0.1493	0.2553
781	782	43	1	0	0.195	0.0269	0.1452	0.2502
786	787	42	1	0	0.1903	0.0267	0.1411	0.2452
810	811	41	1	0	0.1857	0.0264	0.1371	0.2401
827	828	40	1	0	0.181	0.0262	0.133	0.2351
842	843	39	1	0	0.1764	0.0259	0.129	0.23
844	845	38	1	0	0.1718	0.0257	0.1249	0.2249
885	886	37	1	0	0.1671	0.0254	0.1209	0.2198
888	889	36	1	0	0.1625	0.0251	0.1169	0.2147
892	893	35	1	0	0.1578	0.0248	0.1129	0.2096
909	910	34	2	0	0.1485	0.0242	0.1049	0.1993
931	932	32	1	0	0.1439	0.0239	0.101	0.1941
934	935	31	1	0	0.1393	0.0236	0.0971	0.189
949	950	30	1	0	0.1346	0.0232	0.0931	0.1838
966	967	29	1	0	0.13	0.0229	0.0892	0.1785
972	973	28	1	0	0.1253	0.0225	0.0854	0.1733
976	977	27	1	0	0.1207	0.0222	0.0815	0.1681
1021	1022	26	1	0	0.1161	0.0218	0.0777	0.1628
1023	1024	25	1	0	0.1114	0.0214	0.0739	0.1575
1041	1042	24	1	0	0.1068	0.021	0.0701	0.1522
1042	1043	23	1	0	0.1021	0.0206	0.0663	0.1468
1048	1049	22	1	0	0.0975	0.0202	0.0626	0.1415
1054	1055	21	1	0	0.0928	0.0198	0.0589	0.1361
1089	1090	20	1	0	0.0882	0.0193	0.0552	0.1307
1206	1207	19	1	0	0.0836	0.0188	0.0515	0.1253
1218	1219	18	1	0	0.0789	0.0184	0.0479	0.1198
1236	1237	17	1	0	0.0743	0.0179	0.0443	0.1143
1327	1328	16	1	0	0.0696	0.0173	0.0408	0.1087
1418	1419	15	1	0	0.065	0.0168	0.0373	0.1032
1420	1421	14	1	0	0.0603	0.0162	0.0338	0.0975

1561	1562	13	1	0	0.0557	0.0156	0.0304	0.0919
1653	1654	12	0	1	0.0557	0.0156	0.0304	0.0919
1697	1698	11	0	1	0.0557	0.0156	0.0304	0.0919
1710	1711	10	0	1	0.0557	0.0156	0.0304	0.0919
1757	1758	9	1	0	0.0495	0.0151	0.0256	0.085
1788	1789	8	0	1	0.0495	0.0151	0.0256	0.085
1814	1815	7	0	1	0.0495	0.0151	0.0256	0.085
1835	1836	6	0	1	0.0495	0.0151	0.0256	0.085
1862	1863	5	0	1	0.0495	0.0151	0.0256	0.085
1883	1884	4	1	1	0.0354	0.0161	0.0127	0.0773
1996	1997	2	0	1	0.0354	0.0161	0.0127	0.0773
2010	2011	1	0	1	0.0354	0.0161	0.0127	0.0773

b. Time to disease progression or death (PFS) Kaplan-Meier analysis based on investigator assessment, stratified by treatment arm (eribulin vs TPC).

Interval TPC		Total	Deaths	Lost	Survival	Error	[95% Conf. Int.]	
1	2	122	11	9	0.9064	0.0269	0.8373	0.947
8	9	102	1	0	0.8975	0.028	0.8265	0.9405
11	12	101	1	0	0.8886	0.0291	0.8159	0.9338
22	23	100	2	0	0.8708	0.0311	0.7949	0.9201
23	24	98	1	0	0.862	0.0321	0.7845	0.9131
24	25	97	1	0	0.8531	0.0329	0.7742	0.906
28	29	96	1	0	0.8442	0.0338	0.764	0.8989
29	30	95	1	0	0.8353	0.0346	0.7539	0.8917
32	33	94	1	0	0.8264	0.0353	0.7439	0.8844
36	37	93	2	0	0.8086	0.0367	0.724	0.8696
37	38	91	1	0	0.7997	0.0374	0.7141	0.8622
39	40	90	1	0	0.7909	0.038	0.7043	0.8547
42	43	89	3	0	0.7642	0.0397	0.6752	0.8319
43	44	86	1	0	0.7553	0.0403	0.6655	0.8241

45	46	85	1	0	0.7464	0.0407	0.656	0.8164
47	48	84	1	0	0.7375	0.0412	0.6464	0.8086
48	49	83	1	0	0.7287	0.0417	0.637	0.8008
49	50	82	3	0	0.702	0.0429	0.6088	0.7771
50	51	79	4	0	0.6665	0.0443	0.5717	0.7449
51	52	75	1	0	0.6576	0.0445	0.5625	0.7368
52	53	74	2	0	0.6398	0.0451	0.5442	0.7205
53	54	72	1	0	0.6309	0.0453	0.5351	0.7123
54	55	71	2	0	0.6131	0.0458	0.517	0.6958
55	56	69	2	0	0.5954	0.0461	0.4991	0.6791
56	57	67	2	2	0.5773	0.0465	0.4809	0.6622
57	58	63	4	1	0.5404	0.047	0.444	0.6272
58	59	58	4	0	0.5031	0.0473	0.4072	0.5914
59	60	54	2	0	0.4845	0.0474	0.3891	0.5733
60	61	52	4	0	0.4472	0.0472	0.3532	0.5368
62	63	48	1	0	0.4379	0.0472	0.3443	0.5276
63	64	47	2	0	0.4193	0.047	0.3266	0.509
64	65	45	2	1	0.4004	0.0467	0.3088	0.4902
66	67	42	2	0	0.3813	0.0464	0.291	0.471
68	69	40	1	1	0.3717	0.0462	0.282	0.4613
71	72	38	1	0	0.3619	0.046	0.2729	0.4514
84	85	37	1	0	0.3521	0.0458	0.2638	0.4415
87	88	36	1	0	0.3424	0.0456	0.2548	0.4315
89	90	35	1	0	0.3326	0.0453	0.2459	0.4215
95	96	34	1	0	0.3228	0.045	0.237	0.4115
97	98	33	1	0	0.313	0.0447	0.2281	0.4014
99	100	32	0	1	0.313	0.0447	0.2281	0.4014
107	108	31	1	0	0.3029	0.0444	0.2189	0.391
113	114	30	2	0	0.2827	0.0437	0.2008	0.37
114	115	28	1	0	0.2726	0.0432	0.1919	0.3595
115	116	27	1	0	0.2625	0.0428	0.183	0.3488
116	117	26	2	0	0.2423	0.0418	0.1654	0.3274

119	120	24	3	0	0.212	0.0401	0.1395	0.2948
125	126	21	1	0	0.2019	0.0394	0.1311	0.2838
152	153	20	1	0	0.1918	0.0387	0.1227	0.2727
157	158	19	1	0	0.1817	0.038	0.1144	0.2616
165	166	18	1	0	0.1716	0.0372	0.1062	0.2503
167	168	17	1	0	0.1616	0.0364	0.0981	0.239
175	176	16	1	0	0.1515	0.0355	0.0901	0.2276
176	177	15	2	0	0.1313	0.0335	0.0745	0.2044
180	181	13	1	0	0.1212	0.0324	0.0668	0.1927
191	192	12	1	0	0.1111	0.0312	0.0594	0.1808
227	228	11	0	1	0.1111	0.0312	0.0594	0.1808
229	230	10	0	1	0.1111	0.0312	0.0594	0.1808
247	248	9	1	0	0.0987	0.0301	0.0499	0.1672
252	253	8	1	0	0.0864	0.0288	0.0409	0.1532
260	261	7	1	0	0.074	0.0272	0.0323	0.1388
281	282	6	1	0	0.0617	0.0253	0.0243	0.124
297	298	5	1	0	0.0494	0.023	0.0169	0.1086
324	325	4	1	0	0.037	0.0203	0.0104	0.0927
440	441	3	0	1	0.037	0.0203	0.0104	0.0927
460	461	2	1	0	0.0185	0.0166	0.002	0.0765
763	764	1	1	0	0	.	.	.

Interval							[95% Conf. Int.]	
Eribulin		Total	Deaths	Lost	Survival	Error		
1	2	223	7	7	0.9681	0.0119	0.9343	0.9847
12	13	209	1	0	0.9635	0.0127	0.9283	0.9816
16	17	208	1	0	0.9588	0.0134	0.9224	0.9784
23	24	207	1	0	0.9542	0.0141	0.9166	0.9751
26	27	206	1	0	0.9496	0.0148	0.9108	0.9718
28	29	205	1	0	0.9449	0.0155	0.9051	0.9684
34	35	204	2	0	0.9357	0.0166	0.8938	0.9614
35	36	202	1	0	0.9311	0.0172	0.8882	0.9579
36	37	201	1	0	0.9264	0.0177	0.8827	0.9543

40	41	200	2	0	0.9172	0.0187	0.8717	0.947
41	42	198	1	0	0.9125	0.0192	0.8663	0.9433
43	44	197	3	0	0.8986	0.0205	0.8501	0.9321
44	45	194	3	0	0.8847	0.0217	0.8342	0.9206
45	46	191	1	0	0.8801	0.0221	0.8289	0.9167
48	49	190	3	0	0.8662	0.0231	0.8132	0.905
49	50	187	4	0	0.8477	0.0244	0.7925	0.8892
50	51	183	5	0	0.8245	0.0259	0.7669	0.8691
52	53	178	1	0	0.8199	0.0261	0.7619	0.865
53	54	177	3	0	0.806	0.0269	0.7467	0.8527
54	55	174	1	0	0.8014	0.0271	0.7417	0.8486
55	56	173	3	0	0.7875	0.0278	0.7267	0.8362
56	57	170	4	0	0.7689	0.0287	0.7068	0.8196
57	58	166	6	0	0.7411	0.0298	0.6773	0.7943
58	59	160	4	0	0.7226	0.0304	0.6578	0.7773
59	60	156	3	0	0.7087	0.0309	0.6432	0.7644
60	61	153	2	0	0.6994	0.0312	0.6335	0.7558
61	62	151	2	0	0.6902	0.0315	0.6239	0.7472
62	63	149	3	0	0.6763	0.0318	0.6095	0.7342
63	64	146	4	0	0.6578	0.0323	0.5904	0.7168
64	65	142	1	0	0.6531	0.0324	0.5856	0.7124
65	66	141	1	0	0.6485	0.0325	0.5808	0.708
67	68	140	2	0	0.6392	0.0327	0.5714	0.6993
69	70	138	2	0	0.63	0.0328	0.5619	0.6904
70	71	136	2	0	0.6207	0.033	0.5524	0.6816
71	72	134	1	0	0.6161	0.0331	0.5477	0.6772
72	73	133	2	0	0.6068	0.0332	0.5383	0.6683
73	74	131	1	0	0.6022	0.0333	0.5336	0.6639
78	79	130	2	0	0.5929	0.0334	0.5243	0.655
83	84	128	1	0	0.5883	0.0335	0.5196	0.6505
85	86	127	3	0	0.5744	0.0336	0.5056	0.6371
92	93	124	2	0	0.5651	0.0337	0.4963	0.6282

100	101	122	1	0	0.5605	0.0338	0.4917	0.6237
101	102	121	4	0	0.542	0.0339	0.4732	0.6056
102	103	117	1	0	0.5373	0.0339	0.4686	0.6011
103	104	116	1	0	0.5327	0.0339	0.464	0.5966
107	108	115	2	0	0.5234	0.034	0.4548	0.5875
108	109	113	3	0	0.5095	0.034	0.441	0.5739
109	110	110	0	1	0.5095	0.034	0.441	0.5739
112	113	109	2	0	0.5002	0.034	0.4318	0.5647
113	114	107	3	0	0.4862	0.034	0.418	0.5508
114	115	104	4	0	0.4675	0.034	0.3997	0.5323
115	116	100	1	0	0.4628	0.034	0.3951	0.5277
116	117	99	0	1	0.4628	0.034	0.3951	0.5277
117	118	98	1	0	0.4581	0.0339	0.3905	0.523
118	119	97	1	0	0.4533	0.0339	0.3859	0.5183
120	121	96	1	0	0.4486	0.0339	0.3813	0.5136
121	122	95	4	0	0.4297	0.0337	0.363	0.4947
122	123	91	2	0	0.4203	0.0337	0.3538	0.4852
123	124	89	1	1	0.4155	0.0336	0.3493	0.4804
125	126	87	3	0	0.4012	0.0335	0.3355	0.466
126	127	84	0	1	0.4012	0.0335	0.3355	0.466
127	128	83	1	0	0.3964	0.0334	0.3308	0.4611
130	131	82	1	0	0.3915	0.0333	0.3262	0.4562
133	134	81	1	0	0.3867	0.0333	0.3215	0.4513
134	135	80	4	1	0.3672	0.033	0.3029	0.4316
139	140	75	1	0	0.3624	0.0329	0.2983	0.4266
142	143	74	1	0	0.3575	0.0328	0.2936	0.4217
147	148	73	1	0	0.3526	0.0327	0.289	0.4167
150	151	72	1	0	0.3477	0.0327	0.2843	0.4117
151	152	71	1	0	0.3428	0.0326	0.2797	0.4066
157	158	70	1	0	0.3379	0.0325	0.2751	0.4016
158	159	69	0	1	0.3379	0.0325	0.2751	0.4016
160	161	68	1	1	0.3329	0.0324	0.2703	0.3965

162	163	66	1	0	0.3278	0.0323	0.2656	0.3914
165	166	65	1	0	0.3228	0.0322	0.2608	0.3862
168	169	64	1	0	0.3177	0.0321	0.2561	0.381
169	170	63	2	0	0.3076	0.0318	0.2466	0.3706
171	172	61	1	0	0.3026	0.0317	0.2419	0.3654
174	175	60	2	0	0.2925	0.0314	0.2325	0.355
175	176	58	1	2	0.2874	0.0313	0.2277	0.3497
176	177	55	2	0	0.2769	0.031	0.218	0.3388
183	184	53	3	0	0.2613	0.0306	0.2035	0.3225
184	185	50	1	2	0.2559	0.0304	0.1986	0.317
185	186	47	0	1	0.2559	0.0304	0.1986	0.317
187	188	46	1	0	0.2504	0.0302	0.1934	0.3112
188	189	45	1	0	0.2448	0.0301	0.1883	0.3054
189	190	44	1	0	0.2392	0.0299	0.1831	0.2996
191	192	43	1	0	0.2337	0.0297	0.178	0.2938
192	193	42	1	0	0.2281	0.0295	0.173	0.288
197	198	41	1	0	0.2225	0.0293	0.1679	0.2821
202	203	40	1	0	0.217	0.0291	0.1629	0.2763
204	205	39	2	0	0.2059	0.0287	0.1528	0.2645
205	206	37	1	0	0.2003	0.0284	0.1478	0.2586
220	221	36	1	0	0.1947	0.0282	0.1429	0.2526
221	222	35	1	0	0.1892	0.0279	0.1379	0.2467
226	227	34	1	0	0.1836	0.0276	0.133	0.2407
230	231	33	1	0	0.178	0.0274	0.1281	0.2347
231	232	32	1	0	0.1725	0.0271	0.1232	0.2287
233	234	31	1	0	0.1669	0.0268	0.1184	0.2227
235	236	30	1	0	0.1613	0.0264	0.1136	0.2166
240	241	29	1	0	0.1558	0.0261	0.1088	0.2105
248	249	28	2	1	0.1445	0.0254	0.0991	0.1981
271	272	25	2	0	0.1329	0.0247	0.0892	0.1854
274	275	23	0	1	0.1329	0.0247	0.0892	0.1854
276	277	22	1	0	0.1269	0.0243	0.0841	0.1787

281	282	21	1	0	0.1208	0.0238	0.079	0.172
290	291	20	1	0	0.1148	0.0234	0.074	0.1653
295	296	19	1	0	0.1087	0.0229	0.069	0.1586
303	304	18	1	0	0.1027	0.0224	0.0641	0.1518
312	313	17	1	0	0.0967	0.0219	0.0592	0.1449
314	315	16	1	0	0.0906	0.0214	0.0544	0.138
338	339	15	1	0	0.0846	0.0208	0.0497	0.131
344	345	14	1	0	0.0785	0.0202	0.045	0.124
347	348	13	1	0	0.0725	0.0195	0.0404	0.1168
351	352	12	1	0	0.0664	0.0188	0.0359	0.1097
353	354	11	0	1	0.0664	0.0188	0.0359	0.1097
372	373	10	1	0	0.0598	0.018	0.031	0.1019
381	382	9	1	0	0.0532	0.0172	0.0262	0.0941
482	483	8	1	0	0.0465	0.0163	0.0215	0.0861
488	489	7	1	0	0.0399	0.0153	0.0171	0.0779
497	498	6	1	0	0.0332	0.0141	0.013	0.0695
567	568	5	1	0	0.0266	0.0127	0.0091	0.0608
579	580	4	1	0	0.0199	0.0112	0.0056	0.0519
620	621	3	1	0	0.0133	0.0092	0.0027	0.0426
623	624	2	0	1	0.0133	0.0092	0.0027	0.0426
645	646	1	0	1	0.0133	0.0092	0.0027	0.0426

c. Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis stratified by treatment arm (eribulin vs TPC).

Interval TPC		Total	Deaths	Lost	Survival	Error	[95% Conf. Int.]	
1	2	122	11	9	0.9064	0.0269	0.8373	0.947
8	9	102	1	0	0.8975	0.028	0.8265	0.9405
11	12	101	1	0	0.8886	0.0291	0.8159	0.9338
22	23	100	2	0	0.8708	0.0311	0.7949	0.9201

23	24	98	1	0	0.862	0.0321	0.7845	0.9131
24	25	97	1	0	0.8531	0.0329	0.7742	0.906
28	29	96	1	0	0.8442	0.0338	0.764	0.8989
29	30	95	1	0	0.8353	0.0346	0.7539	0.8917
32	33	94	1	0	0.8264	0.0353	0.7439	0.8844
36	37	93	2	0	0.8086	0.0367	0.724	0.8696
37	38	91	1	0	0.7997	0.0374	0.7141	0.8622
39	40	90	1	0	0.7909	0.038	0.7043	0.8547
42	43	89	3	0	0.7642	0.0397	0.6752	0.8319
43	44	86	1	0	0.7553	0.0403	0.6655	0.8241
45	46	85	1	0	0.7464	0.0407	0.656	0.8164
47	48	84	1	0	0.7375	0.0412	0.6464	0.8086
48	49	83	1	0	0.7287	0.0417	0.637	0.8008
49	50	82	3	0	0.702	0.0429	0.6088	0.7771
50	51	79	4	0	0.6665	0.0443	0.5717	0.7449
51	52	75	1	0	0.6576	0.0445	0.5625	0.7368
52	53	74	2	0	0.6398	0.0451	0.5442	0.7205
53	54	72	1	0	0.6309	0.0453	0.5351	0.7123
54	55	71	2	0	0.6131	0.0458	0.517	0.6958
55	56	69	2	0	0.5954	0.0461	0.4991	0.6791
56	57	67	2	2	0.5773	0.0465	0.4809	0.6622
57	58	63	4	1	0.5404	0.047	0.444	0.6272
58	59	58	4	0	0.5031	0.0473	0.4072	0.5914
59	60	54	2	0	0.4845	0.0474	0.3891	0.5733
60	61	52	4	0	0.4472	0.0472	0.3532	0.5368
62	63	48	1	0	0.4379	0.0472	0.3443	0.5276
63	64	47	2	0	0.4193	0.047	0.3266	0.509
64	65	45	2	1	0.4004	0.0467	0.3088	0.4902
66	67	42	2	0	0.3813	0.0464	0.291	0.471
68	69	40	1	1	0.3717	0.0462	0.282	0.4613
71	72	38	1	0	0.3619	0.046	0.2729	0.4514
84	85	37	1	0	0.3521	0.0458	0.2638	0.4415

87	88	36	1	0	0.3424	0.0456	0.2548	0.4315
89	90	35	1	0	0.3326	0.0453	0.2459	0.4215
95	96	34	1	0	0.3228	0.045	0.237	0.4115
97	98	33	1	0	0.313	0.0447	0.2281	0.4014
99	100	32	0	1	0.313	0.0447	0.2281	0.4014
107	108	31	1	0	0.3029	0.0444	0.2189	0.391
113	114	30	2	0	0.2827	0.0437	0.2008	0.37
114	115	28	1	0	0.2726	0.0432	0.1919	0.3595
115	116	27	1	0	0.2625	0.0428	0.183	0.3488
116	117	26	2	0	0.2423	0.0418	0.1654	0.3274
119	120	24	3	0	0.212	0.0401	0.1395	0.2948
125	126	21	1	0	0.2019	0.0394	0.1311	0.2838
152	153	20	1	0	0.1918	0.0387	0.1227	0.2727
157	158	19	1	0	0.1817	0.038	0.1144	0.2616
165	166	18	1	0	0.1716	0.0372	0.1062	0.2503
167	168	17	1	0	0.1616	0.0364	0.0981	0.239
175	176	16	1	0	0.1515	0.0355	0.0901	0.2276
176	177	15	2	0	0.1313	0.0335	0.0745	0.2044
180	181	13	1	0	0.1212	0.0324	0.0668	0.1927
191	192	12	1	0	0.1111	0.0312	0.0594	0.1808
227	228	11	0	1	0.1111	0.0312	0.0594	0.1808
229	230	10	0	1	0.1111	0.0312	0.0594	0.1808
247	248	9	1	0	0.0987	0.0301	0.0499	0.1672
252	253	8	1	0	0.0864	0.0288	0.0409	0.1532
260	261	7	1	0	0.074	0.0272	0.0323	0.1388
281	282	6	1	0	0.0617	0.0253	0.0243	0.124
297	298	5	1	0	0.0494	0.023	0.0169	0.1086
324	325	4	1	0	0.037	0.0203	0.0104	0.0927
440	441	3	0	1	0.037	0.0203	0.0104	0.0927
460	461	2	1	0	0.0185	0.0166	0.002	0.0765
763	764	1	1	0	0	.	.	.
Interval		**Total**	**Deaths**	**Lost**	**Survival**	**Error**	**[95% Conf. Int.]**	

eribulin								
1	2	223	7	7	0.9681	0.0119	0.9343	0.9847
12	13	209	1	0	0.9635	0.0127	0.9283	0.9816
16	17	208	1	0	0.9588	0.0134	0.9224	0.9784
23	24	207	1	0	0.9542	0.0141	0.9166	0.9751
26	27	206	1	0	0.9496	0.0148	0.9108	0.9718
28	29	205	1	0	0.9449	0.0155	0.9051	0.9684
34	35	204	2	0	0.9357	0.0166	0.8938	0.9614
35	36	202	1	0	0.9311	0.0172	0.8882	0.9579
36	37	201	1	0	0.9264	0.0177	0.8827	0.9543
40	41	200	2	0	0.9172	0.0187	0.8717	0.947
41	42	198	1	0	0.9125	0.0192	0.8663	0.9433
43	44	197	3	0	0.8986	0.0205	0.8501	0.9321
44	45	194	3	0	0.8847	0.0217	0.8342	0.9206
45	46	191	1	0	0.8801	0.0221	0.8289	0.9167
48	49	190	3	0	0.8662	0.0231	0.8132	0.905
49	50	187	4	0	0.8477	0.0244	0.7925	0.8892
50	51	183	5	0	0.8245	0.0259	0.7669	0.8691
52	53	178	1	0	0.8199	0.0261	0.7619	0.865
53	54	177	3	0	0.806	0.0269	0.7467	0.8527
54	55	174	1	0	0.8014	0.0271	0.7417	0.8486
55	56	173	3	0	0.7875	0.0278	0.7267	0.8362
56	57	170	4	0	0.7689	0.0287	0.7068	0.8196
57	58	166	6	0	0.7411	0.0298	0.6773	0.7943
58	59	160	4	0	0.7226	0.0304	0.6578	0.7773
59	60	156	3	0	0.7087	0.0309	0.6432	0.7644
60	61	153	2	0	0.6994	0.0312	0.6335	0.7558
61	62	151	2	0	0.6902	0.0315	0.6239	0.7472
62	63	149	3	0	0.6763	0.0318	0.6095	0.7342
63	64	146	4	0	0.6578	0.0323	0.5904	0.7168
64	65	142	1	0	0.6531	0.0324	0.5856	0.7124
65	66	141	1	0	0.6485	0.0325	0.5808	0.708

67	68	140	2	0	0.6392	0.0327	0.5714	0.6993
69	70	138	2	0	0.63	0.0328	0.5619	0.6904
70	71	136	2	0	0.6207	0.033	0.5524	0.6816
71	72	134	1	0	0.6161	0.0331	0.5477	0.6772
72	73	133	2	0	0.6068	0.0332	0.5383	0.6683
73	74	131	1	0	0.6022	0.0333	0.5336	0.6639
78	79	130	2	0	0.5929	0.0334	0.5243	0.655
83	84	128	1	0	0.5883	0.0335	0.5196	0.6505
85	86	127	3	0	0.5744	0.0336	0.5056	0.6371
92	93	124	2	0	0.5651	0.0337	0.4963	0.6282
100	101	122	1	0	0.5605	0.0338	0.4917	0.6237
101	102	121	4	0	0.542	0.0339	0.4732	0.6056
102	103	117	1	0	0.5373	0.0339	0.4686	0.6011
103	104	116	1	0	0.5327	0.0339	0.464	0.5966
107	108	115	2	0	0.5234	0.034	0.4548	0.5875
108	109	113	3	0	0.5095	0.034	0.441	0.5739
109	110	110	0	1	0.5095	0.034	0.441	0.5739
112	113	109	2	0	0.5002	0.034	0.4318	0.5647
113	114	107	3	0	0.4862	0.034	0.418	0.5508
114	115	104	4	0	0.4675	0.034	0.3997	0.5323
115	116	100	1	0	0.4628	0.034	0.3951	0.5277
116	117	99	0	1	0.4628	0.034	0.3951	0.5277
117	118	98	1	0	0.4581	0.0339	0.3905	0.523
118	119	97	1	0	0.4533	0.0339	0.3859	0.5183
120	121	96	1	0	0.4486	0.0339	0.3813	0.5136
121	122	95	4	0	0.4297	0.0337	0.363	0.4947
122	123	91	2	0	0.4203	0.0337	0.3538	0.4852
123	124	89	1	1	0.4155	0.0336	0.3493	0.4804
125	126	87	3	0	0.4012	0.0335	0.3355	0.466
126	127	84	0	1	0.4012	0.0335	0.3355	0.466
127	128	83	1	0	0.3964	0.0334	0.3308	0.4611
130	131	82	1	0	0.3915	0.0333	0.3262	0.4562

133	134	81	1	0	0.3867	0.0333	0.3215	0.4513
134	135	80	4	1	0.3672	0.033	0.3029	0.4316
139	140	75	1	0	0.3624	0.0329	0.2983	0.4266
142	143	74	1	0	0.3575	0.0328	0.2936	0.4217
147	148	73	1	0	0.3526	0.0327	0.289	0.4167
150	151	72	1	0	0.3477	0.0327	0.2843	0.4117
151	152	71	1	0	0.3428	0.0326	0.2797	0.4066
157	158	70	1	0	0.3379	0.0325	0.2751	0.4016
158	159	69	0	1	0.3379	0.0325	0.2751	0.4016
160	161	68	1	1	0.3329	0.0324	0.2703	0.3965
162	163	66	1	0	0.3278	0.0323	0.2656	0.3914
165	166	65	1	0	0.3228	0.0322	0.2608	0.3862
168	169	64	1	0	0.3177	0.0321	0.2561	0.381
169	170	63	2	0	0.3076	0.0318	0.2466	0.3706
171	172	61	1	0	0.3026	0.0317	0.2419	0.3654
174	175	60	2	0	0.2925	0.0314	0.2325	0.355
175	176	58	1	2	0.2874	0.0313	0.2277	0.3497
176	177	55	2	0	0.2769	0.031	0.218	0.3388
183	184	53	3	0	0.2613	0.0306	0.2035	0.3225
184	185	50	1	2	0.2559	0.0304	0.1986	0.317
185	186	47	0	1	0.2559	0.0304	0.1986	0.317
187	188	46	1	0	0.2504	0.0302	0.1934	0.3112
188	189	45	1	0	0.2448	0.0301	0.1883	0.3054
189	190	44	1	0	0.2392	0.0299	0.1831	0.2996
191	192	43	1	0	0.2337	0.0297	0.178	0.2938
192	193	42	1	0	0.2281	0.0295	0.173	0.288
197	198	41	1	0	0.2225	0.0293	0.1679	0.2821
202	203	40	1	0	0.217	0.0291	0.1629	0.2763
204	205	39	2	0	0.2059	0.0287	0.1528	0.2645
205	206	37	1	0	0.2003	0.0284	0.1478	0.2586
220	221	36	1	0	0.1947	0.0282	0.1429	0.2526
221	222	35	1	0	0.1892	0.0279	0.1379	0.2467

226	227	34	1	0	0.1836	0.0276	0.133	0.2407
230	231	33	1	0	0.178	0.0274	0.1281	0.2347
231	232	32	1	0	0.1725	0.0271	0.1232	0.2287
233	234	31	1	0	0.1669	0.0268	0.1184	0.2227
235	236	30	1	0	0.1613	0.0264	0.1136	0.2166
240	241	29	1	0	0.1558	0.0261	0.1088	0.2105
248	249	28	2	1	0.1445	0.0254	0.0991	0.1981
271	272	25	2	0	0.1329	0.0247	0.0892	0.1854
274	275	23	0	1	0.1329	0.0247	0.0892	0.1854
276	277	22	1	0	0.1269	0.0243	0.0841	0.1787
281	282	21	1	0	0.1208	0.0238	0.079	0.172
290	291	20	1	0	0.1148	0.0234	0.074	0.1653
295	296	19	1	0	0.1087	0.0229	0.069	0.1586
303	304	18	1	0	0.1027	0.0224	0.0641	0.1518
312	313	17	1	0	0.0967	0.0219	0.0592	0.1449
314	315	16	1	0	0.0906	0.0214	0.0544	0.138
338	339	15	1	0	0.0846	0.0208	0.0497	0.131
344	345	14	1	0	0.0785	0.0202	0.045	0.124
347	348	13	1	0	0.0725	0.0195	0.0404	0.1168
351	352	12	1	0	0.0664	0.0188	0.0359	0.1097
353	354	11	0	1	0.0664	0.0188	0.0359	0.1097
372	373	10	1	0	0.0598	0.018	0.031	0.1019
381	382	9	1	0	0.0532	0.0172	0.0262	0.0941
482	483	8	1	0	0.0465	0.0163	0.0215	0.0861
488	489	7	1	0	0.0399	0.0153	0.0171	0.0779
497	498	6	1	0	0.0332	0.0141	0.013	0.0695
567	568	5	1	0	0.0266	0.0127	0.0091	0.0608
579	580	4	1	0	0.0199	0.0112	0.0056	0.0519
620	621	3	1	0	0.0133	0.0092	0.0027	0.0426
623	624	2	0	1	0.0133	0.0092	0.0027	0.0426
645	646	1	0	1	0.0133	0.0092	0.0027	0.0426

d. Time to treatment discontinuation Kaplan-Meier analysis stratified by treatment arm (eribulin vs TPC).

Interval TPC		Total	Deaths	Lost	Survival	Error	[95% Conf. Int.]	
2	3	8	1	0	0.875	0.1169	0.387	0.9814
10	11	7	1	0	0.75	0.1531	0.3148	0.9309
35	36	6	1	0	0.625	0.1712	0.2293	0.8607
91	92	5	1	0	0.5	0.1768	0.152	0.7749
192	193	4	1	0	0.375	0.1712	0.087	0.6744
307	308	3	1	0	0.25	0.1531	0.0371	0.5581
768	769	2	1	0	0.125	0.1169	0.0066	0.4227
833	834	1	1	0	0	.	.	.
Interval eribulin		**Total**	**Deaths**	**Lost**	**Survival**	**Error**	**[95% Conf. Int.]**	
129	130	10	1	0	0.9	0.0949	0.473	0.9853
203	204	9	1	0	0.8	0.1265	0.4087	0.9459
234	235	8	1	0	0.7	0.1449	0.3287	0.8919
410	411	7	1	0	0.6	0.1549	0.2527	0.8272
449	450	6	1	0	0.5	0.1581	0.1836	0.7532
521	522	5	1	0	0.4	0.1549	0.1227	0.6702
605	606	4	1	0	0.3	0.1449	0.0711	0.5779
862	863	3	1	0	0.2	0.1265	0.0309	0.4747
1065	1066	2	1	0	0.1	0.0949	0.0057	0.3581
1133	1134	1	1	0	0	.	.	.

Rationale for clarification requests:

- B1: All Kaplan-Meier analyses with alternative censoring rule – when trials are stopped early or subject to early analysis the conventional censoring rule (censor when last contacted/reviewed) always understates the time exposed to risk but is much less likely to understate events, especially deaths. The result is that the hazard rate calculated by Kaplan-Meier algorithm are exaggerated when multiple patients are censored in any period. The resulting Kaplan-Meier estimated time-to-event trends may therefore be distorted by ‘informative censoring’ and poorly reflect the true profile of time-to-event. In some of the specified analyses there are suggestive indications that such effects are

present, but it is not possible to confirm or refute this possibility without having access to re-analysis using the alternative censoring rule.

- B1 (a, b & c): Survival gain for eribulin versus comparator is the most important parameter governing cost-effectiveness. Careful analysis of OS and its components (PFS and PPS) is essential to validation of the survival gains estimated by the decision model.

- B1 (d): Time to treatment discontinuation offers an alternative to PFS as a basis for estimating treatment costs in both trial arms. This analysis will allow the sensitivity of incremental costs to the method of estimation to be assessed.

B2. **Priority Question**: For Subgroup 2 of study 305, please provide the analysis of baseline characteristics as shown in Table 31 of the CS for:

a. Patients still alive and uncensored 12 months after randomisation.

b. Patients still alive and uncensored 24 months after randomisation.

As requested, please see overleaf a table with the analysis of baselines characteristics for Subgroup 2 for patients still alive and uncensored 12 and 24 months after randomisation.

Demographic Characteristics, Patients Alive and Uncensored 12 or 24 Months after Randomization
ITT Population (Post-Capecitabine patients (95% OS cutoff))

Characteristic	Alive after 12 Months			Alive after 24 Months		
	Eribulin (N=199)	TPC (N=77)	Total (N=276)	Eribulin (N=73)	TPC (N=34)	Total (N=107)
Age (years), n (%)						
<=40	16 (8.0)	8 (10.4)	24 (8.7)	5 (6.8)	4 (11.8)	9 (8.4)
>40 to <65	147 (73.9)	51 (66.2)	198 (71.7)	59 (80.8)	19 (55.9)	78 (72.9)
>=65	36 (18.1)	18 (23.4)	54 (19.6)	9 (12.3)	11 (32.4)	20 (18.7)
Race, n (%)						
BLACK	5 (2.5)	4 (5.2)	9 (3.3)	1 (1.4)	1 (2.9)	2 (1.9)
WHITE	189 (95.0)	70 (90.9)	259 (93.8)	70 (95.9)	32 (94.1)	102 (95.3)
ASIAN/PACIFIC ISLANDER	1 (0.5)	2 (2.6)	3 (1.1)	0	1 (2.9)	1 (0.9)
OTHER	4 (2.0)	1 (1.3)	5 (1.8)	2 (2.7)	0	2 (1.9)
ER status, n (%)						
Positive	149 (74.9)	63 (81.8)	212 (76.8)	56 (76.7)	27 (79.4)	83 (77.6)
Negative	41 (20.6)	11 (14.3)	52 (18.8)	14 (19.2)	6 (17.6)	20 (18.7)
Not Done	8 (4.0)	3 (3.9)	11 (4.0)	3 (4.1)	1 (2.9)	4 (3.7)
Unknown	1 (0.5)	0	1 (0.4)	0	0	0
Triple negative (ER/PR/HER2-negative), n (%)	29 (14.6)	7 (9.1)	36 (13.0)	9 (12.3)	5 (14.7)	14 (13.1)

Note: Post-Capecitabine patients include all patients who previously received Capecitabine as anti-cancer therapy before study. Patients still alive and uncensored (at risk) 12 or 24 months after randomization.

Demographic Characteristics, Patients Alive and Uncensored 12 or 24 Months after Randomization
ITT Population (Post-Capecitabine patients (95% OS cutoff))

Characteristic	Alive after 12 Months			Alive after 24 Months		
	Eribulin (N=199)	TPC (N=77)	Total (N=276)	Eribulin (N=73)	TPC (N=34)	Total (N=107)
Number of organs involved, n (%)						
1	41 (20.6)	11 (14.3)	52 (18.8)	15 (20.5)	7 (20.6)	22 (20.6)
2	76 (38.2)	29 (37.7)	105 (38.0)	28 (38.4)	12 (35.3)	40 (37.4)
>=3	81 (40.7)	37 (48.1)	118 (42.8)	30 (41.1)	15 (44.1)	45 (42.1)
ECOG performance status at screening, n (%)						
0	102 (51.3)	44 (57.1)	146 (52.9)	42 (57.5)	21 (61.8)	63 (58.9)
1	85 (42.7)	32 (41.6)	117 (42.4)	25 (34.2)	13 (38.2)	38 (35.5)
2	8 (4.0)	0	8 (2.9)	3 (4.1)	0	3 (2.8)

Note: Post-Capecitabine patients include all patients who previously received Capecitabine as anti-cancer therapy before study.
Patients still alive and uncensored (at risk) 12 or 24 months after randomization.

Source: Eisai Ltd data on file 95% OS data additional info for ERG

Section C: Textual clarifications and additional points

C1. **Priority Question**: Please provide the Statistical Analysis Plans for Study 305.

Please see the SAP for Study 305 which has been uploaded separately via NICE docs.

C2. **Priority Question**: Please provide the trial protocol for Study 305.

Please see the trial protocol for Study 305 which has been uploaded separately via NICE docs.

C3. Table 40, appears to be missing text as the following appears to be an incomplete sentence: "the adverse events prevalence will depend on the MS in the trial, but" Please clarify.

The corrected table is provided below. Eisai apologises for this oversight.

Table 1 Methodological issues of pooled patient data versus individual studies' patient level data

Parameters	*Pooled patient data*	*Individual Studies' patient data*
Trial effect bias	The pooled analysis is a combination of 301/305 trials patient-level datasets. Due to the different study characteristics between the two studies (e.g. lines of therapy, a "study" effect was tested in the Cox model considering different stratification factors (Study, prior cape, and region), and covariates (ER status and #organs involved) and it was found to be significant. While the trial effect can be managed properly in survival analysis using a parameter in the cox model, the data is less robust for extrapolation in a cost-effectiveness analysis model, because of different cut off points.	No trial effect in studies 301 and 305
Adverse events	Adverse events in each study were collected for the respective treatment arms of eribulin and capecitabine in study 301 and eribulin and TPC in study 305. The prevalence of the AEs, thus, is dependent on the proportions captured in each study. Pooling these proportions or making assumptions about them can lead to biases in the CEA results for TPC.	Studies 301 and 305 area head-to-head trials and thus the adverse event profiles of each comparator are clean.

Further ERG clarification questions

Dear company,

The ERG, while cross checking their report and validating the model, have noted certain errors with the model, or more specifically, the data they requested during clarification.

Subgroup 2 group should consist of 370 patients in the eribulin arm and 189 patients in the TPC arm. However, they note that:

- The K-M OS analysis shows only 219 eribulin patients and 126 TPC patients.
- The K-M analyses for PFS and PPS show only 223 eribulin patients and 122 TPC patients.

In addition, they have identified one other anomaly:

- Regarding baseline characteristics provided in response to question A7, there are more patients with unknown HER2 status in Subgroup 2 than with unknown HER2 status in the overall trial population;

The ERG therefore have the following requests:

- Please could you run the K-M analyses for OS, PFS and PPS again using the correct Subgroup 2 population?

- Can the company provide a breakdown of the numbers of patients receiving each agent in the TPC arm for Subgroup 2 (i.e. similar to Table 15 of the company submission but for Subgroup 2) for both clinical effectiveness evidence (which should equal 189 patients) and as used in the model (if this differs to the clinical effectiveness evidence)?

- Can company check the data provided in response to A7 is correct and to provide any corrected data as necessary?

The ERG needs to validate the central parameters of the model and provide the information that thee Committee requires to make an informed decision.

As requested, Eisai have run the K-M analyses for OS, PFS and PPS again using the correct Subgroup 2 population and have included below the corrected response to question B1.

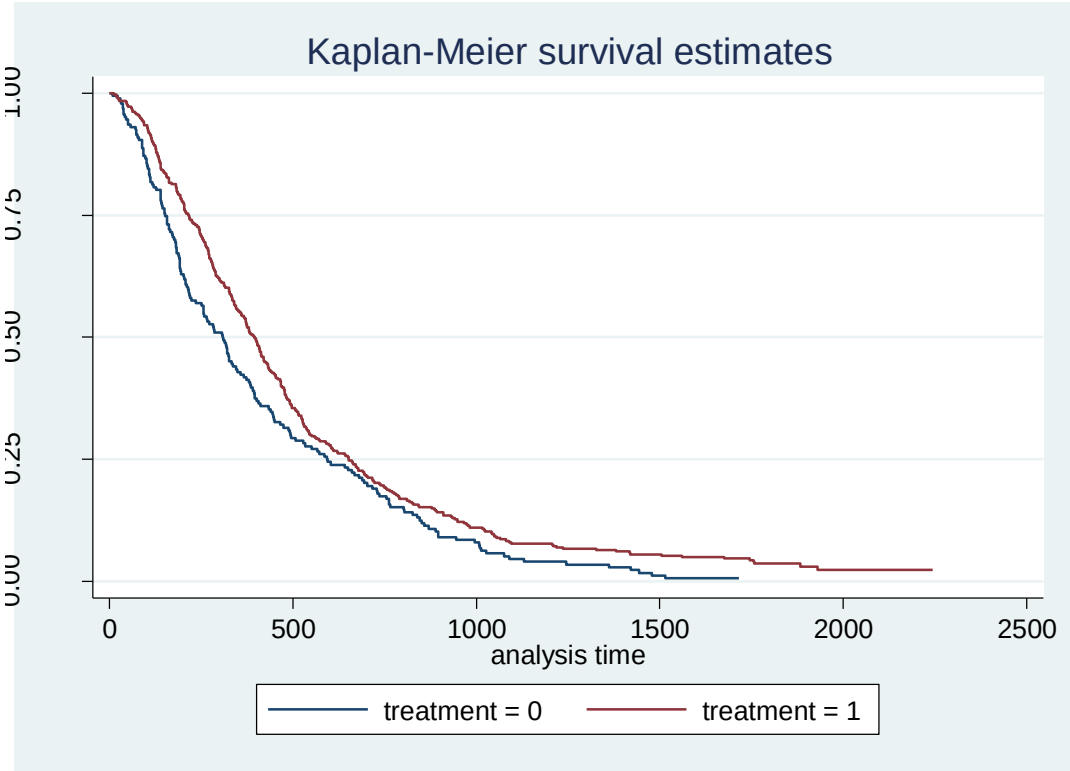
B1. **Priority Question**: Please provide the following Kaplan-Meier analyses (listed in a to d below) to the following specification:

Population: Use subset of Study 305 patients who have progressed after two chemotherapeutic regimens and had received capecitabine previously, including all patients lost to follow-up or withdrawing from trial.

Trial data set: Study 305 latest data cut.

Format: Please present analysis outputs using the format of the sample table (B1) in this clarification.

a. Time to death from any cause (OS) Kaplan-Meier analysis stratified by treatment arm (eribulin vs Treatment of Physician's Choice [TPC]).



Interval		Total	Deaths	Lost	Survival	Error	[95% Conf. Int.]	
TPC								
8	9	189	1	0	0.9947	0.0053	0.963	0.9993
10	11	188	0	1	0.9947	0.0053	0.963	0.9993
22	23	187	1	0	0.9894	0.0075	0.9582	0.9973
29	30	186	1	0	0.9841	0.0091	0.9514	0.9948
31	32	185	1	0	0.9788	0.0105	0.9444	0.992
35	36	184	0	1	0.9788	0.0105	0.9444	0.992
36	37	183	2	0	0.9681	0.0128	0.9303	0.9855
37	38	181	2	0	0.9574	0.0148	0.9165	0.9784
42	43	179	1	0	0.952	0.0156	0.9098	0.9747
44	45	178	1	0	0.9467	0.0164	0.9031	0.9709
49	50	177	2	0	0.936	0.0179	0.89	0.9631
57	58	175	1	0	0.9306	0.0186	0.8835	0.9591
70	71	174	1	0	0.9253	0.0192	0.8771	0.955
72	73	173	1	0	0.9199	0.0198	0.8707	0.9509
73	74	172	1	0	0.9146	0.0204	0.8643	0.9468
76	77	171	1	0	0.9092	0.021	0.858	0.9426
79	80	170	1	0	0.9039	0.0215	0.8518	0.9383
88	89	169	1	0	0.8985	0.0221	0.8455	0.934
89	90	168	2	0	0.8878	0.0231	0.8332	0.9254
91	92	166	3	1	0.8717	0.0244	0.8148	0.9121
97	98	162	1	0	0.8664	0.0249	0.8086	0.9076
100	101	161	2	0	0.8556	0.0257	0.7965	0.8986
102	103	159	1	0	0.8502	0.0261	0.7905	0.8941
104	105	158	1	0	0.8448	0.0265	0.7845	0.8895
108	109	157	2	0	0.8341	0.0272	0.7725	0.8803
109	110	155	1	0	0.8287	0.0276	0.7665	0.8756
110	111	154	1	0	0.8233	0.0279	0.7606	0.871
111	112	153	1	0	0.8179	0.0282	0.7547	0.8663
116	117	152	1	0	0.8125	0.0286	0.7488	0.8616
120	121	151	1	0	0.8072	0.0289	0.7429	0.8569
127	128	150	1	0	0.8018	0.0292	0.737	0.8522
138	139	149	2	0	0.791	0.0298	0.7253	0.8427
139	140	147	2	0	0.7803	0.0303	0.7137	0.8331
141	142	145	1	0	0.7749	0.0306	0.7079	0.8284
143	144	144	1	0	0.7695	0.0308	0.7021	0.8235

144	145	143	1	0	0.7641	0.0311	0.6964	0.8187
149	150	142	2	0	0.7534	0.0316	0.6849	0.809
151	152	140	1	0	0.748	0.0318	0.6791	0.8042
156	157	139	2	0	0.7372	0.0322	0.6677	0.7944
157	158	137	1	0	0.7318	0.0325	0.662	0.7895
161	162	136	1	0	0.7264	0.0327	0.6564	0.7846
162	163	135	1	0	0.7211	0.0329	0.6507	0.7797
165	166	134	1	0	0.7157	0.033	0.645	0.7747
171	172	133	1	0	0.7103	0.0332	0.6394	0.7698
172	173	132	1	0	0.7049	0.0334	0.6338	0.7648
175	176	131	1	0	0.6995	0.0336	0.6281	0.7599
179	180	130	1	0	0.6942	0.0338	0.6225	0.7549
180	181	129	2	0	0.6834	0.0341	0.6113	0.7449
182	183	127	2	0	0.6726	0.0344	0.6002	0.7349
188	189	125	1	0	0.6673	0.0345	0.5946	0.7299
190	191	124	1	0	0.6619	0.0347	0.5891	0.7248
191	192	123	4	0	0.6403	0.0352	0.5669	0.7046
192	193	119	0	1	0.6403	0.0352	0.5669	0.7046
193	194	118	1	0	0.6349	0.0353	0.5614	0.6995
194	195	117	1	0	0.6295	0.0354	0.5558	0.6944
201	202	116	1	0	0.6241	0.0355	0.5503	0.6892
204	205	115	1	0	0.6186	0.0356	0.5448	0.6841
206	207	114	1	0	0.6132	0.0357	0.5392	0.6789
207	208	113	1	0	0.6078	0.0358	0.5337	0.6738
210	211	112	1	0	0.6024	0.0359	0.5282	0.6686
213	214	111	1	0	0.5969	0.036	0.5227	0.6634
215	216	110	1	0	0.5915	0.0361	0.5172	0.6582
218	219	109	1	0	0.5861	0.0361	0.5118	0.653
219	220	108	1	0	0.5807	0.0362	0.5063	0.6478
223	224	107	1	0	0.5752	0.0363	0.5008	0.6426
235	236	106	1	0	0.5698	0.0363	0.4954	0.6374
250	251	105	1	0	0.5644	0.0364	0.4899	0.6321
255	256	104	2	0	0.5535	0.0365	0.4791	0.6216
256	257	102	1	0	0.5481	0.0365	0.4737	0.6164
257	258	101	1	0	0.5427	0.0366	0.4683	0.6111
265	266	100	1	0	0.5372	0.0366	0.4629	0.6058
266	267	99	1	0	0.5318	0.0366	0.4575	0.6006

272	273	98	1	0	0.5264	0.0367	0.4521	0.5953
281	282	97	1	0	0.521	0.0367	0.4467	0.59
283	284	96	1	0	0.5155	0.0367	0.4414	0.5847
286	287	95	1	0	0.5101	0.0367	0.436	0.5793
306	307	94	1	0	0.5047	0.0367	0.4307	0.574
308	309	93	1	0	0.4993	0.0367	0.4253	0.5687
309	310	92	1	0	0.4938	0.0367	0.42	0.5633
314	315	91	1	0	0.4884	0.0367	0.4147	0.558
316	317	90	1	0	0.483	0.0367	0.4094	0.5526
319	320	89	1	0	0.4775	0.0367	0.4041	0.5473
321	322	88	2	0	0.4667	0.0367	0.3935	0.5365
324	325	86	1	0	0.4613	0.0366	0.3882	0.5311
326	327	85	2	0	0.4504	0.0366	0.3777	0.5203
332	333	83	1	0	0.445	0.0365	0.3724	0.5149
336	337	82	1	0	0.4396	0.0365	0.3672	0.5095
344	345	81	1	0	0.4341	0.0364	0.362	0.504
348	349	80	1	0	0.4287	0.0364	0.3567	0.4986
356	357	79	1	0	0.4233	0.0363	0.3515	0.4931
365	366	78	1	0	0.4179	0.0363	0.3463	0.4877
373	374	77	1	0	0.4124	0.0362	0.3411	0.4822
380	381	76	1	0	0.407	0.0361	0.3359	0.4767
383	384	75	1	0	0.4016	0.036	0.3308	0.4713
385	386	74	1	0	0.3961	0.036	0.3256	0.4658
390	391	73	1	0	0.3907	0.0359	0.3204	0.4603
394	395	72	1	0	0.3853	0.0358	0.3153	0.4547
396	397	71	2	0	0.3744	0.0356	0.305	0.4437
400	401	69	1	0	0.369	0.0355	0.2999	0.4382
405	406	68	1	0	0.3636	0.0354	0.2948	0.4326
411	412	67	1	0	0.3582	0.0353	0.2897	0.4271
433	434	66	1	0	0.3527	0.0351	0.2846	0.4215
439	440	65	1	0	0.3473	0.035	0.2795	0.4159
444	445	64	1	0	0.3419	0.0349	0.2744	0.4103
446	447	63	1	0	0.3365	0.0348	0.2693	0.4047
448	449	62	1	0	0.331	0.0346	0.2643	0.3991
449	450	61	1	0	0.3256	0.0345	0.2592	0.3935
465	466	60	1	0	0.3202	0.0343	0.2542	0.3879
473	474	59	1	0	0.3147	0.0342	0.2492	0.3823

488	489	58	1	0	0.3093	0.034	0.2442	0.3766
492	493	57	1	0	0.3039	0.0338	0.2392	0.371
493	494	56	1	0	0.2985	0.0337	0.2342	0.3653
495	496	55	1	0	0.293	0.0335	0.2292	0.3596
506	507	54	1	0	0.2876	0.0333	0.2242	0.3539
527	528	53	1	0	0.2822	0.0331	0.2193	0.3482
533	534	52	1	0	0.2768	0.0329	0.2143	0.3425
551	552	51	1	0	0.2713	0.0327	0.2094	0.3368
566	567	50	1	0	0.2659	0.0325	0.2045	0.3311
571	572	49	1	0	0.2605	0.0323	0.1996	0.3253
586	587	48	1	0	0.2551	0.0321	0.1947	0.3196
592	593	47	1	0	0.2496	0.0319	0.1898	0.3138
594	595	46	1	0	0.2442	0.0316	0.1849	0.308
603	604	45	1	0	0.2388	0.0314	0.1801	0.3022
642	643	44	1	0	0.2333	0.0311	0.1752	0.2964
650	651	43	1	0	0.2279	0.0309	0.1704	0.2906
661	662	42	1	0	0.2225	0.0306	0.1656	0.2848
668	669	41	1	0	0.2171	0.0303	0.1608	0.279
680	681	40	1	0	0.2116	0.0301	0.156	0.2731
689	690	39	1	0	0.2062	0.0298	0.1512	0.2672
694	695	38	1	0	0.2008	0.0295	0.1465	0.2613
703	704	37	1	0	0.1954	0.0292	0.1418	0.2554
717	718	36	1	0	0.1899	0.0289	0.137	0.2495
728	729	35	1	0	0.1845	0.0286	0.1323	0.2436
731	732	34	1	0	0.1791	0.0282	0.1277	0.2376
735	736	33	1	0	0.1737	0.0279	0.123	0.2316
754	755	32	1	0	0.1682	0.0275	0.1184	0.2256
761	762	31	2	0	0.1574	0.0268	0.1091	0.2136
765	766	29	1	0	0.1519	0.0264	0.1046	0.2076
802	803	28	1	0	0.1465	0.026	0.1	0.2015
804	805	27	1	0	0.1411	0.0256	0.0955	0.1954
826	827	26	1	0	0.1357	0.0252	0.091	0.1893
833	834	25	0	1	0.1357	0.0252	0.091	0.1893
839	840	24	1	0	0.13	0.0248	0.0863	0.1829
846	847	23	1	0	0.1244	0.0243	0.0816	0.1766
851	852	22	1	0	0.1187	0.0239	0.077	0.1702
857	858	21	1	0	0.1131	0.0234	0.0724	0.1637

869	870	20	1	0	0.1074	0.0229	0.0678	0.1573
889	890	19	1	0	0.1018	0.0224	0.0633	0.1507
895	896	18	1	0	0.0961	0.0219	0.0588	0.1442
896	897	17	1	0	0.0904	0.0213	0.0544	0.1376
945	946	16	1	0	0.0848	0.0207	0.05	0.131
996	997	15	1	0	0.0791	0.0201	0.0457	0.1243
1008	1009	14	1	0	0.0735	0.0194	0.0414	0.1175
1010	1011	13	1	0	0.0678	0.0187	0.0373	0.1107
1013	1014	12	1	0	0.0622	0.018	0.0331	0.1039
1026	1027	11	1	0	0.0565	0.0172	0.0291	0.0969
1076	1077	10	1	0	0.0509	0.0164	0.0252	0.0899
1089	1090	9	1	0	0.0452	0.0155	0.0213	0.0828
1129	1130	8	1	0	0.0396	0.0146	0.0176	0.0756
1244	1245	7	1	0	0.0339	0.0135	0.0141	0.0682
1361	1362	6	1	0	0.0283	0.0124	0.0107	0.0607
1421	1422	5	1	0	0.0226	0.0111	0.0075	0.053
1443	1444	4	1	0	0.017	0.0097	0.0047	0.0451
1479	1480	3	1	0	0.0113	0.0079	0.0023	0.037
1515	1516	2	1	0	0.0057	0.0056	0.0005	0.0288
1716	1717	1	0	1	0.0057	0.0056	0.0005	0.0288

Interval		Total	Deaths	Lost	Survival	Error	[95% Conf. Int.]	
Halaven								
12	13	370	1	0	0.9973	0.0027	0.981	0.9996
18	19	369	1	0	0.9946	0.0038	0.9786	0.9986
19	20	368	1	0	0.9919	0.0047	0.9751	0.9974
22	23	367	1	0	0.9892	0.0054	0.9715	0.9959
25	26	366	1	0	0.9865	0.006	0.9678	0.9944
26	27	365	1	0	0.9838	0.0066	0.9643	0.9927
44	45	364	1	0	0.9811	0.0071	0.9607	0.9909
47	48	363	1	0	0.9784	0.0076	0.9572	0.9891
48	49	362	1	0	0.9757	0.008	0.9538	0.9873
50	51	361	1	0	0.973	0.0084	0.9504	0.9854
58	59	360	1	0	0.9703	0.0088	0.947	0.9834
61	62	359	1	0	0.9676	0.0092	0.9436	0.9815
62	63	358	2	0	0.9622	0.0099	0.9369	0.9774
69	70	356	1	0	0.9595	0.0103	0.9337	0.9754
72	73	355	1	0	0.9568	0.0106	0.9304	0.9733

78	79	354	1	0	0.9541	0.0109	0.9271	0.9712
81	82	353	1	0	0.9514	0.0112	0.9239	0.9691
83	84	352	1	0	0.9486	0.0115	0.9207	0.9669
87	88	351	1	0	0.9459	0.0118	0.9175	0.9648
89	90	350	1	0	0.9432	0.012	0.9143	0.9626
91	92	349	1	0	0.9405	0.0123	0.9111	0.9604
93	94	348	2	0	0.9351	0.0128	0.9048	0.956
102	103	346	1	0	0.9324	0.013	0.9016	0.9538
103	104	345	1	0	0.9297	0.0133	0.8985	0.9516
104	105	344	2	0	0.9243	0.0137	0.8923	0.9471
106	107	342	2	0	0.9189	0.0142	0.8861	0.9426
109	110	340	1	0	0.9162	0.0144	0.883	0.9403
110	111	339	1	0	0.9135	0.0146	0.8799	0.938
112	113	338	1	0	0.9108	0.0148	0.8768	0.9358
113	114	337	1	0	0.9081	0.015	0.8738	0.9335
115	116	336	2	0	0.9027	0.0154	0.8677	0.9288
116	117	334	1	0	0.9	0.0156	0.8646	0.9265
118	119	333	1	0	0.8973	0.0158	0.8616	0.9242
119	120	332	1	0	0.8946	0.016	0.8586	0.9219
121	122	331	1	0	0.8919	0.0161	0.8556	0.9195
125	126	330	2	0	0.8865	0.0165	0.8495	0.9148
126	127	328	1	0	0.8838	0.0167	0.8465	0.9125
127	128	327	2	0	0.8784	0.017	0.8405	0.9077
129	130	325	0	1	0.8784	0.017	0.8405	0.9077
130	131	324	2	0	0.873	0.0173	0.8345	0.903
131	132	322	1	0	0.8702	0.0175	0.8315	0.9006
133	134	321	1	0	0.8675	0.0176	0.8286	0.8982
134	135	320	1	0	0.8648	0.0178	0.8256	0.8958
135	136	319	1	0	0.8621	0.0179	0.8226	0.8934
136	137	318	1	0	0.8594	0.0181	0.8196	0.891
137	138	317	1	0	0.8567	0.0182	0.8167	0.8886
138	139	316	3	0	0.8486	0.0186	0.8078	0.8813
139	140	313	1	0	0.8458	0.0188	0.8048	0.8789
141	142	312	1	0	0.8431	0.0189	0.8019	0.8765
145	146	311	1	0	0.8404	0.019	0.7989	0.874
147	148	310	1	0	0.8377	0.0192	0.796	0.8716
151	152	309	1	0	0.835	0.0193	0.7931	0.8691

155	156	308	2	0	0.8296	0.0196	0.7872	0.8642
157	158	306	1	0	0.8269	0.0197	0.7843	0.8618
161	162	305	2	0	0.8214	0.0199	0.7784	0.8569
162	163	303	2	0	0.816	0.0202	0.7726	0.8519
168	169	301	1	0	0.8133	0.0203	0.7697	0.8495
180	181	300	1	0	0.8106	0.0204	0.7668	0.847
181	182	299	1	0	0.8079	0.0205	0.7639	0.8445
182	183	298	2	0	0.8025	0.0207	0.7581	0.8396
183	184	296	1	0	0.7998	0.0208	0.7552	0.8371
184	185	295	1	0	0.797	0.0209	0.7523	0.8346
186	187	294	1	0	0.7943	0.021	0.7494	0.8321
188	189	293	1	0	0.7916	0.0211	0.7465	0.8296
192	193	292	2	0	0.7862	0.0213	0.7408	0.8246
193	194	290	1	0	0.7835	0.0214	0.7379	0.8221
196	197	289	2	0	0.7781	0.0216	0.7322	0.8171
199	200	287	1	0	0.7754	0.0217	0.7293	0.8146
201	202	286	1	0	0.7726	0.0218	0.7264	0.8121
203	204	285	1	0	0.7699	0.0219	0.7236	0.8096
204	205	284	3	0	0.7618	0.0222	0.715	0.802
205	206	281	1	0	0.7591	0.0223	0.7121	0.7995
207	208	280	1	0	0.7564	0.0223	0.7093	0.797
209	210	279	1	0	0.7537	0.0224	0.7064	0.7944
213	214	278	1	0	0.751	0.0225	0.7036	0.7919
216	217	277	1	0	0.7482	0.0226	0.7007	0.7894
217	218	276	1	0	0.7455	0.0227	0.6979	0.7868
218	219	275	1	0	0.7428	0.0227	0.695	0.7843
219	220	274	1	0	0.7401	0.0228	0.6922	0.7818
225	226	273	2	0	0.7347	0.023	0.6865	0.7767
227	228	271	1	0	0.732	0.023	0.6837	0.7741
233	234	270	1	0	0.7293	0.0231	0.6809	0.7716
234	235	269	0	1	0.7293	0.0231	0.6809	0.7716
239	240	268	1	0	0.7265	0.0232	0.678	0.769
243	244	267	1	0	0.7238	0.0233	0.6752	0.7665
244	245	266	1	0	0.7211	0.0233	0.6724	0.7639
245	246	265	2	0	0.7157	0.0235	0.6667	0.7588
246	247	263	1	0	0.7129	0.0235	0.6639	0.7562
247	248	262	1	0	0.7102	0.0236	0.661	0.7536

248	249	261	1	0	0.7075	0.0237	0.6582	0.7511
250	251	260	1	0	0.7048	0.0237	0.6554	0.7485
253	254	259	1	0	0.7021	0.0238	0.6526	0.7459
254	255	258	1	0	0.6993	0.0239	0.6497	0.7433
256	257	257	1	0	0.6966	0.0239	0.6469	0.7408
258	259	256	1	0	0.6939	0.024	0.6441	0.7382
260	261	255	2	0	0.6885	0.0241	0.6385	0.733
263	264	253	1	0	0.6857	0.0242	0.6357	0.7304
264	265	252	1	0	0.683	0.0242	0.6329	0.7278
268	269	251	2	0	0.6776	0.0243	0.6273	0.7226
269	270	249	1	0	0.6748	0.0244	0.6244	0.72
270	271	248	2	0	0.6694	0.0245	0.6189	0.7148
271	272	246	2	0	0.664	0.0246	0.6133	0.7096
272	273	244	1	0	0.6612	0.0246	0.6105	0.707
275	276	243	1	0	0.6585	0.0247	0.6077	0.7044
276	277	242	1	0	0.6558	0.0247	0.6049	0.7018
278	279	241	1	0	0.6531	0.0248	0.6021	0.6992
280	281	240	2	0	0.6476	0.0249	0.5965	0.694
281	282	238	1	0	0.6449	0.0249	0.5937	0.6914
282	283	237	1	0	0.6422	0.025	0.591	0.6888
283	284	236	1	0	0.6395	0.025	0.5882	0.6861
286	287	235	1	0	0.6368	0.025	0.5854	0.6835
287	288	234	1	0	0.634	0.0251	0.5826	0.6809
288	289	233	2	0	0.6286	0.0252	0.5771	0.6756
289	290	231	1	0	0.6259	0.0252	0.5743	0.673
292	293	230	1	0	0.6231	0.0252	0.5715	0.6704
296	297	229	1	0	0.6204	0.0253	0.5688	0.6678
300	301	228	1	0	0.6177	0.0253	0.566	0.6651
301	302	227	1	0	0.615	0.0253	0.5632	0.6625
304	305	226	1	0	0.6123	0.0254	0.5605	0.6599
311	312	225	2	0	0.6068	0.0254	0.555	0.6546
314	315	223	1	0	0.6041	0.0255	0.5522	0.652
315	316	222	1	0	0.6014	0.0255	0.5494	0.6493
326	327	221	3	0	0.5932	0.0256	0.5412	0.6414
327	328	218	1	0	0.5905	0.0256	0.5384	0.6387
328	329	217	1	0	0.5878	0.0256	0.5357	0.6361
330	331	216	1	0	0.585	0.0257	0.5329	0.6334

332	333	215	1	0	0.5823	0.0257	0.5302	0.6308
334	335	214	1	0	0.5796	0.0257	0.5275	0.6281
335	336	213	1	0	0.5769	0.0257	0.5247	0.6255
336	337	212	1	0	0.5742	0.0258	0.522	0.6228
339	340	211	3	0	0.566	0.0258	0.5138	0.6148
343	344	208	1	0	0.5633	0.0258	0.511	0.6122
344	345	207	2	0	0.5578	0.0259	0.5056	0.6068
348	349	205	1	0	0.5551	0.0259	0.5028	0.6042
351	352	204	1	0	0.5524	0.0259	0.5001	0.6015
355	356	203	1	0	0.5497	0.0259	0.4974	0.5988
359	360	202	1	0	0.547	0.0259	0.4947	0.5962
360	361	201	1	0	0.5442	0.026	0.4919	0.5935
365	366	200	1	0	0.5415	0.026	0.4892	0.5908
367	368	199	1	0	0.5388	0.026	0.4865	0.5881
370	371	198	2	0	0.5333	0.026	0.4811	0.5828
371	372	196	1	0	0.5306	0.026	0.4783	0.5801
373	374	195	2	0	0.5252	0.026	0.4729	0.5747
374	375	193	1	0	0.5225	0.026	0.4702	0.572
375	376	192	1	0	0.5197	0.026	0.4675	0.5694
379	380	191	3	0	0.5116	0.0261	0.4594	0.5613
382	383	188	1	0	0.5089	0.0261	0.4567	0.5586
384	385	187	1	0	0.5061	0.0261	0.454	0.5559
390	391	186	1	0	0.5034	0.0261	0.4513	0.5532
394	395	185	1	0	0.5007	0.0261	0.4486	0.5505
395	396	184	1	0	0.498	0.0261	0.4459	0.5478
399	400	183	2	0	0.4925	0.0261	0.4405	0.5424
401	402	181	1	0	0.4898	0.0261	0.4378	0.5397
402	403	180	1	0	0.4871	0.0261	0.4351	0.537
403	404	179	1	0	0.4844	0.026	0.4324	0.5343
404	405	178	1	0	0.4816	0.026	0.4297	0.5316
407	408	177	2	0	0.4762	0.026	0.4244	0.5262
409	410	175	1	0	0.4735	0.026	0.4217	0.5234
410	411	174	1	1	0.4708	0.026	0.419	0.5207
412	413	172	1	0	0.468	0.026	0.4163	0.518
413	414	171	2	0	0.4625	0.026	0.4109	0.5125
414	415	169	1	0	0.4598	0.026	0.4082	0.5098
419	420	168	1	0	0.4571	0.026	0.4055	0.5071

420	421	167	2	0	0.4516	0.0259	0.4001	0.5016
421	422	165	1	0	0.4489	0.0259	0.3975	0.4988
427	428	164	1	0	0.4461	0.0259	0.3948	0.4961
430	431	163	1	0	0.4434	0.0259	0.3921	0.4934
431	432	162	2	0	0.4379	0.0259	0.3867	0.4879
434	435	160	1	0	0.4352	0.0259	0.384	0.4851
435	436	159	1	0	0.4324	0.0258	0.3814	0.4824
438	439	158	1	0	0.4297	0.0258	0.3787	0.4796
442	443	157	1	0	0.427	0.0258	0.376	0.4769
448	449	156	1	0	0.4242	0.0258	0.3733	0.4741
449	450	155	0	1	0.4242	0.0258	0.3733	0.4741
451	452	154	1	0	0.4215	0.0258	0.3707	0.4713
452	453	153	1	0	0.4187	0.0257	0.368	0.4686
453	454	152	1	0	0.416	0.0257	0.3653	0.4658
458	459	151	1	0	0.4132	0.0257	0.3626	0.463
465	466	150	1	0	0.4105	0.0257	0.3599	0.4602
466	467	149	1	0	0.4077	0.0256	0.3572	0.4575
467	468	148	3	0	0.3994	0.0256	0.3492	0.4491
470	471	145	1	0	0.3967	0.0255	0.3465	0.4463
475	476	144	1	0	0.3939	0.0255	0.3439	0.4435
476	477	143	1	0	0.3912	0.0255	0.3412	0.4407
478	479	142	3	0	0.3829	0.0254	0.3332	0.4324
480	481	139	1	0	0.3801	0.0253	0.3305	0.4296
481	482	138	1	0	0.3774	0.0253	0.3279	0.4268
482	483	137	1	0	0.3746	0.0253	0.3252	0.424
484	485	136	1	0	0.3719	0.0252	0.3225	0.4212
489	490	135	1	0	0.3691	0.0252	0.3199	0.4184
491	492	134	1	0	0.3664	0.0252	0.3172	0.4156
492	493	133	1	0	0.3636	0.0251	0.3146	0.4128
493	494	132	1	0	0.3609	0.0251	0.3119	0.41
496	497	131	1	0	0.3581	0.025	0.3093	0.4071
497	498	130	1	0	0.3554	0.025	0.3066	0.4043
505	506	129	1	0	0.3526	0.025	0.304	0.4015
506	507	128	1	0	0.3498	0.0249	0.3013	0.3987
511	512	127	1	0	0.3471	0.0249	0.2987	0.3959
513	514	126	1	0	0.3443	0.0248	0.296	0.3931
514	515	125	1	0	0.3416	0.0248	0.2934	0.3902

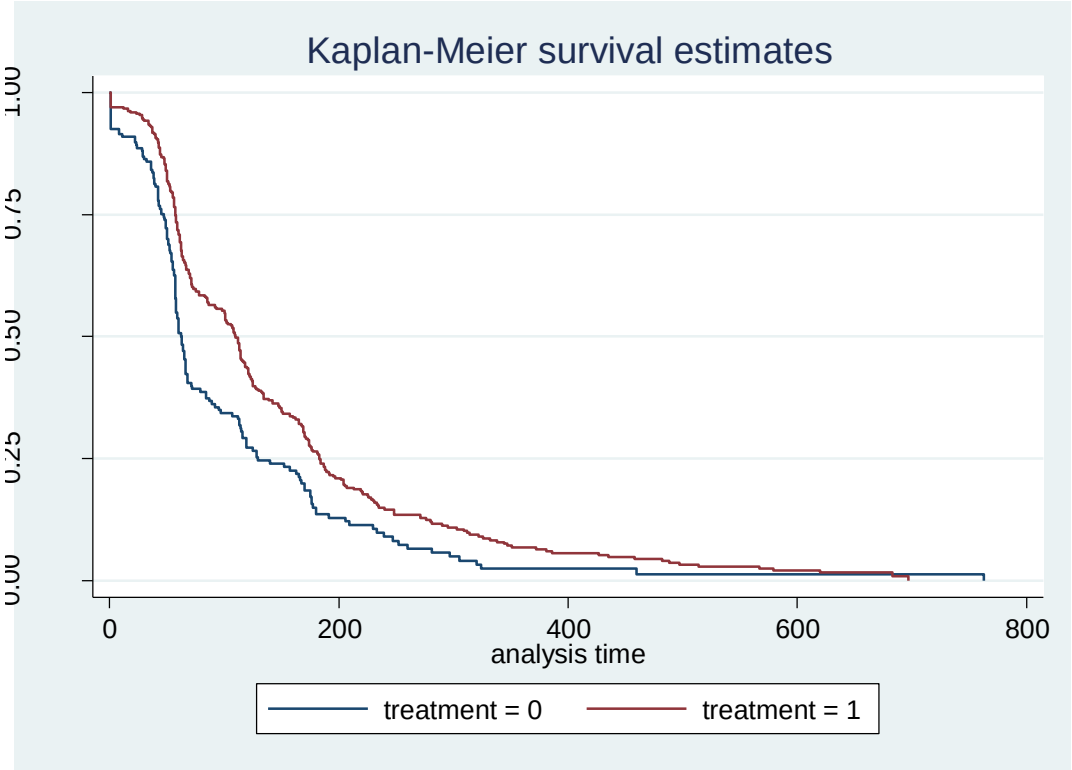
515	516	124	1	0	0.3388	0.0247	0.2908	0.3874
522	523	123	1	0	0.3361	0.0247	0.2881	0.3846
523	524	122	1	0	0.3333	0.0246	0.2855	0.3818
524	525	121	1	0	0.3306	0.0246	0.2829	0.3789
526	527	120	2	0	0.3251	0.0245	0.2776	0.3733
527	528	118	1	0	0.3223	0.0244	0.275	0.3704
529	530	117	1	0	0.3195	0.0244	0.2724	0.3676
530	531	116	1	0	0.3168	0.0243	0.2697	0.3648
535	536	115	1	0	0.314	0.0243	0.2671	0.3619
537	538	114	1	0	0.3113	0.0242	0.2645	0.3591
539	540	113	1	0	0.3085	0.0242	0.2619	0.3563
542	543	112	1	0	0.3058	0.0241	0.2593	0.3534
543	544	111	1	0	0.303	0.024	0.2567	0.3506
545	546	110	1	0	0.3003	0.024	0.2541	0.3477
551	552	109	1	0	0.2975	0.0239	0.2515	0.3449
559	560	108	1	0	0.2948	0.0238	0.2488	0.342
562	563	107	1	0	0.292	0.0238	0.2462	0.3392
570	571	106	1	0	0.2892	0.0237	0.2436	0.3363
573	574	105	1	0	0.2865	0.0236	0.241	0.3334
589	590	104	1	0	0.2837	0.0236	0.2384	0.3306
591	592	103	1	0	0.281	0.0235	0.2359	0.3277
597	598	102	1	0	0.2782	0.0234	0.2333	0.3248
603	604	101	1	0	0.2755	0.0234	0.2307	0.322
605	606	100	1	0	0.2727	0.0233	0.2281	0.3191
608	609	99	1	0	0.27	0.0232	0.2255	0.3162
610	611	98	1	0	0.2672	0.0232	0.2229	0.3134
621	622	97	1	0	0.2645	0.0231	0.2203	0.3105
622	623	96	1	0	0.2617	0.023	0.2178	0.3076
642	643	95	1	0	0.2589	0.0229	0.2152	0.3047
643	644	94	1	0	0.2562	0.0228	0.2126	0.3019
650	651	93	1	0	0.2534	0.0228	0.21	0.299
651	652	92	1	0	0.2507	0.0227	0.2075	0.2961
652	653	91	1	0	0.2479	0.0226	0.2049	0.2932
661	662	90	1	0	0.2452	0.0225	0.2023	0.2903
662	663	89	1	0	0.2424	0.0224	0.1998	0.2874
663	664	88	1	0	0.2397	0.0223	0.1972	0.2845
670	671	87	1	0	0.2369	0.0223	0.1947	0.2816

671	672	86	1	0	0.2342	0.0222	0.1921	0.2787
674	675	85	1	0	0.2314	0.0221	0.1895	0.2758
677	678	84	2	0	0.2259	0.0219	0.1845	0.27
690	691	82	1	0	0.2231	0.0218	0.1819	0.2671
693	694	81	1	0	0.2204	0.0217	0.1794	0.2642
696	697	80	1	0	0.2176	0.0216	0.1768	0.2612
701	702	79	1	0	0.2149	0.0215	0.1743	0.2583
704	705	78	1	0	0.2121	0.0214	0.1718	0.2554
717	718	77	2	0	0.2066	0.0212	0.1667	0.2495
719	720	75	1	0	0.2038	0.0211	0.1642	0.2466
722	723	74	1	0	0.2011	0.021	0.1617	0.2437
736	737	73	1	0	0.1983	0.0209	0.1592	0.2407
739	740	72	1	0	0.1956	0.0208	0.1566	0.2378
747	748	71	1	0	0.1928	0.0207	0.1541	0.2349
752	753	70	1	0	0.1901	0.0206	0.1516	0.2319
756	757	69	1	0	0.1873	0.0204	0.1491	0.229
763	764	68	1	0	0.1846	0.0203	0.1466	0.226
770	771	67	1	0	0.1818	0.0202	0.1441	0.2231
776	777	66	1	0	0.1791	0.0201	0.1416	0.2201
781	782	65	1	0	0.1763	0.02	0.1391	0.2171
786	787	64	1	0	0.1735	0.0198	0.1366	0.2142
790	791	63	2	0	0.168	0.0196	0.1317	0.2082
810	811	61	1	0	0.1653	0.0195	0.1292	0.2053
817	818	60	1	0	0.1625	0.0193	0.1267	0.2023
825	826	59	1	0	0.1598	0.0192	0.1243	0.1993
827	828	58	1	0	0.157	0.0191	0.1218	0.1963
842	843	57	1	0	0.1543	0.0189	0.1193	0.1933
844	845	56	1	0	0.1515	0.0188	0.1169	0.1903
879	880	55	1	0	0.1488	0.0186	0.1144	0.1873
885	886	54	1	0	0.146	0.0185	0.112	0.1843
888	889	53	1	0	0.1432	0.0184	0.1095	0.1813
892	893	52	1	0	0.1405	0.0182	0.1071	0.1783
909	910	51	2	0	0.135	0.0179	0.1022	0.1723
931	932	49	1	0	0.1322	0.0178	0.0998	0.1692
934	935	48	1	0	0.1295	0.0176	0.0974	0.1662
941	942	47	1	0	0.1267	0.0174	0.095	0.1632
949	950	46	2	0	0.1212	0.0171	0.0902	0.1571

966	967	44	1	0	0.1185	0.0169	0.0878	0.154
972	973	43	1	0	0.1157	0.0168	0.0854	0.151
976	977	42	1	0	0.1129	0.0166	0.083	0.1479
981	982	41	1	0	0.1102	0.0164	0.0806	0.1449
1016	1017	40	1	0	0.1074	0.0162	0.0783	0.1418
1021	1022	39	1	0	0.1047	0.0161	0.0759	0.1387
1023	1024	38	1	0	0.1019	0.0159	0.0735	0.1356
1041	1042	37	1	0	0.0992	0.0157	0.0712	0.1325
1042	1043	36	1	0	0.0964	0.0155	0.0688	0.1294
1048	1049	35	1	0	0.0937	0.0153	0.0665	0.1263
1049	1050	34	1	0	0.0909	0.0151	0.0642	0.1232
1054	1055	33	1	0	0.0882	0.0149	0.0619	0.1201
1065	1066	32	1	0	0.0854	0.0147	0.0596	0.1169
1080	1081	31	1	0	0.0826	0.0144	0.0572	0.1138
1089	1090	30	1	0	0.0799	0.0142	0.055	0.1107
1095	1096	29	1	0	0.0771	0.014	0.0527	0.1075
1206	1207	28	1	0	0.0744	0.0138	0.0504	0.1043
1209	1210	27	1	0	0.0716	0.0135	0.0481	0.1012
1218	1219	26	1	0	0.0689	0.0133	0.0459	0.098
1236	1237	25	1	0	0.0661	0.013	0.0436	0.0948
1327	1328	24	1	0	0.0634	0.0128	0.0414	0.0916
1380	1381	23	1	0	0.0606	0.0125	0.0392	0.0883
1418	1419	22	1	0	0.0578	0.0122	0.037	0.0851
1420	1421	21	1	0	0.0551	0.012	0.0348	0.0819
1504	1505	20	1	0	0.0523	0.0117	0.0327	0.0786
1561	1562	19	1	0	0.0496	0.0114	0.0305	0.0753
1653	1654	18	0	1	0.0496	0.0114	0.0305	0.0753
1676	1677	17	1	0	0.0467	0.0111	0.0282	0.0719
1696	1697	16	0	1	0.0467	0.0111	0.0282	0.0719
1697	1698	15	0	1	0.0467	0.0111	0.0282	0.0719
1710	1711	14	0	1	0.0467	0.0111	0.0282	0.0719
1745	1746	13	1	0	0.0431	0.0108	0.0253	0.0679
1756	1757	12	1	0	0.0395	0.0105	0.0225	0.0638
1757	1758	11	1	0	0.0359	0.0101	0.0197	0.0597
1788	1789	10	0	1	0.0359	0.0101	0.0197	0.0597
1814	1815	9	0	1	0.0359	0.0101	0.0197	0.0597
1835	1836	8	0	1	0.0359	0.0101	0.0197	0.0597

1862	1863	7	0	1	0.0359	0.0101	0.0197	0.0597
1883	1884	6	1	1	0.0294	0.0102	0.0139	0.0545
1930	1931	4	1	0	0.022	0.0099	0.0082	0.0485
1996	1997	3	0	1	0.022	0.0099	0.0082	0.0485
2010	2011	2	0	1	0.022	0.0099	0.0082	0.0485
2245	2246	1	0	1	0.022	0.0099	0.0082	0.0485

b. Time to disease progression or death (PFS) Kaplan-Meier analysis based on investigator assessment, stratified by treatment arm (eribulin vs TPC).



Interval		Total	Deaths	Lost	Survival	Error	[95% Conf. Int.]	
TPC								
1	2	189	14	11	0.9237	0.0196	0.8746	0.9541
8	9	164	2	0	0.9124	0.0209	0.861	0.9454
11	12	162	1	0	0.9068	0.0215	0.8544	0.941
22	23	161	2	0	0.8955	0.0227	0.8411	0.9321
23	24	159	1	0	0.8899	0.0232	0.8345	0.9275
24	25	158	1	0	0.8843	0.0238	0.828	0.923
28	29	157	1	0	0.8786	0.0243	0.8215	0.9184
29	30	156	2	0	0.8674	0.0252	0.8086	0.9091
30	31	154	1	0	0.8617	0.0257	0.8022	0.9044
32	33	153	1	0	0.8561	0.0261	0.7959	0.8997
36	37	152	3	0	0.8392	0.0274	0.7769	0.8854
37	38	149	1	0	0.8336	0.0278	0.7706	0.8806
38	39	148	2	0	0.8223	0.0285	0.7582	0.8709
39	40	146	2	0	0.8111	0.0292	0.7458	0.8611
40	41	144	1	1	0.8054	0.0295	0.7396	0.8562
42	43	142	5	0	0.777	0.0311	0.7087	0.8313
43	44	137	2	0	0.7657	0.0317	0.6965	0.8212
44	45	135	1	0	0.76	0.0319	0.6904	0.8161
45	46	134	2	0	0.7487	0.0325	0.6783	0.8059
47	48	132	1	0	0.743	0.0327	0.6722	0.8008
48	49	131	1	0	0.7373	0.0329	0.6662	0.7957
49	50	130	3	0	0.7203	0.0336	0.6482	0.7802
50	51	127	4	0	0.6976	0.0344	0.6244	0.7594
51	52	123	2	1	0.6863	0.0348	0.6125	0.7489
52	53	120	2	0	0.6748	0.0351	0.6006	0.7383
53	54	118	1	0	0.6691	0.0353	0.5947	0.733
54	55	117	3	0	0.6519	0.0358	0.5769	0.7169
55	56	114	3	0	0.6348	0.0362	0.5593	0.7008
56	57	111	2	2	0.6232	0.0364	0.5475	0.69
57	58	107	8	2	0.5762	0.0373	0.4997	0.6453
58	59	97	5	0	0.5465	0.0376	0.4698	0.6168
59	60	92	2	0	0.5346	0.0377	0.4579	0.6053
60	61	90	5	0	0.5049	0.0379	0.4284	0.5764
62	63	85	1	0	0.499	0.0379	0.4226	0.5706
63	64	84	3	0	0.4812	0.0379	0.4051	0.5531

64	65	81	2	1	0.4692	0.0379	0.3934	0.5413
65	66	78	3	0	0.4512	0.0379	0.3758	0.5235
66	67	75	5	0	0.4211	0.0377	0.3467	0.4935
68	69	70	3	1	0.4029	0.0375	0.3293	0.4753
71	72	66	1	0	0.3968	0.0374	0.3234	0.4691
72	73	65	1	0	0.3907	0.0373	0.3176	0.463
79	80	64	1	0	0.3846	0.0372	0.3118	0.4568
84	85	63	2	0	0.3724	0.037	0.3002	0.4444
87	88	61	1	0	0.3663	0.0369	0.2944	0.4382
89	90	60	1	0	0.3602	0.0368	0.2887	0.432
92	93	59	1	0	0.3541	0.0367	0.2829	0.4258
95	96	58	1	0	0.348	0.0366	0.2772	0.4196
97	98	57	1	0	0.3419	0.0364	0.2715	0.4133
99	100	56	0	1	0.3419	0.0364	0.2715	0.4133
107	108	55	1	0	0.3356	0.0363	0.2656	0.4069
111	112	54	0	1	0.3356	0.0363	0.2656	0.4069
112	113	53	1	1	0.3293	0.0362	0.2596	0.4004
113	114	51	2	0	0.3163	0.0359	0.2475	0.3872
114	115	49	1	0	0.3099	0.0357	0.2415	0.3806
115	116	48	1	0	0.3034	0.0356	0.2355	0.3739
116	117	47	2	0	0.2905	0.0352	0.2236	0.3606
119	120	45	3	0	0.2711	0.0346	0.2059	0.3404
125	126	42	1	0	0.2647	0.0344	0.2	0.3336
127	128	41	0	1	0.2647	0.0344	0.2	0.3336
128	129	40	2	0	0.2515	0.0339	0.188	0.3198
129	130	38	1	0	0.2448	0.0336	0.182	0.3128
140	141	37	1	0	0.2382	0.0334	0.176	0.3058
149	150	36	0	1	0.2382	0.0334	0.176	0.3058
152	153	35	1	0	0.2314	0.0331	0.1699	0.2987
157	158	34	1	0	0.2246	0.0328	0.1638	0.2915
163	164	33	1	0	0.2178	0.0325	0.1577	0.2843
165	166	32	1	0	0.211	0.0322	0.1517	0.277
166	167	31	1	0	0.2042	0.0319	0.1457	0.2697
167	168	30	1	0	0.1974	0.0315	0.1397	0.2624
170	171	29	2	0	0.1838	0.0308	0.1279	0.2477
175	176	27	2	1	0.1699	0.03	0.1159	0.2327
176	177	24	2	0	0.1557	0.0291	0.1039	0.2172

177	178	22	1	0	0.1487	0.0286	0.0979	0.2094
180	181	21	2	0	0.1345	0.0276	0.0862	0.1937
191	192	19	1	0	0.1274	0.027	0.0804	0.1857
206	207	18	1	0	0.1203	0.0265	0.0746	0.1777
209	210	17	1	0	0.1133	0.0258	0.069	0.1697
227	228	16	0	1	0.1133	0.0258	0.069	0.1697
229	230	15	0	1	0.1133	0.0258	0.069	0.1697
230	231	14	1	0	0.1052	0.0252	0.0624	0.1607
233	234	13	1	0	0.0971	0.0245	0.0559	0.1517
239	240	12	1	0	0.089	0.0238	0.0496	0.1426
247	248	11	1	0	0.0809	0.023	0.0434	0.1333
252	253	10	1	0	0.0728	0.022	0.0374	0.1238
260	261	9	1	0	0.0647	0.021	0.0316	0.1142
281	282	8	1	0	0.0566	0.0199	0.026	0.1045
297	298	7	1	0	0.0485	0.0186	0.0207	0.0945
305	306	6	1	0	0.0405	0.0172	0.0156	0.0842
320	321	5	1	0	0.0324	0.0155	0.011	0.0737
324	325	4	1	0	0.0243	0.0136	0.0068	0.0628
440	441	3	0	1	0.0243	0.0136	0.0068	0.0628
460	461	2	1	0	0.0121	0.0109	0.0014	0.0521
763	764	1	1	0	0	.	.	.

Interval		Total	Deaths	Lost	Survival	Error	[95% Conf. Int.]	
Halaven								
1	2	370	11	9	0.9699	0.0089	0.9463	0.9832
12	13	350	1	0	0.9671	0.0093	0.9428	0.9812
16	17	349	2	0	0.9616	0.0101	0.936	0.9771
18	19	347	1	0	0.9588	0.0104	0.9326	0.975
23	24	346	1	0	0.956	0.0107	0.9293	0.9728
26	27	345	1	0	0.9533	0.0111	0.9259	0.9707
28	29	344	2	0	0.9477	0.0117	0.9193	0.9663
29	30	342	1	0	0.945	0.012	0.916	0.9641
30	31	341	1	0	0.9422	0.0122	0.9127	0.9619
34	35	340	3	0	0.9339	0.013	0.903	0.9552
35	36	337	1	0	0.9311	0.0133	0.8997	0.9529
36	37	336	1	0	0.9283	0.0135	0.8965	0.9506
37	38	335	4	0	0.9173	0.0145	0.8838	0.9414
39	40	331	1	0	0.9145	0.0147	0.8806	0.9391

40	41	330	3	0	0.9062	0.0153	0.8712	0.932
41	42	327	1	0	0.9034	0.0155	0.868	0.9297
42	43	326	2	0	0.8979	0.0159	0.8618	0.9249
43	44	324	4	0	0.8868	0.0167	0.8494	0.9153
44	45	320	5	0	0.8729	0.0175	0.834	0.9032
45	46	315	2	0	0.8674	0.0178	0.8279	0.8983
47	48	313	1	0	0.8646	0.018	0.8248	0.8959
48	49	312	4	0	0.8535	0.0186	0.8127	0.8861
49	50	308	5	0	0.8397	0.0193	0.7976	0.8737
50	51	303	8	0	0.8175	0.0203	0.7737	0.8536
51	52	295	2	0	0.8119	0.0206	0.7677	0.8486
52	53	293	2	1	0.8064	0.0208	0.7618	0.8435
53	54	290	3	0	0.7981	0.0211	0.7528	0.8359
54	55	287	1	0	0.7953	0.0212	0.7499	0.8334
55	56	286	4	0	0.7842	0.0216	0.738	0.8231
56	57	282	7	0	0.7647	0.0223	0.7174	0.8051
57	58	275	6	0	0.748	0.0229	0.6999	0.7896
58	59	269	5	0	0.7341	0.0233	0.6853	0.7766
59	60	264	6	0	0.7174	0.0237	0.6679	0.7609
60	61	258	3	0	0.7091	0.0239	0.6592	0.753
61	62	255	6	0	0.6924	0.0243	0.6419	0.7372
62	63	249	6	0	0.6757	0.0247	0.6247	0.7213
63	64	243	4	0	0.6646	0.0249	0.6133	0.7107
64	65	239	3	0	0.6562	0.025	0.6047	0.7027
65	66	236	2	0	0.6507	0.0251	0.599	0.6974
66	67	234	2	0	0.6451	0.0252	0.5933	0.6921
67	68	232	3	0	0.6368	0.0253	0.5848	0.684
69	70	229	3	0	0.6284	0.0255	0.5763	0.676
70	71	226	3	0	0.6201	0.0256	0.5678	0.668
71	72	223	5	0	0.6062	0.0257	0.5537	0.6545
72	73	218	2	0	0.6006	0.0258	0.5481	0.6491
73	74	216	1	0	0.5978	0.0258	0.5453	0.6464
75	76	215	2	0	0.5923	0.0259	0.5396	0.641
77	78	213	0	1	0.5923	0.0259	0.5396	0.641
78	79	212	3	0	0.5839	0.026	0.5312	0.6328
83	84	209	1	0	0.5811	0.026	0.5284	0.6301
84	85	208	1	0	0.5783	0.026	0.5255	0.6274

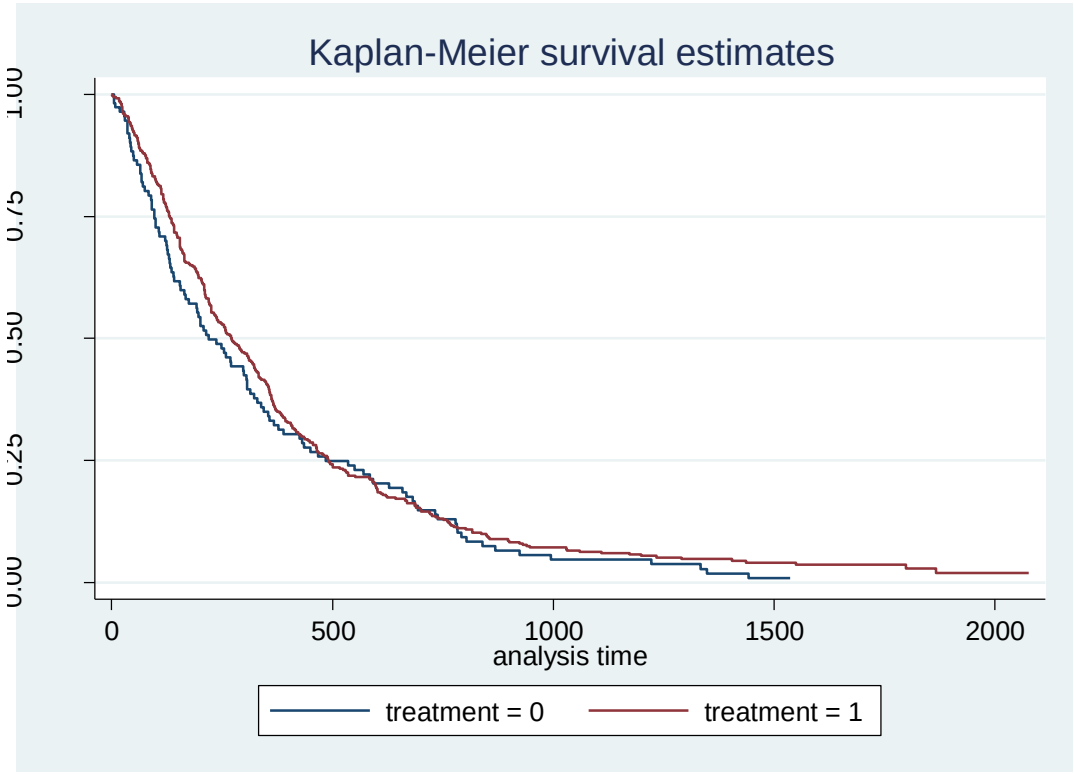
85	86	207	3	0	0.5699	0.0261	0.5171	0.6192
86	87	204	2	0	0.5643	0.0261	0.5115	0.6138
92	93	202	2	0	0.5588	0.0262	0.5059	0.6083
93	94	200	1	0	0.556	0.0262	0.5031	0.6056
98	99	199	1	0	0.5532	0.0262	0.5003	0.6028
100	101	198	2	0	0.5476	0.0262	0.4947	0.5973
101	102	196	5	0	0.5336	0.0263	0.4807	0.5836
102	103	191	2	0	0.528	0.0263	0.4751	0.5781
103	104	189	1	0	0.5252	0.0263	0.4723	0.5753
106	107	188	1	0	0.5224	0.0263	0.4696	0.5726
107	108	187	2	1	0.5168	0.0264	0.464	0.5671
108	109	184	3	0	0.5084	0.0264	0.4556	0.5587
109	110	181	2	1	0.5028	0.0264	0.45	0.5532
110	111	178	2	0	0.4971	0.0264	0.4444	0.5476
112	113	176	4	0	0.4858	0.0264	0.4332	0.5364
113	114	172	5	0	0.4717	0.0264	0.4192	0.5223
114	115	167	6	0	0.4548	0.0263	0.4026	0.5054
115	116	161	1	0	0.4519	0.0263	0.3998	0.5026
116	117	160	1	2	0.4491	0.0263	0.397	0.4997
117	118	157	1	0	0.4462	0.0263	0.3942	0.4969
118	119	156	3	0	0.4377	0.0262	0.3858	0.4883
120	121	153	1	0	0.4348	0.0262	0.383	0.4854
121	122	152	4	0	0.4233	0.0261	0.3718	0.4739
122	123	148	2	0	0.4176	0.0261	0.3662	0.4682
123	124	146	2	1	0.4119	0.026	0.3606	0.4624
124	125	143	1	0	0.409	0.026	0.3578	0.4595
125	126	142	4	0	0.3975	0.0259	0.3466	0.4479
126	127	138	0	1	0.3975	0.0259	0.3466	0.4479
127	128	137	1	0	0.3946	0.0259	0.3437	0.4449
128	129	136	1	0	0.3917	0.0259	0.3409	0.442
130	131	135	1	0	0.3888	0.0258	0.3381	0.4391
132	133	134	1	0	0.3859	0.0258	0.3353	0.4361
133	134	133	1	0	0.383	0.0258	0.3325	0.4332
134	135	132	4	1	0.3713	0.0256	0.3212	0.4214
139	140	127	1	0	0.3684	0.0256	0.3184	0.4184
142	143	126	2	0	0.3626	0.0255	0.3127	0.4125
143	144	124	0	1	0.3626	0.0255	0.3127	0.4125

147	148	123	2	0	0.3567	0.0255	0.307	0.4065
148	149	121	1	0	0.3537	0.0254	0.3042	0.4035
150	151	120	3	0	0.3449	0.0253	0.2957	0.3945
151	152	117	1	0	0.3419	0.0252	0.2929	0.3915
157	158	116	2	0	0.336	0.0251	0.2872	0.3855
158	159	114	0	1	0.336	0.0251	0.2872	0.3855
160	161	113	1	1	0.333	0.0251	0.2843	0.3824
162	163	111	1	0	0.33	0.0251	0.2815	0.3793
165	166	110	3	0	0.321	0.0249	0.2728	0.3701
167	168	107	1	0	0.318	0.0248	0.27	0.3671
168	169	106	1	0	0.315	0.0248	0.2671	0.364
169	170	105	4	1	0.303	0.0246	0.2556	0.3516
170	171	100	3	0	0.2939	0.0244	0.247	0.3422
171	172	97	1	0	0.2909	0.0243	0.2441	0.3391
173	174	96	1	0	0.2878	0.0243	0.2412	0.336
174	175	95	4	0	0.2757	0.024	0.2298	0.3234
175	176	91	1	1	0.2727	0.0239	0.2269	0.3203
176	177	89	2	0	0.2665	0.0238	0.2211	0.3139
177	178	87	1	0	0.2635	0.0237	0.2182	0.3108
179	180	86	0	1	0.2635	0.0237	0.2182	0.3108
181	182	85	1	0	0.2604	0.0236	0.2153	0.3075
182	183	84	1	0	0.2573	0.0235	0.2124	0.3043
183	184	83	3	0	0.248	0.0233	0.2037	0.2946
184	185	80	3	2	0.2386	0.023	0.1949	0.2848
185	186	75	0	1	0.2386	0.023	0.1949	0.2848
187	188	74	2	0	0.2321	0.0228	0.1889	0.2781
188	189	72	2	0	0.2257	0.0227	0.1828	0.2714
189	190	70	1	0	0.2224	0.0226	0.1798	0.268
191	192	69	1	0	0.2192	0.0225	0.1768	0.2646
192	193	68	1	0	0.216	0.0224	0.1739	0.2612
195	196	67	1	0	0.2128	0.0223	0.1709	0.2578
196	197	66	0	1	0.2128	0.0223	0.1709	0.2578
197	198	65	1	0	0.2095	0.0222	0.1678	0.2544
202	203	64	1	0	0.2062	0.0221	0.1648	0.251
204	205	63	3	0	0.1964	0.0217	0.1558	0.2406
205	206	60	1	0	0.1931	0.0216	0.1527	0.2371
207	208	59	1	0	0.1899	0.0215	0.1497	0.2337

210	211	58	0	1	0.1899	0.0215	0.1497	0.2337
213	214	57	1	0	0.1865	0.0214	0.1467	0.2301
217	218	56	0	1	0.1865	0.0214	0.1467	0.2301
219	220	55	1	0	0.1831	0.0212	0.1436	0.2266
220	221	54	1	0	0.1797	0.0211	0.1405	0.223
221	222	53	1	1	0.1763	0.021	0.1373	0.2193
225	226	51	1	0	0.1729	0.0209	0.1342	0.2157
226	227	50	1	0	0.1694	0.0207	0.131	0.212
228	229	49	1	0	0.1659	0.0206	0.1279	0.2083
230	231	48	1	0	0.1625	0.0205	0.1248	0.2047
231	232	47	1	0	0.159	0.0203	0.1216	0.201
233	234	46	1	0	0.1556	0.0202	0.1185	0.1973
234	235	45	1	0	0.1521	0.02	0.1154	0.1936
235	236	44	1	0	0.1487	0.0198	0.1123	0.1898
240	241	43	1	0	0.1452	0.0197	0.1092	0.1861
245	246	42	0	1	0.1452	0.0197	0.1092	0.1861
248	249	41	3	1	0.1344	0.0192	0.0996	0.1745
271	272	37	2	0	0.1272	0.0188	0.0931	0.1667
274	275	35	0	1	0.1272	0.0188	0.0931	0.1667
276	277	34	1	0	0.1234	0.0186	0.0898	0.1627
280	281	33	1	0	0.1197	0.0184	0.0865	0.1586
281	282	32	1	0	0.116	0.0182	0.0832	0.1545
290	291	31	1	0	0.1122	0.018	0.08	0.1505
295	296	30	1	0	0.1085	0.0178	0.0767	0.1464
303	304	29	1	0	0.1047	0.0176	0.0735	0.1423
309	310	28	1	0	0.101	0.0174	0.0703	0.1381
312	313	27	1	0	0.0973	0.0171	0.0671	0.134
314	315	26	1	0	0.0935	0.0169	0.0639	0.1298
322	323	25	1	0	0.0898	0.0166	0.0607	0.1257
326	327	24	1	0	0.086	0.0163	0.0576	0.1215
332	333	23	1	0	0.0823	0.016	0.0545	0.1173
338	339	22	1	0	0.0786	0.0157	0.0514	0.113
344	345	21	1	0	0.0748	0.0154	0.0483	0.1088
347	348	20	1	0	0.0711	0.0151	0.0453	0.1045
351	352	19	1	0	0.0673	0.0148	0.0423	0.1002
353	354	18	0	1	0.0673	0.0148	0.0423	0.1002
372	373	17	1	0	0.0634	0.0144	0.0391	0.0956

381	382	16	1	0	0.0594	0.014		0.0359	0.0911
386	387	15	1	0	0.0554	0.0137		0.0328	0.0865
427	428	14	1	0	0.0515	0.0132		0.0297	0.0819
435	436	13	1	0	0.0475	0.0128		0.0267	0.0772
458	459	12	1	0	0.0436	0.0123		0.0237	0.0724
482	483	11	1	0	0.0396	0.0118		0.0208	0.0677
488	489	10	1	0	0.0356	0.0113		0.018	0.0628
497	498	9	1	0	0.0317	0.0107		0.0153	0.0579
514	515	8	1	0	0.0277	0.0101		0.0126	0.0529
567	568	7	1	0	0.0238	0.0094		0.0101	0.0478
579	580	6	1	0	0.0198	0.0086		0.0076	0.0426
620	621	5	1	0	0.0158	0.0077		0.0054	0.0373
623	624	4	0	1	0.0158	0.0077		0.0054	0.0373
645	646	3	0	1	0.0158	0.0077		0.0054	0.0373
683	684	2	1	0	0.0079	0.0068		0.0011	0.0329
697	698	1	1	0	0	.	.	.	

c. Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis stratified by treatment arm (eribulin vs TPC).



Interval TPC		Total	Deaths	Lost	Survival	Error	[95% Conf. Int.]	
0	1	189	11	0	0.9418	0.017	0.8974	0.9673
5	6	178	2	0	0.9312	0.0184	0.8845	0.9595
8	9	176	1	0	0.9259	0.019	0.8781	0.9554
9	10	175	0	1	0.9259	0.019	0.8781	0.9554
14	15	174	1	0	0.9206	0.0197	0.8718	0.9514
18	19	173	1	0	0.9153	0.0203	0.8654	0.9472
28	29	172	1	0	0.91	0.0208	0.8592	0.943
30	31	171	1	0	0.9046	0.0214	0.8529	0.9388
34	35	170	0	1	0.9046	0.0214	0.8529	0.9388

35	36	169	1	0	0.8993	0.0219	0.8467	0.9345
36	37	168	3	0	0.8832	0.0234	0.8281	0.9215
40	41	165	1	0	0.8779	0.0239	0.822	0.9171
41	42	164	1	0	0.8725	0.0243	0.8158	0.9127
43	44	163	1	0	0.8672	0.0247	0.8098	0.9082
44	45	162	1	0	0.8618	0.0252	0.8037	0.9037
45	46	161	1	0	0.8565	0.0256	0.7977	0.8992
46	47	160	1	0	0.8511	0.026	0.7917	0.8947
47	48	159	1	0	0.8458	0.0263	0.7857	0.8902
48	49	158	1	0	0.8404	0.0267	0.7797	0.8856
49	50	157	0	1	0.8404	0.0267	0.7797	0.8856
50	51	156	1	0	0.835	0.0271	0.7737	0.881
53	54	155	1	0	0.8296	0.0274	0.7678	0.8763
54	55	154	2	0	0.8189	0.0281	0.7559	0.867
58	59	152	1	0	0.8135	0.0284	0.75	0.8623
64	65	151	1	0	0.8081	0.0288	0.7441	0.8576
65	66	150	1	1	0.8027	0.0291	0.7381	0.8529
67	68	148	2	0	0.7918	0.0297	0.7263	0.8433
70	71	146	1	1	0.7864	0.03	0.7204	0.8385
71	72	144	2	0	0.7755	0.0305	0.7086	0.8288
74	75	142	1	0	0.77	0.0308	0.7027	0.824
79	80	141	1	0	0.7645	0.0311	0.6969	0.8191
83	84	140	2	0	0.7536	0.0316	0.6852	0.8093
87	88	138	1	0	0.7482	0.0318	0.6793	0.8044
89	90	137	1	0	0.7427	0.032	0.6735	0.7994
90	91	136	3	0	0.7263	0.0327	0.6561	0.7845
91	92	133	1	0	0.7209	0.0329	0.6504	0.7796
94	95	132	1	0	0.7154	0.0331	0.6446	0.7746
97	98	131	3	0	0.699	0.0337	0.6274	0.7595
99	100	128	2	0	0.6881	0.034	0.616	0.7494
106	107	126	1	0	0.6826	0.0342	0.6103	0.7443
107	108	125	2	0	0.6717	0.0345	0.599	0.7342
108	109	123	1	0	0.6662	0.0346	0.5934	0.7291
110	111	122	1	0	0.6608	0.0348	0.5877	0.724
113	114	121	1	0	0.6553	0.0349	0.5821	0.7189
121	122	120	1	0	0.6499	0.0351	0.5765	0.7138
122	123	119	1	0	0.6444	0.0352	0.5708	0.7086

124	125	118	1	0	0.6389	0.0353	0.5652	0.7035
125	126	117	1	0	0.6335	0.0354	0.5597	0.6983
126	127	116	1	0	0.628	0.0355	0.5541	0.6932
127	128	115	1	0	0.6226	0.0357	0.5485	0.688
130	131	114	1	0	0.6171	0.0358	0.5429	0.6828
131	132	113	1	0	0.6116	0.0359	0.5374	0.6776
133	134	112	1	0	0.6062	0.0359	0.5318	0.6724
136	137	111	1	0	0.6007	0.036	0.5263	0.6672
139	140	110	1	0	0.5953	0.0361	0.5208	0.662
140	141	109	1	0	0.5898	0.0362	0.5153	0.6568
142	143	108	1	0	0.5843	0.0363	0.5097	0.6515
144	145	107	1	0	0.5789	0.0363	0.5042	0.6463
145	146	106	1	0	0.5734	0.0364	0.4988	0.641
147	148	105	1	0	0.5679	0.0365	0.4933	0.6358
155	156	104	3	0	0.5516	0.0366	0.4769	0.62
156	157	101	1	0	0.5461	0.0367	0.4714	0.6147
165	166	100	1	0	0.5406	0.0367	0.466	0.6094
167	168	99	1	0	0.5352	0.0367	0.4606	0.604
172	173	98	1	0	0.5297	0.0368	0.4552	0.5987
174	175	97	1	0	0.5243	0.0368	0.4498	0.5934
187	188	96	1	0	0.5188	0.0368	0.4444	0.5881
189	190	95	1	0	0.5133	0.0368	0.439	0.5827
192	193	94	1	0	0.5079	0.0368	0.4336	0.5774
193	194	93	1	0	0.5024	0.0368	0.4282	0.572
196	197	92	1	0	0.497	0.0368	0.4228	0.5666
197	198	91	1	0	0.4915	0.0368	0.4175	0.5613
201	202	90	2	0	0.4806	0.0368	0.4068	0.5505
208	209	88	1	0	0.4751	0.0368	0.4015	0.5451
214	215	87	2	0	0.4642	0.0368	0.3908	0.5342
219	220	85	1	0	0.4587	0.0367	0.3855	0.5288
228	229	84	1	0	0.4533	0.0367	0.3802	0.5234
237	238	83	1	0	0.4478	0.0367	0.3749	0.5179
248	249	82	1	0	0.4423	0.0366	0.3697	0.5125
255	256	81	1	0	0.4369	0.0366	0.3644	0.507
259	260	80	1	0	0.4314	0.0365	0.3591	0.5015
261	262	79	1	0	0.426	0.0365	0.3539	0.496
269	270	78	1	0	0.4205	0.0364	0.3486	0.4906

270	271	77	1	0	0.415	0.0363	0.3434	0.4851
272	273	76	1	0	0.4096	0.0363	0.3382	0.4796
284	285	75	1	0	0.4041	0.0362	0.333	0.474
285	286	74	1	0	0.3987	0.0361	0.3277	0.4685
298	299	73	1	0	0.3932	0.036	0.3226	0.463
299	300	72	1	0	0.3877	0.0359	0.3174	0.4574
305	306	71	1	0	0.3823	0.0358	0.3122	0.4519
306	307	70	1	0	0.3768	0.0357	0.307	0.4463
307	308	69	1	0	0.3713	0.0356	0.3019	0.4408
314	315	68	2	0	0.3604	0.0354	0.2916	0.4296
322	323	66	2	0	0.3495	0.0352	0.2813	0.4184
330	331	64	1	0	0.344	0.0351	0.2762	0.4128
338	339	63	1	0	0.3386	0.0349	0.2711	0.4071
344	345	62	1	0	0.3331	0.0348	0.266	0.4015
354	355	61	1	0	0.3277	0.0346	0.2609	0.3959
357	358	60	1	0	0.3222	0.0345	0.2559	0.3902
367	368	59	1	0	0.3167	0.0343	0.2508	0.3845
377	378	58	1	0	0.3113	0.0342	0.2458	0.3789
389	390	57	1	0	0.3058	0.034	0.2407	0.3732
397	398	56	1	0	0.3004	0.0338	0.2357	0.3675
399	400	55	1	0	0.2949	0.0337	0.2307	0.3618
425	426	54	1	0	0.2894	0.0335	0.2257	0.3561
431	432	53	1	0	0.284	0.0333	0.2207	0.3503
435	436	52	1	0	0.2785	0.0331	0.2157	0.3446
437	438	51	1	0	0.2731	0.0329	0.2108	0.3388
450	451	50	1	0	0.2676	0.0327	0.2058	0.3331
454	455	49	1	0	0.2621	0.0325	0.2009	0.3273
467	468	48	1	0	0.2567	0.0322	0.1959	0.3215
485	486	47	1	0	0.2512	0.032	0.191	0.3157
495	496	46	1	0	0.2457	0.0318	0.1861	0.3099
526	527	45	1	0	0.2403	0.0315	0.1812	0.3041
532	533	44	1	0	0.2348	0.0313	0.1764	0.2982
536	537	43	1	0	0.2294	0.031	0.1715	0.2924
540	541	42	1	0	0.2239	0.0308	0.1667	0.2865
541	542	41	1	0	0.2184	0.0305	0.1618	0.2806
550	551	40	1	0	0.213	0.0302	0.157	0.2747
551	552	39	1	0	0.2075	0.0299	0.1522	0.2688

570	571	38	1	0	0.2021	0.0297	0.1474	0.2629
572	573	37	1	0	0.1966	0.0293	0.1427	0.257
584	585	36	1	0	0.1911	0.029	0.1379	0.251
590	591	35	1	0	0.1857	0.0287	0.1332	0.245
592	593	34	1	0	0.1802	0.0284	0.1285	0.239
622	623	33	1	0	0.1748	0.028	0.1238	0.233
628	629	32	1	0	0.1693	0.0277	0.1191	0.227
634	635	31	1	0	0.1638	0.0273	0.1145	0.221
658	659	30	1	0	0.1584	0.027	0.1098	0.2149
667	668	29	1	0	0.1529	0.0266	0.1052	0.2088
681	682	28	1	0	0.1474	0.0262	0.1007	0.2027
686	687	27	1	0	0.142	0.0258	0.0961	0.1966
693	694	26	2	0	0.1311	0.0249	0.0871	0.1842
704	705	24	1	0	0.1256	0.0245	0.0826	0.178
706	707	23	1	0	0.1201	0.024	0.0781	0.1718
733	734	22	1	0	0.1147	0.0235	0.0737	0.1656
738	739	21	1	0	0.1092	0.023	0.0693	0.1593
747	748	20	1	0	0.1038	0.0225	0.065	0.1529
779	780	19	1	0	0.0983	0.022	0.0607	0.1466
782	783	18	1	0	0.0928	0.0214	0.0564	0.1402
783	784	17	1	0	0.0874	0.0209	0.0522	0.1338
792	793	16	1	0	0.0819	0.0203	0.048	0.1273
803	804	15	1	0	0.0765	0.0196	0.0439	0.1208
839	840	14	1	0	0.071	0.019	0.0398	0.1142
849	850	13	1	0	0.0655	0.0183	0.0358	0.1076
868	869	12	1	0	0.0601	0.0176	0.0318	0.1009
924	925	11	1	0	0.0546	0.0168	0.028	0.0941
975	976	10	1	0	0.0491	0.016	0.0242	0.0873
995	996	9	1	0	0.0437	0.0151	0.0205	0.0803
1084	1085	8	1	0	0.0382	0.0142	0.0169	0.0733
1222	1223	7	1	0	0.0328	0.0132	0.0135	0.0662
1273	1274	6	1	0	0.0273	0.012	0.0103	0.0589
1321	1322	5	1	0	0.0218	0.0108	0.0072	0.0514
1334	1335	4	1	0	0.0164	0.0094	0.0045	0.0437
1348	1349	3	1	0	0.0109	0.0077	0.0022	0.0358
1442	1443	2	1	0	0.0055	0.0054	0.0005	0.0279
1536	1537	1	0	1	0.0055	0.0054	0.0005	0.0279

Interval		Total	Deaths	Lost	Survival	Error	[95% Conf. Int.]	
Halaven								
0	1	370	12	0	0.9676	0.0092	0.9436	0.9815
1	2	358	1	0	0.9649	0.0096	0.9403	0.9794
4	5	357	1	0	0.9622	0.0099	0.9369	0.9774
10	11	356	1	0	0.9595	0.0103	0.9337	0.9754
17	18	355	2	0	0.9541	0.0109	0.9271	0.9712
20	21	353	1	0	0.9514	0.0112	0.9239	0.9691
21	22	352	1	1	0.9486	0.0115	0.9207	0.9669
22	23	350	1	0	0.9459	0.0118	0.9174	0.9648
23	24	349	1	0	0.9432	0.012	0.9142	0.9626
24	25	348	3	0	0.9351	0.0128	0.9047	0.956
25	26	345	2	0	0.9297	0.0133	0.8984	0.9516
29	30	343	1	0	0.927	0.0135	0.8953	0.9493
31	32	342	1	0	0.9243	0.0138	0.8922	0.9471
37	38	341	1	0	0.9215	0.014	0.8891	0.9448
39	40	340	3	0	0.9134	0.0146	0.8798	0.938
42	43	337	1	0	0.9107	0.0148	0.8767	0.9357
43	44	336	2	0	0.9053	0.0152	0.8706	0.9311
45	46	334	1	0	0.9026	0.0154	0.8675	0.9287
46	47	333	1	0	0.8999	0.0156	0.8645	0.9264
47	48	332	1	0	0.8971	0.0158	0.8614	0.9241
49	50	331	1	0	0.8944	0.016	0.8584	0.9217
50	51	330	1	0	0.8917	0.0162	0.8553	0.9194
51	52	329	1	0	0.889	0.0163	0.8523	0.917
52	53	328	1	0	0.8863	0.0165	0.8493	0.9147
56	57	327	1	0	0.8836	0.0167	0.8463	0.9123
58	59	326	1	0	0.8809	0.0169	0.8433	0.91
59	60	325	2	0	0.8755	0.0172	0.8373	0.9052
60	61	323	2	0	0.87	0.0175	0.8313	0.9004
61	62	321	2	0	0.8646	0.0178	0.8253	0.8956
62	63	319	1	0	0.8619	0.018	0.8224	0.8932
63	64	318	1	0	0.8592	0.0181	0.8194	0.8908
65	66	317	1	0	0.8565	0.0182	0.8164	0.8884
69	70	316	1	0	0.8538	0.0184	0.8135	0.886
71	72	315	1	0	0.8511	0.0185	0.8105	0.8836
75	76	314	1	0	0.8484	0.0187	0.8075	0.8812

76	77	313	1	0	0.8456	0.0188	0.8046	0.8787
77	78	312	1	0	0.8429	0.0189	0.8017	0.8763
78	79	311	1	0	0.8402	0.0191	0.7987	0.8739
80	81	310	1	0	0.8375	0.0192	0.7958	0.8714
81	82	309	2	0	0.8321	0.0195	0.7899	0.8665
85	86	307	1	0	0.8294	0.0196	0.787	0.8641
86	87	306	1	0	0.8267	0.0197	0.7841	0.8616
87	88	305	1	0	0.824	0.0198	0.7811	0.8592
88	89	304	2	0	0.8185	0.0201	0.7753	0.8543
89	90	302	2	0	0.8131	0.0203	0.7695	0.8493
90	91	300	1	0	0.8104	0.0204	0.7666	0.8468
92	93	299	2	0	0.805	0.0206	0.7608	0.8419
98	99	297	2	0	0.7996	0.0208	0.755	0.8369
100	101	295	1	0	0.7969	0.0209	0.7521	0.8344
101	102	294	1	0	0.7942	0.021	0.7492	0.832
102	103	293	1	0	0.7914	0.0211	0.7463	0.8295
103	104	292	1	0	0.7887	0.0212	0.7434	0.827
106	107	291	1	0	0.786	0.0213	0.7406	0.8245
111	112	290	2	0	0.7806	0.0215	0.7348	0.8195
112	113	288	4	0	0.7698	0.0219	0.7233	0.8094
116	117	284	1	0	0.767	0.022	0.7205	0.8069
117	118	283	3	0	0.7589	0.0223	0.7119	0.7993
118	119	280	2	0	0.7535	0.0224	0.7062	0.7943
121	122	278	1	0	0.7508	0.0225	0.7034	0.7918
122	123	277	2	0	0.7454	0.0227	0.6977	0.7867
124	125	275	1	0	0.7427	0.0228	0.6948	0.7842
125	126	274	1	0	0.7399	0.0228	0.692	0.7816
126	127	273	1	0	0.7372	0.0229	0.6892	0.7791
128	129	272	0	1	0.7372	0.0229	0.6892	0.7791
129	130	271	1	0	0.7345	0.023	0.6863	0.7765
130	131	270	3	0	0.7264	0.0232	0.6778	0.7689
131	132	267	1	0	0.7236	0.0233	0.675	0.7663
133	134	266	1	0	0.7209	0.0234	0.6721	0.7637
135	136	265	2	0	0.7155	0.0235	0.6665	0.7586
136	137	263	1	0	0.7127	0.0236	0.6636	0.756
138	139	262	1	0	0.71	0.0236	0.6608	0.7535
140	141	261	1	0	0.7073	0.0237	0.658	0.7509

141	142	260	4	0	0.6964	0.0239	0.6467	0.7406
142	143	256	1	0	0.6937	0.024	0.6439	0.738
147	148	255	2	0	0.6883	0.0241	0.6383	0.7328
148	149	253	1	0	0.6855	0.0242	0.6355	0.7302
149	150	252	1	0	0.6828	0.0242	0.6327	0.7277
154	155	251	5	0	0.6692	0.0245	0.6187	0.7147
155	156	246	2	0	0.6638	0.0246	0.6131	0.7095
156	157	244	1	0	0.6611	0.0247	0.6103	0.7069
159	160	243	1	0	0.6583	0.0247	0.6075	0.7043
160	161	242	2	0	0.6529	0.0248	0.6019	0.699
163	164	240	1	0	0.6502	0.0248	0.5991	0.6964
164	165	239	1	0	0.6475	0.0249	0.5963	0.6938
165	166	238	4	0	0.6366	0.0251	0.5852	0.6834
168	169	234	1	0	0.6339	0.0251	0.5824	0.6807
173	174	233	0	1	0.6339	0.0251	0.5824	0.6807
174	175	232	1	0	0.6311	0.0251	0.5797	0.6781
177	178	231	1	0	0.6284	0.0252	0.5769	0.6755
184	185	230	1	0	0.6257	0.0252	0.5741	0.6728
188	189	229	1	0	0.6229	0.0253	0.5713	0.6702
190	191	228	1	0	0.6202	0.0253	0.5685	0.6676
191	192	227	1	0	0.6175	0.0253	0.5657	0.6649
192	193	226	1	0	0.6147	0.0254	0.563	0.6623
195	196	225	2	0	0.6093	0.0254	0.5574	0.657
197	198	223	2	0	0.6038	0.0255	0.5519	0.6517
202	203	221	1	0	0.6011	0.0255	0.5491	0.649
203	204	220	2	0	0.5956	0.0256	0.5436	0.6437
205	206	218	1	0	0.5929	0.0256	0.5408	0.6411
206	207	217	1	0	0.5901	0.0256	0.5381	0.6384
209	210	216	1	0	0.5874	0.0257	0.5353	0.6358
210	211	215	3	0	0.5792	0.0257	0.527	0.6278
211	212	212	3	0	0.571	0.0258	0.5188	0.6198
212	213	209	2	0	0.5656	0.0258	0.5133	0.6144
213	214	207	1	0	0.5628	0.0259	0.5105	0.6117
219	220	206	2	0	0.5574	0.0259	0.505	0.6064
220	221	204	1	0	0.5546	0.0259	0.5023	0.6037
221	222	203	1	0	0.5519	0.0259	0.4996	0.601
223	224	202	1	0	0.5492	0.0259	0.4968	0.5984

225	226	201	2	0	0.5437	0.026	0.4914	0.593
226	227	199	3	0	0.5355	0.026	0.4832	0.5849
231	232	196	1	0	0.5328	0.026	0.4804	0.5822
233	234	195	1	0	0.53	0.026	0.4777	0.5796
236	237	194	1	0	0.5273	0.026	0.475	0.5769
237	238	193	1	0	0.5246	0.026	0.4723	0.5742
238	239	192	1	0	0.5218	0.0261	0.4695	0.5715
239	240	191	1	0	0.5191	0.0261	0.4668	0.5688
242	243	190	1	0	0.5164	0.0261	0.4641	0.5661
247	248	189	1	0	0.5136	0.0261	0.4614	0.5634
250	251	188	1	0	0.5109	0.0261	0.4587	0.5607
254	255	187	1	0	0.5082	0.0261	0.456	0.558
255	256	186	1	0	0.5054	0.0261	0.4532	0.5553
257	258	185	2	0	0.5	0.0261	0.4478	0.5498
258	259	183	1	0	0.4972	0.0261	0.4451	0.5471
259	260	182	1	0	0.4945	0.0261	0.4424	0.5444
262	263	181	1	0	0.4918	0.0261	0.4397	0.5417
268	269	180	1	0	0.4891	0.0261	0.437	0.539
270	271	179	2	0	0.4836	0.0261	0.4316	0.5336
272	273	177	1	0	0.4809	0.0261	0.4289	0.5308
273	274	176	1	0	0.4781	0.0261	0.4262	0.5281
276	277	175	1	0	0.4754	0.0261	0.4235	0.5254
279	280	174	1	0	0.4727	0.026	0.4208	0.5227
283	284	173	1	0	0.4699	0.026	0.4181	0.52
288	289	172	1	0	0.4672	0.026	0.4154	0.5172
289	290	171	1	0	0.4645	0.026	0.4127	0.5145
291	292	170	1	0	0.4617	0.026	0.4101	0.5118
294	295	169	1	0	0.459	0.026	0.4074	0.509
295	296	168	1	0	0.4563	0.026	0.4047	0.5063
301	302	167	1	0	0.4535	0.026	0.402	0.5036
306	307	166	1	0	0.4508	0.026	0.3993	0.5008
307	308	165	1	0	0.4481	0.026	0.3966	0.4981
309	310	164	1	0	0.4453	0.0259	0.394	0.4954
311	312	163	2	0	0.4399	0.0259	0.3886	0.4899
315	316	161	1	0	0.4371	0.0259	0.3859	0.4871
318	319	160	1	0	0.4344	0.0259	0.3833	0.4844
319	320	159	1	0	0.4317	0.0259	0.3806	0.4817

322	323	158	1	0	0.4289	0.0258	0.3779	0.4789
323	324	157	1	0	0.4262	0.0258	0.3752	0.4762
324	325	156	1	0	0.4235	0.0258	0.3726	0.4734
325	326	155	1	0	0.4207	0.0258	0.3699	0.4707
327	328	154	1	0	0.418	0.0257	0.3673	0.4679
329	330	153	1	0	0.4153	0.0257	0.3646	0.4651
332	333	152	2	0	0.4098	0.0257	0.3593	0.4596
333	334	150	1	0	0.4071	0.0256	0.3566	0.4569
335	336	149	1	0	0.4044	0.0256	0.354	0.4541
339	340	148	1	0	0.4016	0.0256	0.3513	0.4513
343	344	147	0	1	0.4016	0.0256	0.3513	0.4513
346	347	146	1	0	0.3989	0.0256	0.3486	0.4486
349	350	145	1	0	0.3961	0.0255	0.346	0.4458
350	351	144	1	0	0.3934	0.0255	0.3433	0.443
353	354	143	1	0	0.3906	0.0255	0.3406	0.4402
354	355	142	1	0	0.3879	0.0254	0.338	0.4374
355	356	141	2	0	0.3824	0.0254	0.3327	0.4318
357	358	139	2	0	0.3769	0.0253	0.3273	0.4262
358	359	137	1	0	0.3741	0.0253	0.3247	0.4235
359	360	136	1	0	0.3714	0.0252	0.322	0.4207
362	363	135	3	0	0.3631	0.0251	0.3141	0.4122
363	364	132	1	0	0.3604	0.0251	0.3114	0.4094
365	366	131	1	0	0.3576	0.025	0.3088	0.4066
366	367	130	2	0	0.3521	0.025	0.3035	0.401
368	369	128	1	0	0.3494	0.0249	0.3009	0.3982
369	370	127	1	0	0.3466	0.0249	0.2982	0.3954
370	371	126	1	0	0.3439	0.0248	0.2956	0.3926
372	373	125	1	0	0.3411	0.0248	0.2929	0.3898
374	375	124	1	0	0.3384	0.0247	0.2903	0.3869
381	382	123	1	0	0.3356	0.0247	0.2877	0.3841
383	384	122	1	0	0.3329	0.0246	0.2851	0.3813
384	385	121	1	0	0.3301	0.0246	0.2824	0.3785
387	388	120	1	0	0.3274	0.0245	0.2798	0.3756
392	393	119	1	0	0.3246	0.0245	0.2772	0.3728
393	394	118	1	0	0.3218	0.0244	0.2746	0.37
394	395	117	1	0	0.3191	0.0244	0.2719	0.3672
398	399	116	1	0	0.3163	0.0243	0.2693	0.3643

405	406	115	1	0	0.3136	0.0243	0.2667	0.3615
407	408	114	1	0	0.3108	0.0242	0.2641	0.3586
409	410	113	1	0	0.3081	0.0241	0.2615	0.3558
410	411	112	1	0	0.3053	0.0241	0.2589	0.353
414	415	111	1	0	0.3026	0.024	0.2563	0.3501
417	418	110	1	0	0.2998	0.024	0.2537	0.3473
418	419	109	1	0	0.2971	0.0239	0.2511	0.3444
423	424	108	1	0	0.2943	0.0238	0.2485	0.3416
426	427	107	1	0	0.2916	0.0238	0.2459	0.3387
429	430	106	1	0	0.2888	0.0237	0.2433	0.3359
436	437	105	1	0	0.2861	0.0236	0.2407	0.333
437	438	104	1	0	0.2833	0.0236	0.2381	0.3302
444	445	103	1	0	0.2806	0.0235	0.2355	0.3273
449	450	102	1	0	0.2778	0.0234	0.2329	0.3244
455	456	101	1	0	0.2751	0.0234	0.2303	0.3216
456	457	100	1	0	0.2723	0.0233	0.2277	0.3187
463	464	99	2	0	0.2668	0.0231	0.2226	0.313
464	465	97	2	0	0.2613	0.023	0.2174	0.3072
466	467	95	1	0	0.2586	0.0229	0.2148	0.3043
469	470	94	1	0	0.2558	0.0228	0.2123	0.3015
477	478	93	1	0	0.2531	0.0227	0.2097	0.2986
481	482	92	1	0	0.2503	0.0227	0.2071	0.2957
488	489	91	1	0	0.2476	0.0226	0.2046	0.2928
489	490	90	1	0	0.2448	0.0225	0.202	0.2899
490	491	89	1	0	0.2421	0.0224	0.1995	0.287
491	492	88	1	0	0.2393	0.0223	0.1969	0.2841
494	495	87	1	0	0.2366	0.0222	0.1944	0.2812
495	496	86	1	0	0.2338	0.0222	0.1918	0.2783
500	501	85	1	0	0.2311	0.0221	0.1893	0.2754
501	502	84	1	0	0.2283	0.022	0.1867	0.2725
516	517	83	1	0	0.2256	0.0219	0.1842	0.2696
523	524	82	1	0	0.2228	0.0218	0.1816	0.2667
530	531	81	1	0	0.2201	0.0217	0.1791	0.2638
531	532	80	1	0	0.2173	0.0216	0.1766	0.2609
535	536	79	2	0	0.2118	0.0214	0.1715	0.2551
551	552	77	1	0	0.2091	0.0213	0.169	0.2521
583	584	76	1	0	0.2063	0.0212	0.1665	0.2492

585	586	75	1	0	0.2036	0.0211	0.1639	0.2463
591	592	74	2	0	0.1981	0.0209	0.1589	0.2404
595	596	72	1	0	0.1953	0.0208	0.1564	0.2375
597	598	71	1	0	0.1926	0.0206	0.1539	0.2346
598	599	70	1	0	0.1898	0.0205	0.1514	0.2316
599	600	69	1	0	0.1871	0.0204	0.1489	0.2287
600	601	68	1	0	0.1843	0.0203	0.1464	0.2257
602	603	67	2	0	0.1788	0.0201	0.1414	0.2198
609	610	65	1	0	0.1761	0.0199	0.1389	0.2169
614	615	64	1	0	0.1733	0.0198	0.1364	0.2139
621	622	63	1	0	0.1706	0.0197	0.134	0.2109
623	624	62	1	0	0.1678	0.0196	0.1315	0.208
643	644	61	1	0	0.1651	0.0194	0.129	0.205
664	665	60	1	0	0.1623	0.0193	0.1265	0.202
668	669	59	1	0	0.1595	0.0192	0.1241	0.199
669	670	58	1	0	0.1568	0.019	0.1216	0.1961
687	688	57	2	0	0.1513	0.0188	0.1167	0.1901
689	690	55	1	0	0.1485	0.0186	0.1143	0.1871
697	698	54	1	0	0.1458	0.0185	0.1118	0.1841
701	702	53	2	0	0.1403	0.0182	0.107	0.1781
719	720	51	1	0	0.1375	0.018	0.1045	0.1751
720	721	50	1	0	0.1348	0.0179	0.1021	0.172
725	726	49	1	0	0.132	0.0177	0.0997	0.169
734	735	48	1	0	0.1293	0.0176	0.0973	0.166
740	741	47	1	0	0.1265	0.0174	0.0949	0.163
751	752	46	1	0	0.1238	0.0173	0.0925	0.1599
760	761	45	1	0	0.121	0.0171	0.0901	0.1569
762	763	44	1	0	0.1183	0.0169	0.0877	0.1538
765	766	43	1	0	0.1155	0.0168	0.0853	0.1508
768	769	42	1	0	0.1128	0.0166	0.0829	0.1477
774	775	41	1	0	0.11	0.0164	0.0805	0.1447
783	784	40	1	0	0.1073	0.0162	0.0781	0.1416
802	803	39	1	0	0.1045	0.016	0.0758	0.1385
817	818	38	2	0	0.099	0.0157	0.0711	0.1323
837	838	36	1	0	0.0963	0.0155	0.0687	0.1292
848	849	35	1	0	0.0935	0.0153	0.0664	0.1261
850	851	34	1	0	0.0908	0.0151	0.0641	0.123

852	853	33	1	0	0.088	0.0149	0.0618	0.1199
856	857	32	1	0	0.0853	0.0146	0.0595	0.1168
898	899	31	1	0	0.0825	0.0144	0.0572	0.1137
900	901	30	1	0	0.0798	0.0142	0.0549	0.1105
923	924	29	1	0	0.077	0.014	0.0526	0.1074
931	932	28	1	0	0.0743	0.0137	0.0503	0.1042
939	940	27	1	0	0.0715	0.0135	0.0481	0.101
947	948	26	1	0	0.0688	0.0133	0.0458	0.0978
1030	1031	25	1	0	0.066	0.013	0.0436	0.0947
1031	1032	24	1	0	0.0633	0.0128	0.0414	0.0914
1059	1060	23	1	0	0.0605	0.0125	0.0392	0.0882
1109	1110	22	1	0	0.0578	0.0122	0.037	0.085
1172	1173	21	1	0	0.055	0.012	0.0348	0.0818
1199	1200	20	1	0	0.0523	0.0117	0.0326	0.0785
1212	1213	19	0	1	0.0523	0.0117	0.0326	0.0785
1234	1235	18	1	0	0.0494	0.0114	0.0303	0.0751
1235	1236	17	0	1	0.0494	0.0114	0.0303	0.0751
1269	1270	16	0	1	0.0494	0.0114	0.0303	0.0751
1281	1282	15	0	1	0.0494	0.0114	0.0303	0.0751
1290	1291	14	1	0	0.0458	0.0111	0.0274	0.0712
1404	1405	13	1	0	0.0423	0.0108	0.0246	0.0672
1436	1437	12	1	0	0.0388	0.0104	0.0219	0.0631
1517	1518	11	0	1	0.0388	0.0104	0.0219	0.0631
1549	1550	10	1	0	0.0349	0.0101	0.0188	0.0588
1589	1590	9	0	1	0.0349	0.0101	0.0188	0.0588
1596	1597	8	0	1	0.0349	0.0101	0.0188	0.0588
1686	1687	7	0	1	0.0349	0.0101	0.0188	0.0588
1728	1729	6	0	1	0.0349	0.0101	0.0188	0.0588
1798	1799	5	1	0	0.0279	0.0102	0.0126	0.0535
1860	1861	4	0	1	0.0279	0.0102	0.0126	0.0535
1866	1867	3	1	0	0.0186	0.0102	0.0054	0.0477
1894	1895	2	0	1	0.0186	0.0102	0.0054	0.0477
2076	2077	1	0	1	0.0186	0.0102	0.0054	0.0477

d. Time to treatment discontinuation Kaplan-Meier analysis stratified by treatment arm (eribulin vs TPC).

Interval TPC		Total	Deaths	Lost	Survival	Error	[95% Conf. Int.]	
2	3	8	1	0	0.875	0.1169	0.387	0.9814
10	11	7	1	0	0.75	0.1531	0.3148	0.9309
35	36	6	1	0	0.625	0.1712	0.2293	0.8607
91	92	5	1	0	0.5	0.1768	0.152	0.7749
192	193	4	1	0	0.375	0.1712	0.087	0.6744
307	308	3	1	0	0.25	0.1531	0.0371	0.5581
768	769	2	1	0	0.125	0.1169	0.0066	0.4227
833	834	1	1	0	0	.	.	.
Interval eribulin		**Total**	**Deaths**	**Lost**	**Survival**	**Error**	**[95% Conf. Int.]**	
129	130	10	1	0	0.9	0.0949	0.473	0.9853
203	204	9	1	0	0.8	0.1265	0.4087	0.9459
234	235	8	1	0	0.7	0.1449	0.3287	0.8919
410	411	7	1	0	0.6	0.1549	0.2527	0.8272
449	450	6	1	0	0.5	0.1581	0.1836	0.7532
521	522	5	1	0	0.4	0.1549	0.1227	0.6702
605	606	4	1	0	0.3	0.1449	0.0711	0.5779
862	863	3	1	0	0.2	0.1265	0.0309	0.4747
1065	1066	2	1	0	0.1	0.0949	0.0057	0.3581
1133	1134	1	1	0	0	.	.	.

Rationale for clarification requests:

- B1: All Kaplan-Meier analyses with alternative censoring rule – when trials are stopped early or subject to early analysis the conventional censoring rule (censor when last contacted/reviewed) always understates the time exposed to risk but is much less likely to understate events, especially deaths. The result is that the hazard rate calculated by Kaplan-Meier algorithm are exaggerated when multiple patients are censored in any period. The resulting Kaplan-Meier estimated time-to-event trends may therefore be distorted by 'informative censoring' and poorly reflect the true profile of time-to-event. In some of the specified analyses there are suggestive indications that such effects are present, but it is not possible to confirm or refute this possibility without having access to re-analysis using the alternative censoring rule.

- B1 (a, b & c): Survival gain for eribulin versus comparator is the most important parameter governing cost-effectiveness. Careful analysis of OS and its components (PFS and PPS) is essential to validation of the survival gains estimated by the decision model.

- B1 (d): Time to treatment discontinuation offers an alternative to PFS as a basis for estimating treatment costs in both trial arms. This analysis will allow the sensitivity of incremental costs to the method of estimation to be assessed.

As requested, please find below an updated Table 15 from the company submission which now includes the breakdown of the numbers of patients receiving each agent in the TPC arm both for the ITT Population and for Subgroup 2 for the clinical effectiveness evidence.

Treatment of Physician's Choice: Study 305 (EMBRACE)

TPC therapy	ITT Population	Subgroup 2
	TPC (N = 254) n (%)	TPC (N = 189) n (%)
Chemotherapy	238 (93.7%)	174 (92.1%)
Vinorelbine	61 (24.0%)	54 (28.6%)
Gemcitabine	46 (18.1%)	38 (20.1%)
Capecitabine	44 (17.3%)	4 (2.1%)*
Taxanes†	38 (15.0%)	37 (19.6%)
Anthracyclines‡	24 (9.4%)	22 (11.6%)
Others	25 (9.8%)§	19 (10.1%)
Hormonal therapy	9 (3.5%)	9 (4.8%)
Fulvestrant	4 (1.6%)	4 (2.1%)
Letrozole	3 (1.2%)	3 (1.6%)
Exemestane	1 (0.4%)	1 (0.5%)
Tamoxifen	1 (0.4%)	1 (0.5%)

Abbreviations: ITT, Intent-to-treat; TPC, Treatment of Physician's Choice.
†Taxanes in the ITT population included paclitaxel (21 patients), docetaxel (10 patients), nab-paclitaxel (five patients) and ixabepilone (three patients) (one patient received paclitaxel in combination with gemcitabine and was included in the gemcitabine group). Taxanes in subgroup 2 included paclitaxel and nab-paclitaxel (25 patients), docetaxel (9 patients) and ixabepilone (three patients) (one patient received paclitaxel in combination with gemcitabine and was included in the gemcitabine group);
‡Anthracyclines in the ITT population included doxorubicin (19 patients), liposomal doxorubicin (four patients) and mitoxantrone (one patient), Anthracyclines in subgroup 2 included doxorubicin and liposomal doxorubicin (21 patients) and mitoxantrone (one patient),;
§Other chemotherapeutic agents were cisplatin, carboplatin, cyclophosphamide, etoposide, mitomycin, fluorouracil and methotrexate (one patient received cyclophosphamide and methotrexate). * Four patients in the TPC arm received capecitabine in the study even though they were treated with capecitabine prior to the study.
¶The remaining seven patients were discontinued prior to treatment initiation or received eribulin instead of the planned TPC.

As requested, please find below Table 43 in the company submission on page 138 giving the breakdown of the numbers of patients receiving each agent in the TPC arm as used in the cost effectiveness model for subgroup 2.

The proportion of treatment utilisation of the different therapies making up the TPC arm are based on the utilisation rates of the therapies included in the TPC arm of Study 305 (ITT population), excluding capecitabine and treatment with less than a 10% share.

Table 43 Treatment proportion for TPC (primary or secondary therapy)

	Study 305	
Drug Name	**Market Shares (excluding capecitabine)**	**Study 305 patients**
Chemotherapies		
Gemcitabine	27.71%	46
Vinorelbine	36.75%	61
Taxanes		
Docetaxel	6.02%	10
*Paclitaxel**	15.66%	26
*Doxorubicin***	13.86%	23
Total	***100%***	***166***

Source: Study 305 CSR

***** Includes paclitaxel and nab-paclitaxel

** Includes doxorubicin and liposomal doxorubicin

As requested, Eisai have checked the data provided in the previous response to A7 regarding baseline characteristics and have included below an updated table A2 which is consistent with the information in Table 15 of the company submission.

Table A2 Baseline characteristics in Study 305– ITT population and Subgroup 2

Characteristic	ITT population			Subgroup 2		
	Eribulin (n = 508)	TPC (n = 254)	Total (n = 762)	Eribulin (n = 370)	TPC (n = 189)	Total (n =559)
Median Age (range)	55.0 years (28–85)	55.0 years (27–81)	55.0 years (27–85)	55.0 years (28-80)	56.0 years (27-78)	55.0 years (28-80)
Age distribution, n (%)						
< 40 yrs	34 (6.7)	17 (6.7)	51 (6.7)	24 (6.5)	15 (7.9)	39 (7.0)
≥ 40 – < 65 yrs	380 (74.8)	180 (70.9)	560 (73.5)	280 (75.7)	133 (70.4)	413 (73.9)
≥ 65 yrs	94 (18.5)	57 (22.4)	151 (19.8)	66 (17.8)	41 (21.7)	107 (19.1)
Race, n (%)						
Caucasian	470 (92.5)	233 (91.7)	703 (92.3)	346 (93.5)	174 (92.1)	520 (93.0)
Black	20 (3.9)	14 (5.5)	34 (4.5)	13 (3.5)	10 (5.3)	23 (4.1)
Asian/Pacific Islander	3 (0.6)	2 (0.8)	5 (0.7)	1 (0.3)	2 (1.1)	3 (0.5)
Other	15 (3.0)	5 (2.0)	20 (2.6)	10 (2.7)	3 (1.6)	13 (2.3)
Geographic region, n (%)						
North America, Western Europe, Australia	325 (64.0)	163 (64.2)	488 (64.0)	258 (69.7)	131 (69.3)	389 (69.6)
Eastern Europe	129 (25.4)	64 (25.2)	193 (25.3)	77 (20.8)	40 (21.2)	117 (20.9)
Latin America, South Africa	54 (10.6)	27 (10.6)	81 (10.6)	35 (9.5)	18 (9.5)	53 (9.5)
Reproductive status, n (%)						
Fertile	46 (9.1)	20 (7.9)	66 (8.7)	33 (8.9)	14 (7.4)	47 (8.4)
Post-menopausal	379 (74.6)	199 (78.3)	578 (75.9)	280 (75.7)	150 (79.4)	430 (76.9)
Surgically sterile	78 (15.4)	35 (13.8)	113 (14.8)	53 (14.3)	25 (13.2)	78 (14.0)
Infertile	5 (1.0)	0	5 (0.7)	4 (1.1)	0 (0.0)	4 (0.7)
Median time since original diagnosis (range)	5.4 years (0.1, 37.4)	5.1 years (0.6, 22.9)	5.2 years (0.1, 37.4)	5.7 years (0.1, 37.4)	5.3 years (0.6, 22.9)	5.6 years (0.1, 37.4)
ER Status, n (%)†						
+	336 (70.0)	171 (70.4)	507 (70.1)	257 (72.0)	130 (70.7)	387 (71.5)
–	143 (29.8)	72 (29.6)	215 (29.7)	99 (27.7)	54 (29.3)	153 (28.3)
Unknown	1 (0.2)	0	1 (0.1)	1 (0.3)	0	1 (0.2)

Characteristic	ITT population			Subgroup 2		
	Eribulin (n = 508)	TPC (n = 254)	Total (n = 762)	Eribulin (n = 370)	TPC (n = 189)	Total (n =559)
PR Status, n (%)†						
+	254 (56.2)	123 (54.7)	377 (55.7)	195 (57.9)	93 (54.4)	288 (56.7)
–	197 (43.6)	102 (45.3)	299 (44.2)	141 (41.8)	78 (45.6)	219 (43.1)
Unknown	1 (0.2)	0	1 (0.1)	1 (0.3)	0	1 (0.2)
HER2 status, n (%)†						
+	83 (18.0)	40 (17.2)	123 (17.8)	60 (17.3)	29 (16.3)	89 (17.0)
–	373 (81.1)	192 (82.8)	565 (81.6)	285 (82.4)	149 (83.7)	434 (82.8)
Unknown	4 (0.9)	0	4 (0.6)	1 (0.3)	0	1 (0.2)
Triple negative (ER/PR/HER2-negative), n (%)†	93 (18.3)	51 (20.9)	144 (19.8)	68 (18.4)	38 (20.1)	106 (19.0)
No. of organs involved‡, n (%)						
1	85 (16.7)	35 (13.8)	120 (15.7)	61 (16.5)	25 (13.2)	86 (15.3)
2	172 (33.9)	82 (32.3)	254 (33.3)	128 (34.6)	59 (31.2)	187 (33.4)
3	145 (28.5)	77 (30.3)	222 (29.1)	106 (28.6)	60 (31.7)	166 (29.7)
4	71 (14.0)	37 (14.6)	108 (14.2)	49 (13.2)	29 (15.3)	78 (14.0)
5	24 (4.7)	16 (6.3)	40 (5.2)	18 (4.9)	10 (5.3)	28 (5.0)
≥ 6	9 (1.8)	7 (2.8)	16 (2.1)	6 (1.6)	6 (3.2)	12 (2.1)
Tumour sites in > 10% patients overall, n (%)						
Bone	306 (60.2)	158 (62.2)	464 (60.9)	234 (63.2)	120 (63.5)	354 (63.3)
Liver	296 (58.3)	159 (62.6)	455 (59.7)	225 (60.8)	127 (67.2)	352 (63.0)
Lymph nodes	220 (43.3)	118 (46.5)	338 (44.4)	150 (40.5)	87 (46.0)	237 (42.4)
Lung	197 (38.8)	95 (37.4)	292 (38.3)	138 (37.3)	67 (35.4)	205 (36.7)
Pleura	87 (17.1)	42 (16.5)	129 (16.9)	62 (16.8)	34 (18.0)	96 (17.2)
Breast	54 (10.6)	24 (9.4)	78 (10.2)	30 (8.1)	13 (6.9)	43 (7.7)
ECOG performance status, n (%)						
0	217 (42.7)	103 (40.6)	320 (42.0)	154 (41.6)	80 (42.3)	234 (41.9)
1	244 (48.0)	126 (49.6)	370 (48.6)	179 (48.4)	90 (47.6)	269 (44.9)
2	39 (7.7)	22 (8.7)	61 (8.0)	30 (8.1)	16 (8.5)	46 (8.2)

Characteristic	ITT population			Subgroup 2		
	Eribulin (n = 508)	TPC (n = 254)	Total (n = 762)	Eribulin (n = 370)	TPC (n = 189)	Total (n =559)
No. of prior chemotherapy regimens (adjuvant and LABC/MBC setting), n (%)						
1	1 (0.2)	0	1 (0.1)	1 (0.3)	0 (0.0)	1 (0.2)
2	65 (12.8)	31 (12.2)	96 (12.6)	17 (4.6)	11 (5.8)	28 (5.0)
3	176 (34.6)	83 (32.7)	259 (34.0)	122 (33.0)	51 (27.0)	173 (30.9)
4	166 (32.7)	79 (31.1)	245 (32.2)	142 (38.4)	69 (36.5)	211 (37.7)
5	85 (16.7)	51 (20.1)	136 (17.8)	74 (20.0)	48 (25.4)	122 (21.8)
≥ 6	13 (2.6)	9 (3.5)	22 (2.9)	13 (3.5)	9 (4.8)	22 (3.9)
No. of prior regimens in LABC/MBC setting, n (%)						
0	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	8 (1.6)	7 (2.8)	15 (2.0)	2 (0.5)	2 (1.1)	4 (0.7)
2	219 (43.1)	90 (35.4)	309 (40.6)	130 (35.1)	53 (28.0)	183 (32.7)
3	163 (32.1)	83 (32.7)	246 (32.3)	132 (35.7)	67 (35.4)	199 (35.6)
4	92 (18.1)	55 (21.7)	147 (19.3)	81 (21.9)	48 (25.4)	129 (23.1)
5	21 (4.1)	13 (5.1)	34 (4.5)	21 (5.7)	13 (6.9)	24 (6.1)
≥ 6	4 (0.8)	5 (2.0)	9 (1.2)	4 (1.1)	5 (2.6)	9 (1.6)
Duration of last chemotherapy (months), Median (min, max)†	3.57 (0.0, 32.0)	3.50 (0.1, 25.3)	3.53 (0.0, 32.0)	3.8 (0.0, 32.0)	3.7 (0.1, 25.3)	3.7 (0.0, 32.0)
No. of patients who previously (adjuvant and LABC/MBC setting) received: n (%)						
Taxanes	503 (99.0)	251 (98.8)	754 (99.0)	365 (98.6)	186 (98.4)	551 (98.6)
Anthracyclines	502 (98.8)	250 (98.4)	752 (98.7)	365 (98.6)	185 (97.9)	550 (98.4)
Capecitabine	370 (72.8)	189 (74.4)	559 (73.4)	370 (100.0)	189 (100.0)	559 (100.0)

†For the ER, PR, HER2 and triple negative status, the percentages are calculated from the total number of patients tested ‡The number of organs involved was based on the investigator review data.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Eribulin for treating locally advanced or metastatic breast cancer after chemotherapy [ID964]

Liverpool reviews and implementation group thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Breast Cancer Now

Your position in the organisation: [redacted]

Brief description of the organisation: Breast Cancer Now is the UK's largest breast cancer charity, dedicated to funding ground-breaking research into the disease. Our ambition is that by 2050, everyone who develops breast cancer will live. We're bringing together all those affected by the disease to improve the way we prevent, detect, treat and stop breast cancer. And we're committed to working with the NHS and governments across the UK to ensure that breast cancer services are as good as they can be, and that breast cancer patients benefit from advances in research as quickly as possible.

This submission reflects the views of Breast Cancer Now, based on our experience of working with people who are affected by breast cancer. We know that access to effective drugs is hugely important to our supporters and that quality of life is valued just as much as length of life.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Metastatic breast cancer is when cancer originating in the breast has spread to distant parts of the body, most commonly the lungs, brain, bones and liver. There is no cure for metastatic breast cancer, so most medicines aim to extend the length of life or to improve quality of life for patients. A patient can be diagnosed with metastatic (stage 4) cancer to begin with or they can develop the condition many years after treatment for their primary breast cancer has ended. Living with metastatic breast cancer is difficult to come to terms with for both the patient and their family. Patients' time is limited and the treatments usually have some side effects. Patients therefore tell us that

quality of life is just as important to take into account as length of life, as this means that they would be able to spend quality time with their loved ones.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

As mentioned above, both quality of life and extension of life are important to patients with metastatic breast cancer. Patients also value knowing that additional treatment options are available, as it gives them some comfort to know that there are more options available once their cancer progresses on current treatment.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Many of the newer, very effective treatments for secondary breast cancer have not been approved for routine use in the NHS in England. While many newer drugs are currently available through the Cancer Drugs Fund, these drugs are currently being reassessed by NICE and therefore their future availability is uncertain. This means that for many people with secondary breast cancer in England, treatment options could become incredibly limited once all Cancer Drugs Fund medicines are re-appraised.

This appraisal is considering eribulin as a treatment for all secondary breast cancers, regardless of HER2 or ER status, after patients have received chemotherapy. Patients in this situation will have already received at least one regimen of chemotherapy (either a taxane or an anthracycline) and their cancer will have progressed on this treatment. Currently these patients are likely to receive another chemotherapy treatment, such as capecitabine or vinorelbine, as their second line of treatment for secondary breast cancer.

The treatment options for different types of breast cancer will vary greatly, with some patients, whose cancer has ER and HER2 receptors, having access to some targeted therapies. However, patients diagnosed with 'triple negative' breast cancer, will have very limited treatment options, as their cancer has no

receptors and therefore no targeted medicines. This group of patients in particular would benefit from an extra treatment option being available.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

All metastatic breast cancer patients will progress on their current treatment so the option of an additional treatment is important to them. Furthermore, many of the treatments available for advanced or metastatic breast cancer are increasingly available for use in the primary setting. When early breast cancer is treated by these therapies the patient will have an increased risk of drug resistance. This can reduce the treatment options available to them in the metastatic setting. The availability of different treatments is therefore very important as resistance to some therapies will greatly limit treatment options.

Eribulin has been shown in trials to extend life by an average of three months longer than capecitabine, one of the chemotherapy drugs likely to be given to patients with this type and stage of breast cancer. This survival benefit is greater when looking specifically at patients with HER2- breast cancer, an indication where very little progress has been seen in recent years.

While eribulin is a chemotherapy treatment and therefore causes some of the same side effects seen by other chemotherapies, five audits of use of eribulin carried out at hospitals in England have shown that for many patients, eribulin is well tolerated. These audits took place at Castle Hill Hospital in Hull[1], Weston Park Hospital in Sheffield[2], the Christie Hospital in Manchester[3] and Imperial College Healthcare NHS Trust[4] and the Royal Marsden in London[5] and collected 'real world' data about 270 patients receiving eribulin via the old Cancer Drugs Fund. Results from these audits show that eribulin performs as well in clinics as it does in trials with similar survival benefits and toxicities, particularly for patients who have previously received more than one previous chemotherapy regimen for metastatic breast cancer. In addition, we have heard anecdotally that clinicians value having the option of eribulin for patients, particularly at the end of their lives.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Trials and clinical audits have shown this medicine to be effective when treating patients with metastatic breast cancer who have already received one or more regimens of chemotherapy for advanced disease and who are nearing the end of their lives. This medicine is well tolerated by most patients and has been shown to extend life. For patients who have terminal breast cancer and their families, additional good quality time is incredibly valuable. Symptoms, including pain control, was reported to be improved for patients taking this drug.[6,7] This has the potential to offer improvements in quality of life for these patients.

[1] Agarwal, V. et al. 2012. Eribulin: A Cancer Network Experience. http://conference.ncri.org.uk/abstracts/2012/abstracts/A69.html

[2] Sanganalmath, P. et al. 2014. Eribulin monotherapy in heavily pre-treated patients with advanced breast cancer; 'Real world' experience. EBCC, Glasgow, 2014

[3] Walshaw, R. et al. 2014. Eribulin for advanced breast cancer: Clinical experience in the real world. J Clin Oncol 32, 2014 (suppl; abstr e12003)

[4] Ramaswami, R. et al. 2014. Activity of eribulin mesylate in heavily pretreated breast cancer granted access via the Cancer Drugs Fund. Future Oncol. 2014 Feb;10(3):363-76

[5] Thanopoulou, E. et al. 2014. Safety and efficacy of eribulin mesylate (EM) in patients with advanced breast cancer: The Royal Marsden experience. J Clin Oncol 32, 2014 (suppl; abstr e12004)

[6] Twelves, C. et al. 2010. Phase III trials of Eribulin Mesylate (E7389) in extensively pretreated patients with locally recurrent or metastatic breast cancer. Clinical Breast Cancer, 10(2):160-163.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

This drug applies to all metastatic breast cancer patients, who would have had different trajectories and treatments leading up to treatment with eribulin. However, all patients tell us that more options for treatment is very important to them, as it not only gives more options for further treatment but also caters for those patients who are not tolerant of or don't respond well to certain medicines.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Treatments currently available on the NHS for this group of patients are very limited, as eribulin is used after patients have progressed on other chemotherapies and are nearing the end of their lives. For patients who have particularly aggressive forms of breast cancer, another treatment option would be valuable to give them extra time with their families and loved ones.

[7] Cortes, J. et al. 2010. Phase II study of the halichondrin B Analog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with anthracycline, a taxane and capecitabine. ASCO American Society of Clinical Oncology conference

Please list any concerns patients or carers have about the treatment being appraised.

Eribulin is a type of chemotherapy and this type of treatment is associated with many well known side effects. While the side effects experienced will vary from patient to patient, common side effects include hair loss, nausea, vomiting and fatigue.

One secondary breast cancer patient we have spoken to has described chemotherapy as gruelling. Willingness to accept side effects also varies from patient to patient, however, it must not be forgotten that secondary breast cancer is a terminal disease. Patients with secondary breast cancer have limited time left and for many of them, quality of life is as important as length of life. These patients may not feel that a modest survival benefit justifies experiencing serious side effects, particularly at the end of their lives.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Patients will be willing to accept different levels of risk when it comes to side effects. It is important that the benefits and side effects are clearly explained to each patient so that they can make an informed decision about whether a particular treatment is suitable for them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

As mentioned previously, women with advanced or metastatic triple negative breast cancer may benefit more from having this treatment available as their treatment options are very limited. Women with triple negative breast cancer tend to be younger, as it is more common in women under 40. These women are therefore much more likely to have younger children dependent on them, so treatments to prolong life with good quality of life are extremely important.

Patients with other types of breast cancer are also likely to benefit from this treatment, once other therapies stop being effective for these women. All

breast cancer patients eventually progress on their current treatment, therefore patients value knowing that there is another option available for treatment.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Metastatic breast cancer patients should receive targeted therapy first to control their disease. Only when they progress on all targeted therapies, then eribulin would benefit these patient groups, who have become resistant to targeted therapies for their cancer type. So these group of patients do not benefit less from eribulin but later on in their cancer pathway.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

To the best of our knowledge.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Health-related quality of life was recorded as part of the phase 3 open-label randomised trial comparing eribulin to the chemotherapy drug capecitabine. This trial seemed to capture the outcomes that patients would consider important and found that impact on quality of life was similar between the two groups of patients.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not that we are aware of.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Not that we are aware of.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not that we are aware of.

9. Other issues

Do you consider the treatment to be innovative?

☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Are there any other issues that you would like the Appraisal Committee to consider?

We would like data from the five audits across the UK to be considered by the Committee. These took place at Castle Hill Hospital in Hull, Weston Park Hospital in Sheffield, the Christie Hospital in Manchester and Imperial College Healthcare NHS Trust and the Royal Marsden in London and collected 'real world' data about 270 patients receiving eribulin via the old Cancer Drugs Fund.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Secondary breast cancer is a terminal disease for which there are very few treatment options currently available on the NHS. This drug provides a valuable extra option for clinicians treating patients nearing the end of their lives.
- Although it is a systemic chemotherapy drug and is therefore associated with many side effects, eribulin has been shown to be well tolerated by patients who have undergone several round of chemotherapy.
- For patients who experience few side effects, the additional months of good quality life that eribulin can provide are priceless.
- Eribulin is not an expensive medicine and the survival benefits seem modest, but eribulin can be very useful for patients nearing the end of their lives who have progressed on previous treatments and would therefore welcome an extra few months of life.

- Breast cancer patients with ‘triple negative’ breast cancer, would particularly benefit from additional treatment options, as treatments for this group of patients is very limited.

Appendix L – patient expert statement declaration form

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Eribulin for treating locally advanced or metastatic breast cancer after chemotherapy [ID964]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted Breast Cancer Now and consequently I will not be submitting a personal statement.

Name: [redacted]

Signed: .....

Date: ...14 September 2016.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Eribulin for treating locally advanced and metastatic breast cancer after one prior chemotherapy regimen.

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: XXXXXXXXXXXXXXXXXXXXX

Name of your organisation: Guys and St Thomas NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? YES
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Locally advanced or metastatic breast cancer is a common problem in England and Wales. Of the 44000 women diagnosed each year with breast cancer 5-10% will have overt metastases at presentation. Unfortunately, even with good treatments for early breast cancer roughly another 20% will develop metastases in the future. The commonest site of metastasis is bone, followed by liver and lung. Unfortunately, this is still a condition that is incurable but life expectancy is improving. Median survival with bone only metastases is estimated to be approximately four years. If other organs are involved the prognosis is likely to be shorter. There is increasing knowledge of the different subtypes of breast cancer and there are several modalities of treatment available such as classical cytotoxic chemotherapy, biological agents and endocrine therapies.

When a patient has locally advanced or metastatic breast cancer decision-making about treatment will include published efficacy data, sites of metastatic disease, subtype of breast cancer, previous therapies given, co-morbidities/patient fitness and most importantly patient wishes. The patient's case will often be discussed at a multidisciplinary team meeting. Generally, if a patient has had a particular systemic anti-cancer agent previously the tumour cells are likely to have developed resistance and that agent should not be repeated hence the need to have options available for subsequent lines of

therapy. There is a move towards much better individualisation of care which tries to incorporate all of these factors.
Once a treatment recommendation has been made and agreed with the patient then therapy will commence. The response of the locally advanced or metastatic breast cancer to the therapeutic agent will be monitored by imaging (most often CT) and sometimes tumour markers as well as the clinical condition of the patient. Toxicities will also be monitored and interventions made where necessary to try and ameliorate side effects. There are internationally agreed definitions of toxicity severity.

If the patient has a cancer that does not respond to the specific anti-cancer agent then the standard of care would be to change the drug after due discussion with the patient. Likewise, if a treatment has initially worked but the cancer starts to worsen later then the medication would be changed. If a patient remains clinically well (Eastern Collaborative Oncology Group (ECOG) Score 0-2) and there are appropriate alterative anti-cancer therapies then these would be discussed with the patient in terms of risks and benefits.

Eribulin is a cytotoxic chemotherapy drug. It has been available for women with locally advanced or metastatic breast cancer in England since 2011 via the Cancer Drugs Fund. It has been the 7th most commonly used drug from the Cancer Drugs Fund List. It is administered intravenously as a bolus injection on the 1st and 8th days of a 21 day cycle. It should be given in a hospital setting under the supervision of an oncologist. Common side effects include alopecia, nausea, loss of appetite, fatigue, peripheral neuropathy, altered bowel habit and amenorrhoea. Less common side effects include sore mouth, neutropenia, rashes, dizziness, depression, hypokalaemia, deranged liver, kidney and glucose function and eye problems amongst others. The particular advantages of eribulin are that it is quick to administer which enables patients to have much shorter hospital visits, the level of nausea is lower than that seen with some other agents and only 50% will experience hair loss. In addition, it has very little cardiac toxicity.

NHS Hospitals that given cancer treatments will already have the requisite infrastructure to administer eribulin and have been doing so for the last 5 years. As a result, no additional resources would be required if this appraisal was implemented. The Cancer Drugs Fund has given clear criteria for funding of eribulin so to date it has only been used within its licensed indication. As a result, there has not been any variation in access within the jurisdiction of the Cancer Drugs Fund.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Eribulin has been available in England since 2011 via the Cancer Drugs Fund so most, if not all oncologists specialising in breast cancer will have used it before. At Guys and St Thomas we have treated approximately 90 patients with eribulin to date. Hospitals providing systemic anti-cancer therapies will already have the resources and experience to give eribulin safely. There is published 'real world' data from three British NHS Hospitals (The Royal Marsden Hospital, The Chrsitie Hospital and Imperial College Hospitals) that demonstrates that efficacy is comparable with the EMBRACE clinical trial and that the level of side effects was tolerable and manageable. There are no additional tests required to monitor Eribulin above and beyond those necessary for the monitoring of other cancer therapies. I do not think there are any side effects in my experience that were not discovered in the original clinical trials. The side effect most likely to be therapy-limiting is peripheral neuropathy and may often be exacerbated because the patient has previously received other agents that also cause neuropathy such as docetaxel or paclitaxel.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

I do not think that there is likely to be an issue with equality of access as Eribulin is already widely used in England (7th commonest drug accessed via the Cancer Drugs Fund). The key group of patients for whom it may not be suitable in the context of locally advanced or metastatic breast cancer are those who have a significant neuropathy either from previous treatments or a long-standing neurological condition. These issues would be part of the decision-making process involving the patient when choosing therapy as quality of life and ability to remain independent are important for patients.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I do not think there is other evidence that has not already been included in the submission.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

As Eribulin has been widely used in England already and clinicians are familiar with its administration and side effects I do not think there will be difficulty with implementation. I am not able to comment on the situation in Wales as I do not practice there.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Eribulin for treating locally advanced or metastatic breast cancer after chemotherapy [ID964]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/148/11

Completed 26th August 2016

CONTAINS COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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Contributions of authors:

Fleeman N	Project lead, drafted clinical results section and supervised the final report
Bagust A	Checking and validation of the economic model and critique
Richardson M	Critical appraisal of the statistical evidence
Houten R	Summary and critical appraisal of economic evidence
Krishan A	Critical appraisal of the statistical evidence
Beale S	Critical appraisal of the clinical and economic evidence, editorial input
Boland A	Critical appraisal of the clinical and economic evidence, editorial input
Stainthorpe A	Summary and critical appraisal of economic evidence
Kotas E	Critical appraisal of the database searching
Banks L	Critical appraisal of the submission
Thorp N	Clinical advice and critical appraisal of the clinical sections of the company submission

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

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LIST OF ABBREVIATIONS

AEs	adverse events
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
ER	oestrogen receptor
ERG	Evidence Review Group
FAD	final appraisal determination
HER2	human epidermal growth factor receptor 2
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
ITT	intention-to-treat
IV	intravenous
K-M	Kaplan-Meier
LABC/MBC	locally advanced or 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
RCT	randomised controlled trial
SAE	serious adverse event
STA	single technology appraisal
TPC	Treatment of Physician's Choice

1 SUMMARY

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 (TA250). At that time eribulin was licensed 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. In 2014 the European Medicines Agency licence for treatment with eribulin was broadened to include less heavily treated patients. The new licence is for the treatment of adult patients with LABC/MBC who have progressed after at least **one** chemotherapeutic 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 July 2016 the company submitted evidence relating to two different subgroups of the licensed population, one relating to the licence that was valid in 2012 and the other to the 2014 licence. Following discussions between the company, NICE and the ERG, the scope of this STA was amended so that its only focus is a review of TA250. The remainder of this report is therefore only concerned with the evidence submitted by the company for a review of TA250.

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

Clinical effectiveness evidence is derived primarily from the EMBRACE trial and is considered by the company for two populations:

- All patients receiving ≥3 chemotherapy regimens for LABC/MBC: patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease. Prior treatment includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable. This is the EMBRACE trial intention-to-treat (ITT) population.
- Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease and includes capecitabine (if indicated). Prior treatment also includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable. This is a subgroup (73%) of the EMBRACE trial and is referred to by the company (and within this ERG report) as Subgroup 2.

Superseded by Erratum

The populations are the same as those that were the final focus of the Appraisal Committee's TA250 final appraisal determination (FAD) document. However, the comparator for Subgroup 2 patients is different. For both populations in the current STA, the comparator to eribulin is Treatment of Physician's Choice (TPC), whereas in TA250, the comparators were TPC for all patients receiving ≥3 chemotherapy regimens for LABC/MBC and vinorelbine for Subgroup 2 patients. Although the ERG considers that vinorelbine is an appropriate comparator for patients previously treated with capecitabine, the use of TPC is pragmatic and more likely to reflect patient experience in England. The TPC administered during the EMBRACE trial included (but was not limited to) chemotherapy (93.7%) and hormonal therapy (3.5%). The comparators listed in the final scope issued by NICE were vinorelbine, capecitabine and gemcitabine. All three comparators were agents available in the TPC arm of the EMBRACE trial (59.4% of all TPC agents).

Cost effectiveness evidence is only presented for Subgroup 2 patients. As specified in the final scope issued by NICE, the cost effectiveness of eribulin was expressed in terms of the incremental cost per quality adjusted life year gained (QALY) gained. In the base case, outcomes were assessed over a 5-year time horizon, with scenarios considering 10- and 20-year horizons. Costs were considered from an NHS perspective. A simple patient access scheme (PAS), offering a straight discount to the list price, of eribulin was formally agreed with the Department of Health on 14 January 2016. This PAS price is used in the company's cost effectiveness analysis.

1.2 Summary of clinical effectiveness evidence submitted by the company

Clinical effectiveness evidence is derived primarily from the EMBRACE trial, identified via the company's systematic review. This trial was a multi-centre, phase III, open-label, randomised parallel two-arm trial. The primary objective of the EMBRACE trial was to evaluate overall survival (OS) of patients treated with eribulin versus TPC in patients with LABC/MBC who had received two to five prior chemotherapy regimens. All patients were receiving ≥3 chemotherapy regimens for LABC/MBC.

A total of 762 patients were randomised in a 2:1 ratio to receive either eribulin (n=508) or TPC (n=254). Randomisation was stratified according to geographical region, human epidermal growth factor receptor 2 (HER2) status, and prior treatment with capecitabine. The selection of TPC agents took place prior to randomisation.

The median age of patients enrolled in the EMBRACE trial was 55 years. The majority were Caucasian (>90%) and post-menopausal (~75%). Most patients had oestrogen receptor (ER)-positive (~70%) and/or HER2-negative (~80%) disease and an Eastern Cooperative

Oncology Group (ECOG) performance status (PS) of 0 (~42%) or 1 (~48%). The most common sites for metastases were bone (>60%) and liver (>60%). Median time since diagnosis was just over 5 years. Patient characteristics appear to be well balanced across treatment groups. Nearly three-quarters (73%) of patients in the EMBRACE trial had previously received treatment with capecitabine; these are the patients that constitute the Subgroup 2 population.

At the time of the most recent data-cut of the EMBRACE trial (17 June 2013), all patients had discontinued study treatment and 95% of all patients had died. For the ITT population, median OS was 2.7 months longer for patients in the eribulin arm (13.24 months) than for patients in the TPC arm (10.55 months); whilst median progression-free survival (PFS) was 1.4 months longer for patients in the eribulin arm (3.61 months) than for patients in the TPC arm (2.17 months). For patients in Subgroup 2, median OS was 2.9 months longer for patients in the eribulin arm (13.0 months) than for patients in the TPC arm (10.1 months); whilst median PFS was 1.5 months longer for patients in the eribulin arm (3.6 months) than for patients in the TPC arm (2.1 months). The median number of cycles of eribulin in the EMBRACE trial was reported to be between five and six.

Most patients in the EMBRACE trial experienced at least one all-Grade adverse event (AE): 98.8% of patients in the eribulin arm and 93.1% in the TPC arm. Very common all-Grade AEs associated with eribulin included neutropenia (51.7%), asthenia/fatigue (53.7%), alopecia (44.5%), peripheral neuropathy (34.6%), arthralgia/myalgia (21.7%) and nausea (34.6%). Grade ≥3 AEs occurred more frequently in the eribulin arm than in the TPC arm of the trial (90.7% versus 59.5%). The most common Grade ≥3 AE for patients treated with eribulin was neutropenia (49.7%). Febrile neutropenia (4.2%) and neutropenia (1.8%) were the most frequently reported serious AEs associated with treatment with eribulin. There were no notable differences in AE frequencies between the EMBRACE trial safety and Subgroup 2 populations.

Additional evidence was provided from studies not identified via the systematic review:

- supportive 'real world' safety data were reported by the company from five observational studies: three audits of patients whose treatments were funded by the Cancer Drugs Fund (CDF) in England (n=208 across all three studies), and the EUFORIA-1 (n=104) and ERIBEX (n=258) studies which were carried out in Spain and France/Switzerland respectively. Patients included in the CDF audits had, on average, received ≥3 prior lines of chemotherapy for LABC/MBC whilst patients in the international studies had received four or five prior lines of chemotherapy for LABC/MBC (≥80% received previous treatment with capecitabine across the five studies). In most cases, the frequencies of key AEs (asthenia/fatigue, neutropenia, alopecia, peripheral neuropathy and nausea) were lower than the frequencies reported for the EMBRACE trial safety population.

- health-related quality of life (HRQoL) data were derived from Study 301, another multi-centre, phase III, open-label, randomised parallel two-arm trial. Study 301 included patients who had received no more than two regimens for LABC/MBC; this study excluded patients who had been previously treated with capecitabine. Study 301 included 1102 patients, 554 patients randomised to eribulin and 548 patients randomised to capecitabine. The results from Study 301 patients who had received third-line treatment only show that treatment with eribulin does not have an adverse impact on HRQoL as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. Over time, patients in both arms appeared to maintain or improve their baseline global health status/ quality of life.

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

The ERG is satisfied with the clinical effectiveness systematic review process described in the company submission (CS) and is, therefore, confident that the EMBRACE trial is the only trial that is relevant to a review of TA250. The company's systematic review was only designed to find evidence for Subgroup 2 patients (since this is the population on which the cost effectiveness analysis is based) and not for all patients receiving ≥3 chemotherapy regimens for LABC/MBC. The ERG is not aware of additional randomised controlled trials (RCTs) that could have provided evidence for all patients receiving ≥3 chemotherapy regimens for LABC/MBC or for the Subgroup 2 population. Given HRQoL data were not collected in the EMBRACE trial, the ERG considers attempts to derive HRQoL data from other sources (e.g. Study 301) were appropriate. While HRQoL data from the EORTC QLQ-C30 questionnaire are provided for third-line patients in Study 301, patients had not received later lines of treatment in this trial and the comparator arm was capecitabine. Therefore, the generalisability of HRQoL data from Study 301 to all patients receiving ≥3 chemotherapy regimens for LABC/MBC or Subgroup 2 patients may be questioned.

Overall, the ERG is satisfied with the statistical approach employed by the company for the EMBRACE trial, with the exception of a lack of testing of the proportional hazards (PH) assumption. The ERG cautions that the approach taken by the company to calculate hazard ratios (HRs) is only valid if the relevant Kaplan-Meier (K-M) data are proportional to one another, i.e. the HRs are only reliable if the PH assumption holds.

The ERG notes that the baseline characteristics of patients in Subgroup 2 are broadly similar to the baseline characteristics of the ITT population and also that baseline characteristics appear to be well balanced across treatment groups. The main difference between the ITT and Subgroup 2 populations is that Subgroup 2 patients appear to be more heavily pre-treated: approximately 64% of Subgroup 2 patients had received four or more prior chemotherapy regimens (in any setting) compared with approximately 53% of all patients in the ITT population; also, approximately 65% of Subgroup 2 patients had received three or

more prior chemotherapy regimens in the LABC/MBC setting compared with approximately 57% of all patients in the ITT population.

The ERG considers that both the EMBRACE trial and Study 301 were generally well designed and conducted. The ERG agrees with the company's view that both trials were at low risk of bias.

Overall, the ERG considers that the findings from the EMBRACE trial demonstrate an improvement in median OS and median PFS for patients treated with eribulin versus those treated with TPC. This is true for both the ITT and the Subgroup 2 populations. However, the ERG notes that the only the ITT OS HR is reliable; all other HRs (Subgroup 2 OS and PFS for both ITT and Subgroup 2 populations) are derived from K-M data that are not proportional to one another.

The ERG also considers that the safety data from the EMBRACE trial and from 'real world' observational studies show that eribulin has an acceptable safety profile.

1.4 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 with a chemotherapy agent of TPC. 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 the EMBRACE trial. Utility values were mapped to 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 the EMBRACE trial, published sources and clinical experts.

In the base case, eribulin generates more benefits than TPC [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 TPC is £35,624 per QALY gained. The company carried out a range of deterministic sensitivity analyses. The parameter changes that had the effect of changing the base case ICER per QALY gained by more than 10% were decreasing the progressive disease utility from 0.679 to 0.496 (which increased the company's base case ICER by 31.7% to £46,912 per QALY gained) and adjusting the cost of eribulin by ±20% (which led to corresponding ±12.3% change to the company's base case ICER, i.e. £31,226 and £40,022 per QALY gained respectively).

The company's probabilistic sensitivity analysis (PSA) involved varying only a limited number of parameters. There is a 30% probability of treatment with eribulin being cost effective at a threshold of £30,000 per QALY gained and a 72% probability of it being cost effective at a threshold of £50,000 per QALY gained.

The company carried out six scenario analyses. Excluding the cost of drug wastage had the largest impact and lowered the ICER to £16,053 per QALY gained (a 54% reduction in the base case result).

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

The ERG considers that trial data are more reflective of patient experience than projective functions. However, the company has used projective functions to model patient OS and PFS experience over the whole model time horizon. The ERG presents results generated by using the available EMBRACE trial K-M data for OS and PFS directly in the model, and only using projective functions to model the OS experience of three patients who were still alive at the time of the final data-cut.

The ERG has serious doubts about the reliability of the PPS K-M data provided in response to a clarification request and, therefore, was unable to estimate directly the extent of any survival benefit (or disbenefit) arising after disease progression. However, OS and PFS estimates give strong support to a substantial gain in mean survival being experienced by some patients even after recorded disease progression and cessation of treatment with eribulin.

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 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 affect 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 QLQ-C30 quality of life 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 (0.69

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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.

1.6 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:

- Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease which includes capecitabine, have a life expectancy of less than 24 months
- Data from the EMBRACE trial demonstrate that eribulin extends life by more than 3 months compared with TPC.

1.7 ERG commentary on end of life criteria

The ERG agrees with the company that eribulin is a treatment that is indicated in patients with a short life expectancy. The ERG also considers that eribulin is likely to offer an extension to life of at least an additional 3 months compared to current NHS treatment; the ERG estimates a mean OS gain of 3.39 months (95% confidence interval 0.83 to 5.96 months) for patients treated with eribulin compared with patients treated with TPC although this does not achieve statistical significance due to the small trial population.

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

1.8.1 Strengths

Clinical evidence

- The EMBRACE trial compared the efficacy and safety of eribulin with TPC, a comparator arm that reflects the real life choices faced by physicians and patients with an advanced stage of LABC/MBC
- Mature clinical effectiveness data are available (95% of patients have died)
- The EMBRACE trial is the only currently available source of good-quality clinical effectiveness evidence describing the use of treatments available to patients receiving ≥3 chemotherapy regimens for LABC/MBC.

Cost effectiveness evidence

- The availability of mature survival data allows a reliable assessment of the relative effectiveness of treatment with eribulin versus TPC for the Subgroup 2 population.

1.8.2 Weaknesses and areas of uncertainty

Clinical evidence

- HRQoL data were not available from the EMBRACE trial
- Although HRQoL data for third-line patients were available from Study 301, only 28% of all patients in this trial received study treatment as a third-line option for LABC/MBC. The majority of all patients in the ITT population included in the EMBRACE trial (including patients in Subgroup 2) had received a greater number of previous lines of treatment than those participating in Study 301. Study 301 also excluded patients previously treated with capecitabine (unlike the EMBRACE trial). Thus it is unclear if the available HRQoL data are generalisable to all patients receiving ≥3 chemotherapy regimens for LABC/MBC or to Subgroup 2 patients.

Cost effectiveness evidence

- No evidence has been provided to demonstrate the cost effectiveness of treatment with eribulin versus TPC for the ITT population
- Projective functions, rather than mature EMBRACE trial survival data, have been used within the company model to reflect patient PFS and OS experience. This has led to inaccurate estimates of the efficacy of eribulin versus TPC
- Within the company model, costs and benefits have been discounted continuously rather than annually
- The ERG has identified several issues relating to the methods employed by the company to estimate drug acquisition and administration costs
- The company has used an implausibly high post-progression utility value
- The exploration of parameter uncertainty undertaken by the company is insufficient.

1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG implemented nine individual corrections/modifications to the company's model. When these changes are implemented individually for the comparison of the cost effectiveness of treatment with eribulin versus TPC for the Subgroup 2 population, they both increase and decrease the size of the company's base case ICER per QALY gained. The three most influential ERG changes are the revised estimate of the cost of eribulin treatment (base case ICER change: +£12,575), the choice of utility value for the progressive disease health state (base case ICER change: +£11,288), and the method used to cost subsequent lines of treatment (base case ICER change: +£9,811). The combined effect of all of the ERG changes yields an ICER of £66,043 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 £30,418) for the comparison of treatment with eribulin versus TPC in patients with LABC/MBC whose disease

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has progressed after at least two prior chemotherapy regimens for advanced disease and includes capecitabine.

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2 CONTEXT

2.1 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] At the time, eribulin was indicated for the treatment of 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 via regional panels of the Cancer Drugs Fund (CDF).

2.2 New licence for eribulin (2014)

In July 2014, the European Medicines Agency (EMA) granted an extension to the previous indication for eribulin.[2] This enabled eribulin to be used earlier in the treatment pathway. The new 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.

2.3 Current single technology appraisal (2016)

In April 2016, NICE issued a scope for the appraisal of eribulin within its (new) indication for the treatment of adults with breast cancer who have received one or more chemotherapy regimens for locally advanced or metastatic disease.[3] According to information published on the NICE website,[4] the aim of the this new single technology appraisal (STA) was to fully update the previous guidance (TA250). In the company submission (CS)[5] for this 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 relates these two elements to two populations, each of which is supported by evidence from different trials:

- Subgroup 1:
    - **Population**: human epidermal growth factor receptor 2 (HER2)-negative patients with LABC/MBC whose disease has progressed after one prior chemotherapy regimen in the advanced setting
    - **Main evidence source**: Study 301,[6] 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**: the phase III EMBRACE trial[7] in which treatment with eribulin was compared with Treatment of Physician's Choice (TPC)

The company has provided only one economic model but, within that model, the two subgroups are considered separately, with a distinct 'model' being run for each subgroup and cost effectiveness results being presented separately.

Following discussions between the company, NICE and the Evidence Review Group (ERG), it was agreed (on 20 July 2016) that the evidence for the two subgroups should be considered separately, i.e. as two separate STAs. **This current STA focuses only on reviewing TA250, in which eribulin was considered as a third-line (or later) treatment option for patients with LABC/MBC**, i.e. patients receiving ≥3 chemotherapy regimens for LABC/MBC which includes those previously treated with capecitabine (Subgroup 2) as well as those who have not previously been treated with capecitabine (the remainder of the EMBRACE trial ITT population)**.**

2.4 Summary of evidence reviewed for TA250

To inform the original STA (TA250), the company presented evidence to support the clinical and cost effectiveness of eribulin using data from region 1 of the EMBRACE trial (i.e. from patients in North America, Western Europe and Australia). Patients participating in the EMBRACE trial were recruited from three different regions and the company argued that clinical practice in region 1 was likely to be more reflective of UK practice than clinical practice in the other two regions.

The company presented evidence for the effectiveness of treatment with eribulin versus TPC as a whole, as well as versus three (vinorelbine, capecitabine and gemcitabine) of the numerous individual agents that physicians chose to prescribe. At the first Appraisal Committee (AC) meeting, the AC considered that it was more appropriate to use data from all patients rather than restricting the evidence to only those patients in region 1 since the marketing authorisation for eribulin was based on the results of the overall EMBRACE population rather than on any subgroup results. Furthermore, the AC noted that analysis carried out by the ERG showed that mean overall survival (OS) did not differ by region, whilst UK practice differed considerably from some areas included in region 1. The company, therefore, provided additional evidence and this evidence was the focus of discussions that informed the content of the final appraisal determination (FAD) document.

There were two main reasons for these two foci:

1. "The … [EMBRACE] trial should be evaluated as a whole as this was how the study had been designed and powered" (FAD 4.4)[1] and
2. "… a major stratification factor in the EMBRACE trial was pre-treatment with capecitabine (73.4% of patients) and … this was potentially relevant to clinical practice" (FAD 4.11).[1]

The AC's conclusions about the clinical and cost effectiveness of eribulin versus TPC for all patients and eribulin versus vinorelbine for patients previously treated with capecitabine (i.e. Subgroup 2) are presented in the FAD. The FAD includes the following guidance:

> *"Eribulin is not recommended, within its licensed indication, for the treatment of locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease"* (FAD 1.1).[1]

In the current STA, the company also highlights five key conclusions that the AC reached with regard to appropriate evidence and gaps in the evidence relating to the safety of eribulin, health-related quality of life (HRQoL) associated with eribulin, the focus on patients previously treated with capecitabine, modelling OS and estimating and incorporating drug costs in the model. The company states that it has attempted to address all of these issues in the current CS.

2.5 Critique of company's description of underlying health problem

The company's brief description of the underlying health problem is presented in Sections 1.3 and 3 of the CS. Key points from these sections of the CS are reproduced (as bulleted items) in Box 1. The ERG considers that the company's description presents an accurate summary of the underlying health problem.

Box 1 Summary of company's description of underlying health problem

Incidence and survival

- 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
- 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
- Locally advanced breast cancer or metastatic breast cancer (LABC/MBC) is the most advanced form of breast cancer, where the cancer is no longer localised to the breast and has spread to other parts of the body, commonly the lungs, liver, brain and bone
- Although few patients are diagnosed with MBC at the outset (around 5%) as many as 35% of women diagnosed with early breast cancer will eventually progress to or relapse with LABC/MBC
- There is currently no cure for MBC and the long-term prognosis is poor
- The proportion of patients responding to chemotherapy declines through successive lines of treatment
- As reported in the NICE assessment report for lapatinib and trastuzumab, the average length of survival following diagnosis of MBC is 12 months for those receiving no treatment, compared with 18 to 24 months for those receiving chemotherapy

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
- Overall, quality of life is poor in patients with MBC. MBC patients have lower scores than non MBC in all of the functioning subscales of the European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire

Source: CS, Sections 1.3 and 3

2.6 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. Key points from these sections are reproduced (as bulleted items) in Box 2. Overall, the ERG agrees with the company's overview of current service provision. The ERG notes that, as a result of the 2014 licence extension, eribulin is indicated for the treatment of adult patients with LABC/MBC who have progressed after at least one chemotherapeutic regimen 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. For these patients, clinical advice to the ERG is that eribulin is most likely to be considered as an alternative to treatment with either vinorelbine monotherapy or capecitabine monotherapy.

The company considers that patients who have received at least two prior chemotherapy regimens for LABC/MBC would most likely have received capecitabine prior to receiving eribulin. Indeed, as highlighted in Box 2, the company cites data from independent audits which show that more than 80% of patients received prior capecitabine when prescribed eribulin (as a third-line or later treatment) via the CDF.

Information in Box 2 also highlights that, within the current NICE guideline for advanced breast cancer (CG81),[8] recommendations are only made for treatment up to, and including, third-line therapy. Beyond third-line there is no clear standard of care.

Box 2 Summary of company's overview of current service provision

- LABC/MBC is generally managed by a multi-disciplinary healthcare team in tertiary, secondary and primary care
- The aim of treatment for LABC/MBC is to prolong life, without adversely affecting the patient's quality of life
- The chemotherapeutic agents with the best efficacy in breast cancer, the anthracyclines and taxanes, are typically used at earlier stages of the disease, leaving many LABC/MBC patients anthracycline and taxane-resistant, and thereby limiting the number of treatment options at this stage of disease
- Despite recent improvements in the treatment of MBC, there is still no consensus regarding the optimal standard of care for women requiring therapy after initial taxane and anthracycline treatment
- Based on the NICE clinical guideline for advanced breast cancer, 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)
- Whilst the NICE clinical guideline clearly defines vinorelbine monotherapy and capecitabine monotherapy as options for second-line treatment and beyond, in clinical practice, as indicated above, it is apparent that for patients with LABC/MBC, particularly at this advanced point in their treatment, numerous types of treatment may be used. The choice of treatment will depend on factors including HER2-status, prior chemotherapy exposure and response, tolerability, patient preference, availability of drugs, the patient's quality of life and performance status
- Recently published data from independent audits undertaken at the Royal Marsden Hospital, Christie Hospital NHS Foundation Trust and Imperial College Healthcare NHS Trust showed that more than 80% of patients had received prior capecitabine when prescribed eribulin via the Cancer Drugs Fund
- The tolerability of current LABC/MBC treatment varies; chemotherapy agents can be particularly toxic and are recognised to be the most burdensome aspect of cancer management for patients
- Side effects of chemotherapy commonly include peripheral neuropathy, alopecia, mucositis, nausea, vomiting, increased infection, and fatigue. These can adversely affect a patients' quality of life, be costly to manage and lead to early discontinuation of a particular therapy in a significant number of patients, thereby impacting on overall treatment outcomes
- Other issues relating to current practice include the inconvenience to the patient and the treating healthcare professional, and the level of resource use required for administration:
    - The majority of chemotherapy regimens require intravenous (IV) administration and vary in their infusion times (e.g. paclitaxel is administered over 3 hours). Patients may experience difficulties with venous access as a result of multiple prior therapies, while long infusion times can be inconvenient and increase the burden to the patients' lives.
    - Variability exists in frequency of dosing schedules (e.g. vinorelbine requires weekly administration). The lack of consistency and the impact that missing doses may have on clinical outcomes mean that patient outcomes may also be inconsistent.
    - Many IV chemotherapy regimens require reconstitution or dilution before administration (e.g. gemcitabine, vinorelbine), increasing the burden on healthcare resources, and potentially leading to dosing errors. Vinorelbine is also a vesicant
    - Premedication with steroids and/or antihistamines to prevent hypersensitivity reactions during administration is necessary with many chemotherapeutic agents (e.g. docetaxel, paclitaxel). This increases the time required for treatment administration as well as the overall cost of treatment and adds to the potential drug-related adverse effects that the patient may experience

Source: CS, Sections 1.3, 2.4 and 3

2.7 Number of patients potentially eligible for eribulin

The company has estimated that the total number of patients in England and Wales who are potentially eligible to receive treatment with eribulin is 2044. Of these, it is estimated that 1500 will be eligible to receive eribulin following treatment with capecitabine (Subgroup 2). As shown in Table 1, the company's estimates are based on prevalence data.

Table 1 Company estimate for patients potentially eligible for treatment with eribulin

Population	Number	%	Source
Population of England and Wales	57,408,700		Office for National Statistics mid-year estimate, 2014[9]
Prevalence of breast cancer	80,372	0.14	Cancer Mpact database, Kantar Health[10]
Prevalence of metastatic breast cancer	5940	7.39	Cancer Mpact database, Kantar Health[10]
Patients receiving first-line chemotherapy	5940	100.00	Company assumption
Patients receiving second-line chemotherapy	3883	65.37	Cancer Mpact database, Kantar Health[10]
Patients on third-line chemotherapy	2044	52.64	Cancer Mpact database, Kantar Health[10]
Patients treated following treatment with capecitabine (Subgroup 2)	1500	73.40	EMBRACE[7]

Source: CS, Table 86

The ERG notes that alternative estimates can be derived from incidence data. As shown in Table 2, when estimates of the numbers of patients in the ITT and Subgroup 2 populations eligible to receive eribulin are calculated using incidence rather than prevalence data, the resultant figures are similar (ITT population: 2149 patients and Subgroup 2 population: 1578 patients).

Table 2 ERG estimate for patients potentially eligible for treatment with eribulin

Population	Number	%	Source
Breast cancer incidence in England and Wales	44,683		Cancer Research UK[11]
Incidence with known stage of disease	40,101	84.10	Cancer Research UK[12]
Incidence of patients with Stage III to IV disease	6246	13.10	Cancer Research UK[12]
Patients receiving first-line chemotherapy	6246	100.00	Company assumption
Patients receiving second-line chemotherapy	4083	65.37	Cancer Mpact database, Kantar Health[10]
Patients on third-line chemotherapy	2149	52.64	Cancer Mpact database, Kantar Health[10]
Patients treated following treatment with capecitabine (Subgroup 2)	1578	73.40	Cancer Mpact database, Kantar Health[10]

However, the ERG questions the validity of the company assumption that 100% of patients receive first-line chemotherapy. In the original STA for eribulin (TA250), the ERG noted that the company estimated the proportion to be 61.8% based on market share data for the third quarter of 2010.[13] Applying this estimate reduces the prevalence and incidence based estimates to 1263 and 1328 respectively for the EMBRACE trial ITT population and 927 and 975 respectively for Subgroup 2 patients. Clinical opinion received by the ERG is that a more reasonable estimate for patients receiving first-line chemotherapy may be approximately 75%. Assuming the proportion of patients receiving first-line chemotherapy to be 75% changes the estimated patient numbers to between 1533 (company) and 1612 (ERG) for all patients receiving ≥3 chemotherapy regimens for LABC/MBC and to between 1125 (company) and 1183 (ERG) for Subgroup 2 patients.

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 final scope issued by NICE is presented in Table 3. Each parameter is discussed in more detail in the text following the table (Section 1.1 to Section 3.7). **As noted in Section 2.3, the CS provides information relating to two subgroups of patients; however, this ERG report only considers the information provided by the company that facilitates a review of TA250.**

Table 3 Final NICE scope and company's decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the CS
Population	Adults with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease (anthracycline and a taxane, unless these treatments were not suitable)	Clinical and cost effectiveness evidence is presented for Subgroup 2 patients: patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease which includes capecitabine (if indicated). This was one of two populations on which the Appraisal Committee finally focussed on in TA250 Clinical effectiveness evidence is also presented for the broader population of patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease (but who have not received prior capecitabine). This was the other population on which the Appraisal Committee finally focussed on in TA250
Intervention	Eribulin	As per scope
Comparator (s)	• Vinorelbine • Capecitabine • Gemcitabine	Clinical effectiveness: Treatment of Physician's Choice (TPC), including: • Vinorelbine • Capecitabine • Gemcitabine • Anthracyclines (doxorubicin) • Taxanes (paclitaxel and docetaxel) Clinical effectiveness and base case cost effectiveness: Treatment of Physician's Choice (TPC), including: • Vinorelbine • Gemcitabine • Anthracyclines (doxorubicin) • Taxanes (paclitaxel and docetaxel) Cost effectiveness scenario analysis: 57% of population received vinorelbine and 43% received gemcitabine

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Parameter	Final scope issued by NICE	Decision problem addressed in the CS
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health related quality of life	As per scope for all patients in the EMBRACE trial Health-related quality of life data are derived from an alternative trial (Study 301) The only endpoints reported for Subgroup 2 patients are: • Overall survival • Progression-free survival • Adverse effects of treatment (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 economic evaluation utilised patient-level data from the EMBRACE trial. 5-year survival data from this trial were very close to being complete and the company therefore set the base case time horizon to 5 years. Cost effectiveness results from scenario analyses considering 10- and 20-year time horizons were also provided Costs were considered from an NHS perspective A Patient Access Scheme for eribulin has been approved by the Department of Health and this cost has been used in the cost effectiveness analyses
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups according to HER2 status, oestrogen receptor and line of treatment 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	Subgroup 2 patients are representative of patients in current clinical practice in England as observed through the usage of eribulin obtained via the Cancer Drugs Fund (CDF). Recently published data from three audits undertaken in England show that 80% or more of patients who had obtained eribulin via the CDF had received prior capecitabine
Other considerations	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.	Since the licence for eribulin has been updated to enable eribulin to be used earlier in the treatment pathway, and since the current STA is a review of TA250, all patients receiving ≥3 chemotherapy regimens for LABC/MBC and Subgroup 2 patients constitute subgroups of the licensed population. For these heavily pre-treated patients, the company considers eribulin should be considered using NICE's end of life criteria

Source: Final scope issued by NICE and CS, adapted from Table 1

Superseded by Erratum

3.1 Population

The company presents clinical effectiveness evidence for all patients in the EMBRACE trial, i.e. patients with LABC/MBC whose disease has progressed after at least two (and a maximum of five) prior chemotherapeutic regimes for advanced disease (the ITT population). The company also presents clinical effectiveness evidence for patients in the EMBRACE trial whose previous treatment had included capecitabine (if indicated) as well as both an anthracycline and a taxane. This subgroup is referred to in the CS (and in this ERG report) as 'Subgroup 2'. Subgroup 2 was pre-defined and comprises 73% of the EMBRACE trial population. In the CS, cost effectiveness evidence is only presented for Subgroup 2 patients. A summary of detail relation to populations addressed in this STA is presented in Table 4.

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

Population	Clinical effectiveness	Cost effectiveness
Patients receiving ≥3 chemotherapy regimens for LABC/MBC (Original indication for eribulin)	All patients in the EMBRACE trial, i.e. the ITT population (AE results calculated for the safety population)	The company did not carry out any cost effectiveness analyses for this population
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)	Pre-specified subgroup in the EMBRACE trial These patients comprises 73% of the EMBRACE trial population	This population is the focus of the cost effectiveness analyses

AE=adverse events; ITT=intention-to-treat, LABC/MBC=locally advanced breast cancer/metastatic breast cancer

The whole EMBRACE trial population (and Subgroup 2) is a subset of the population specified in the final scope issued by NICE (the population for whom eribulin is now indicated). However, the whole trial population is consistent with the previous indication for eribulin. The whole trial population and Subgroup 2 are the same populations that were the final focus of the AC during TA250. The ERG, therefore, considers that the company presents appropriate clinical effectiveness evidence for a review of TA250. The ERG also notes that the whole EMBRACE trial population is also reflective of the patient population that has been treated with eribulin via the CDF in England to date.

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.[14,15] 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)

chemotherapeutic 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 chemotherapeutic agents currently used in clinical practice.

3.3 Comparators

The comparators specified in the final scope issued by NICE are vinorelbine, capecitabine and gemcitabine. As noted in Section 2.6 of this ERG report, NICE recommend that single agent vinorelbine or single agent capecitabine should be prescribed second- or third-line (if the second-line treatment is vinorelbine then the third-line treatment would be capecitabine and vice versa).[8] As noted in Section 2.6, beyond third-line, there is no standard of care. Given this, using TPC as the comparator in the EMBRACE trial appears reasonable. The TPC used in the trial included (but was not limited to) chemotherapy (93.7%) and hormonal therapy (3.5%). The most common agents (59.4% of all TPC agents, 63.4% of all chemotherapy agents) were the comparators listed in the final scope issued by NICE: vinorelbine, capecitabine and gemcitabine. The other most common agents were anthracyclines (~10%) and taxanes (~15%).

In the EMBRACE trial, patients had to have been previously treated with anthracyclines and taxanes. The company notes that, in clinical practice, some patients are re-challenged with these agents and hence considers that these agents are appropriate for use in the TPC arm. The ERG agrees with the company that, in clinical practice, due to a lack of alternative treatments, taxanes are often used again at this late stage in the treatment pathway. Clinical advice to the ERG is that re-challenge with anthracyclines is uncommon due to dose dependent cardiac toxicity associated with this this type of agent.

In producing its guidance for TA250, the AC considered that TPC was an appropriate comparator for all patients receiving ≥3 chemotherapy regimens for LABC/MBC and that vinorelbine was an appropriate comparator for the Subgroup 2 population. The ERG considers that whilst vinorelbine is an appropriate comparator for Subgroup 2 patients, using data for only one of the TPC agents results in a reduction in the overall volume of admissible EMBRACE trial data and increases the uncertainty around clinical and cost effectiveness results. Given that the ERG also considers that other agents are appropriate comparators at this stage of the treatment pathway, the use of TPC as a comparator for Subgroup 2 patients in the current appraisal appears to be both pragmatic and justified.

3.4 Outcomes

The outcomes specified in the final scope issued by NICE are OS, progression-free survival (PFS), response rates, adverse events (AEs) and HRQoL; these are standard outcomes

used in oncology clinical trials and are the most important outcome measures for this appraisal.

Clinical evidence from the EMBRACE trial is reported in the CS for patients receiving ≥3 chemotherapy regimens for LABC/MBC for all outcomes specified in the final scope issued by NICE, with the exception of HRQoL data. HRQoL data are only available from a subgroup of patients participating in Study 301 who received treatment with either eribulin or capecitabine. For patients in Subgroup 2, data from the EMBRACE trial are only presented in the CS for OS and PFS; information on AEs was provided during the clarification process; HRQoL data for this population have been derived by the company from Study 301.

3.5 Economic analysis

Cost effectiveness evidence is only presented for the Subgroup 2 population. No cost effectiveness evidence is presented for patients receiving ≥3 chemotherapy regimens for LABC/MBC who are capecitabine naive. As specified in the final scope issued by NICE, the company expresses the cost effectiveness of treatments in terms of the incremental cost per 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 scenario analyses. Costs are considered from an NHS perspective. A simple Patient Access Scheme offering a straight discount to the list price of eribulin was formally agreed with the Department of Health on 14 January 2016. This cost is used in the company's cost effectiveness analyses.

3.6 Subgroups

As described in Section 2.3 and Section 1.1, the information in the CS focuses specifically on 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).

3.7 Other considerations

Since the licence for eribulin has been updated to allow eribulin to be used earlier in the treatment pathway, and since the current STA is a review of TA250, all patients receiving ≥3 chemotherapy regimens for LABC/MBC and Subgroup 2 patients constitute subgroups of the licensed population. For these heavily pre-treated patients, the company considers that the cost effectiveness of eribulin should be appraised using NICE's end of life criteria.

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 latter is relevant to this appraisal (see Section 2 of this ERG report) and it is, therefore, only detail relating to the latter that has been summarised and critiqued in this Section.

4.1 Methods

Overall, despite the lack of some detail regarding the methods (see Sections 4.1.1 to 4.1.4 of this ERG report), the ERG is satisfied with the clinical effectiveness systematic review process as described in the CS. The ERG considers that the company's approach to evidence synthesis (see Section 4.1.5 of this ERG report) is appropriate.

4.1.1 Literature search methods

The CS adequately describes the search strategies used to identify relevant studies relating to the use of eribulin for the treatment of patients with LABC/MBC after chemotherapy. The company conducted a systematic search for RCT evidence. Separate searches were conducted for the retrieval of cost effectiveness studies (see Section 5.1 and 5.2 of this report).

Full details of the search terms used to locate clinical evidence are reported in the CS (Section 4.1 and Appendix 2). The company states that they searched the following databases: Medline (via PubMed), Embase (via Scopus) and The Cochrane Library. The date of the searches (23 December 2015) and the full date span (1 January 2009 to 30 November 2015) are appropriately reported by the company (CS, Appendix 2).

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). One clinical trial registry (clinicaltrials.gov) was searched (12 February 2016) as was the company's own clinical trial database (date not reported).

The ERG considers that the search terms used by the company were relevant for the databases searched. The use of free text only was appropriate as the databases that were searched did not have a Medical Subject Headings search function. Whilst Scopus does not include all references that are included in Embase, since the company also searched its clinical trial database for all completed studies from the eribulin clinical trial programme, the ERG is confident that all relevant studies have been identified.

In summary, the ERG is confident that the company's literature search for evidence for clinical effectiveness will have identified all relevant RCTs.

4.1.2 Eligibility criteria

The CS provides a detailed report of the inclusion/exclusion criteria applied to the selection of potentially relevant studies. These are described in Table 5. Two reviewers independently undertook study selection in two stages:

- Stage 1 – review of abstracts
- Stage 2 – review of full text papers.

Table 5 Inclusion and exclusion criteria for treatment evidence for Subgroup 2 patients

Parameter	Inclusion	Exclusion
Population	Adult patients AND [MBC OR Advanced breast cancer (ABC)] AND AND 3L+	Non-human OR Children OR Adolescents OR Males OR Studies with a unique focus on patients from outside Europe/USA were excluded
Intervention	Eribulin (monotherapy)	All other treatments or combinations
Comparator	Any	
Outcomes	PFS, OS (median and per cent survival at 1 year), ORR, TTR, duration response, TTP, adverse events	All others
Study design	RCT (phase II, III or IV) regardless of design (parallel, crossover, open label, single or double blinded) OR Meta-analysis OR Systematic Reviews	Editorials OR Notes OR Comments OR RWE OR Letters OR Other Reviews OR Abstracts without full paper available OR Phase I studies
Language	English	Non-English studies

ABC=advanced breast cancer; MBC=metastatic breast cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial; RWE=real world evidence; TTP=time to progression; TTR=time to response
Source: CS, Table 6

During both stages, publications not meeting the stated inclusion criteria were excluded and listed alongside the reason for exclusion. Where one reviewer included a study and the other did not, the full text paper was examined and was reviewed by both reviewers until agreement was reached.

The ERG notes that the eligibility criteria applied by the company in Table 5 enabled reviewers to exclude studies based on trial outcomes. This could, theoretically, introduce outcome selection bias[16] although the ERG also notes that as a wide range of outcomes were specified there was no need for included studies to report all outcomes and therefore, including or excluding studies based on outcomes is unlikely to be an important issue with regard to bias. However, the eligibility criteria did not include HRQoL as an outcome,

meaning that any studies that only reported HRQoL would have be excluded. Given the importance of HRQoL as a trial outcome, this would have been a major limitation had the company not also conducted a separate search for HRQoL studies. This literature search is described in Appendices to the ERG report, Section 11.1. As with the clinical effectiveness review, two reviewers independently undertook study selection in two stages. The eligibility criteria are described in Appendix 2 to the CS (reproduced in Appendices to this ERG report, Section 11.1).The same process for including or excluding studies was employed for the literature search for HRQoL studies as for the systematic review for clinical effectiveness.

4.1.3 Data extraction

After applying the eligibility criteria to the full texts, all papers meeting the inclusion criteria were retained for data extraction. The methods used for data extraction are not specified in the CS.

4.1.4 Quality assessment methods

A risk of bias assessment of RCTs included in the systematic review of clinical effectiveness was undertaken by the company using the method recommended by NICE.[17] It is, however, unclear whether this was completed by one reviewer, or independently by two reviewers.

4.1.5 Approach to evidence synthesis

The company's literature search led to the identification of only one RCT that was considered to be directly relevant to the decision problem (the EMBRACE trial). With the inclusion of only one relevant study, it was not possible for the company to carry out a meta-analysis.

The EMBRACE trial includes a population that is wider than the Subgroup 2 population and data from the wider population have been presented in the CS.

Since the investigators of the EMBRACE trial did not collect HRQoL data, the company appropriately sought and presented HRQoL evidence from other sources. The relevance of the HRQoL evidence to the decision problem for this STA is explored in Section 4.8.6 of this ERG report.

4.2 Identified studies in the systematic review

The search conducted by the company identified nine relevant citations[7,18-25] for possible inclusion in its systematic review. All of these focus on the EMBRACE trial and include the clinical study report (CSR),[23] the updated CSR[22] and the full published paper from 2011.[7] The additional six citations[18-21,24,25] are two conference abstracts,[24,25] subsequently published

in full,[7] an additional updated analysis of OS and PFS for Subgroup 2 patients[18,22] and three conference abstracts[19-21] providing results from retrospective subgroup analyses.

An appropriate PRISMA[26] flow diagram, describing the review process was provided by the company (CS, Figure 6). The company listed all citations that were excluded from the review (at Stage 1 or Stage 2) in Appendix 2 to the CS. This list includes the following publications describing additional RCT data for the clinical effectiveness of eribulin in a broader patient population:

- Study 301,[6] a phase III RCT comparing eribulin with capecitabine as first-, second-, or third-line therapy for the treatment of LABC/MBC
- A pooled analysis[27] of Study 301 and the EMBRACE trial
- A phase II RCT designed primarily to assess safety (peripheral neuropathy) in patients with LABC/MBC (defined as locally recurrent or MBC).[28]

In Study 301, patients had not been pre-treated with capecitabine. Furthermore, only 28% of patients in Study 301 received third-line chemotherapy for LABC/MBC and no patient received more than third-line treatment. Not all patients were pre-treated with capecitabine and not all patients were receiving ≥3 chemotherapy regimens for LABC/MBC in the pooled analysis (the proportions being 30.0% and 56.6% respectively). Similarly, not all patients in the phase II trial had been pre-treated with capecitabine or received two or more lines of chemotherapy for LABC/MBC; 61.4% had received prior capecitabine and, while patients were required to have had prior taxane therapy and at least one prior cytotoxic chemotherapy for LABC/MBC, it is unclear how many patients had received two previous lines of therapy for LABC/MBC (although 32.7% had received three or more previous chemotherapy regimens in *any* setting). More importantly, the comparator in the phase II trial (Ixabepilone) is not relevant to the current decision problem.

The ERG is, therefore, confident that the EMBRACE trial is the only trial that provides evidence of the clinical effectiveness of eribulin for the Subgroup 2 population.

The only study identified by the company from its HRQoL evidence literature search was a publication by Greenhalgh et al.[29] The company note that this paper summarises the NICE STA (TA251) conducted in 2011 for which "the company extracted HRQoL data from the published literature, specifically Lloyd et al.[30] As relevant patient reported outcomes are now available for inclusion in this submission, these values are no longer needed, although they have been assessed in the deterministic sensitivity analysis" (CS, p158). The relevant patient reported outcomes referred to are HRQoL outcomes from Study 301.

4.3 Summary of trial characteristics and methodology

A summary of the characteristics of the EMBRACE trial and Study 301 (since it was used to as the source of HRQoL data) is provided in Table 6. Both trials were multi-centre, phase III, open-label, RCTs.

The primary objective of the EMBRACE trial was to evaluate the OS of patients treated with eribulin versus TPC in patients with LABC/MBC who had previously received two to five prior chemotherapy regimens. Patients were randomised in a 2:1 ratio to receive either eribulin or TPC, and randomisation was stratified according to geographical region, HER2 status, and prior treatment with capecitabine. The selection of the TPC agent took place prior to randomisation. TPC included (but was not limited to) chemotherapy (vinorelbine, capecitabine, gemcitabine, anthracyclines and taxanes were all permitted) and hormonal therapy.

The primary objective of Study 301 was to evaluate the OS and PFS for patients with LABC/MBC who had previously received no more than three prior chemotherapy regimens. However, only data from the secondary endpoint, HRQoL, were considered relevant to the current STA. Patients were randomised in a 1:1 ratio to receive either eribulin or capecitabine. Randomisation was stratified according to geographical region and HER2 status.

Patients in both trials were required to have been previously treated with an anthracycline and a taxane and, for the most part, eligibility criteria were similar in the two trials. However, unlike the EMBRACE trial, Study 301 excluded patients previously treated with capecitabine and patients were not required to have received previous treatment for LABC/MBC; rather, patients in Study 301 were required to have received no more than two regimens for LABC/MBC. In contrast, in the EMBRACE trial, patients were required to have received at least two regimens for LABC/MBC. Patients in the EMBRACE trial were also permitted to have received prior capecitabine, unlike in Study 301.

Table 6 Summary of the EMBRACE trial and Study 301 characteristics

Parameter	Description	
	EMBRACE trial	**Study 301**
Intervention and comparator	Eribulin (N=508, 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 TPC (N=254, randomised) The selection of the TPC agent took place prior to randomisation	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 2 to 5 chemotherapy regimens, including a taxane and an anthracycline; at least 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	• 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	135 secondary care centres in 19 countries (including UK)	210 secondary care centres in 24 countries
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, any drugs not allowed concomitantly with the selected TPC, according to the relevant package insert	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, any drugs not allowed concomitantly with the selected TPC, according to the relevant package insert
Primary outcomes	Overall survival	Overall survival and progression-free survival
Secondary outcomes	Progression-free survival, objective response rate and safety	Objective response rate, safety and health-related quality of life

ECOG=Eastern Cooperative Oncology Group; G-CSF=granulocyte-colony stimulating factor; HER2=human epidermal growth factor receptor 2; HRQoL=health-related quality of life; IV=intravenous; LABC=locally advanced breast cancer; MBC=metastatic breast cancer; PS=performance status; TPC=Treatment of Physician's Choice
Source: CS, adapted from Table 12

Superseded by Erratum

4.4 Statistical approach adopted for the conduct and analysis of studies included in the systematic review

The ERG has extracted information relevant to the statistical approach adopted for the conduct of, and analysis of data from, the EMBRACE trial from the CSR,[23] updated CSR,[22] the trial statistical analysis plan (TSAP),[31] the trial protocol [32] and the CS. Since Study 301 was only used to derive HRQoL data, the ERG has not critiqued the statistical approach adopted for the conduct of this trial; ERG comment on HRQoL data is provided in Section 4.8.6.

4.4.1 Outcomes analysed

The definitions and measures used to assess the primary and secondary efficacy outcomes from the EMBRACE trial are listed in Table 7.

Table 7 Primary and secondary efficacy outcomes of the EMBRACE trial

Outcome	Definition	Assessment Measures
OS	Defined as the time from the date of randomisation until death from any cause	• Survival was recorded during the study and following treatment discontinuation for any reasons other than consent withdrawal. Follow-up for survival was assessed at three-monthly intervals until death
PFS	Defined as the time from randomisation until disease progression or death due to any cause in the absence of disease progression	• Tumour assessment was performed according to the RECIST methodology. Baseline tumour assessments were performed within 4 weeks of the start of treatment, consisting of: CT or MRI scans of the chest, abdomen, pelvis, and any other areas of suspected disease; photographs of skin lesions (if present); and bone scans • Tumour assessments were performed in all patients at eight-weekly intervals (± 1 week), or sooner if there was suspicion of disease progression. Scans and photography were performed in those areas where disease was found at baseline, and in any new areas of suspected disease. Bone scans were only repeated during the study if clinically indicated. Tumour responses were confirmed by a second assessment ≥ 4 weeks later. Patients with CR/PaR or SD, 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 in a blinded fashion at a central facility • 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
ORR	Defined as the number of patients with a confirmed CR or confirmed PaR divided by the number of patients in the analysis population	• 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 • Tumour response was evaluated according to RECIST criteria • Target and non-target lesions were assigned to response assessment categories, and the overall tumour response determined for all possible combinations of target and non-target lesions, with or without the occurrence of new lesions

CR=complete response; CT=computed tomography; MRI=magnetic resonance imaging; OS=overall survival; ORR=objective response rate; PaR=partial response; PFS=progression-free survival; RECIST=response evaluation criteria in solid tumours; SD=stable disease
Source: CS, adapted from Table 9

Safety data from the EMBRACE trial were presented as summaries of all AEs, serious AEs (SAEs), deaths, treatment-related AEs and treatment discontinuation due to AEs. HRQoL data were not collected during the EMBRACE trial.

4.4.2 ERG critique of statistical approach

The statistical methods employed by the company to analyse the outcome data from the EMBRACE trial are summarised in the Appendices to this ERG report (Section 11.2). The ERG notes that, the company has analysed outcome data from three data-cuts:

- the primary analysis was planned to occur when 411 deaths had been recorded, although the data cut-off point for the primary analysis was actually after 422 (55%) patients had died (12 May 2009)
- an updated analysis of OS was conducted at the request of the regulatory authorities, when 77% of deaths had occurred, representing a more mature dataset with longer follow up (3 March 2010 data cut-off point)
- the most recent OS analysis was performed after 95% of patients had died, and the company presented data for Subgroup 2 patients using this most recent data cut-off (17 June 2013).

During the clarification process the ERG requested results for the ITT population using the data available after 95% of patients had died. The ERG considered that this information was required to allow a comparison of outcomes for the Subgroup 2 and ITT populations. Results for the ITT and Subgroup 2 populations that have been generated using data from the most recent data cut are provided in Section 4.8 of this ERG report.

The analyses carried out by the company to generate OS and PFS hazard ratios (HRs) were conducted using Cox proportional hazards (PH) modelling. The validity of this method relies on the hazards of the two comparator drugs being proportional.

As part of the clarification process, the ERG requested details of any PH testing that had been carried out by the company. The company response explained that no formal testing of the PH assumption had been performed. To test the validity of the PH assumptions required to generate valid HRs the ERG plotted the OS cumulative hazards for patients treated with eribulin against those for patients treated with TPC. The same approach was taken in relation to PFS data. Data sources for, and results from, these analyses are summarised in Table 8

Table 8 Results from the ERG's proportional hazard tests

Outcome	Data source	PH assumption valid?
ITT population		
OS	Cumulative hazards estimated from digitised K-M data presented in the CS Figure 9 (OS) and Figure 11 (PFS)	Yes
PFS		No – validity of company HR unclear and HRs may not be reliable
Subgroup 2 population		
OS	K-M data provided during the clarification process (in response to ERG question B1) used to calculate cumulative hazards.	No – validity of company HR unclear and HRs may not be reliable
PFS		No – validity of company HR unclear and HRs may not be reliable

ERG=Evidence Review Group; HR=hazard ratio; K-M=Kaplan-Meier; OS=overall survival; PFS=progression-free survival

A summary of the checks made by the ERG in relation to the statistical approach adopted by the company to analyse data from the EMBRACE trial is provided in Table 9. With the exception of the lack of PH testing, overall, having carried out these checks, the ERG is satisfied with the statistical approach employed by the company. The ERG therefore has confidence in the validity of the results from the trial, with the exception of the interpretation of HRs where the assumption for PH does not hold.

Table 9 ERG assessment of statistical approach used to analyse data from the EMBRACE trial

Component of statistical approach	Approach taken with ERG comment
Sample size calculation	The ERG was able to replicate the sample size calculation provided in the CS (p64) using the sample size details provided by the company for the original sample size calculation. However, the ERG notes that the company have performed a sample size re-estimation but do not provide further details in order to calculate the sample size re-estimation. The ERG is unable to comment on the sample size calculation as it is unclear whether the sample size re-estimation has affected the power or type 2 error in any way.
Protocol amendments	The ERG notes that four amendments were made to the original EMBRACE trial protocol. These are outlined and provided in the final analysis CSR (Section 8.9). These do not appear to be a cause for concern. However, the ERG also notes that the company made some changes to the planned analyses after database lock including: • To further investigate TPC the agents were grouped into seven groups based on the IVRS data, as capecitabine, vinorelbine, gemcitabine, taxanes, anthracyclines, other chemotherapy and hormonals, and some tables were repeated using these groups. Comparisons between the eribulin and TPC arm were conducted in two ways for some analyses: 1) eribulin patients who would have received that TPC if they had been randomized to that group against those that did, and 2) all patients who received eribulin versus the individual TPC group. • The parameters HER2, prior capecitabine and geographical region were fitted using the strata statement in the Cox model, rather than as covariates. The inclusion of stratification variables as strata rather than covariates in the Cox model produces a hazard ratio which reflects the results from the primary analysis conducted using the stratified log-rank test more appropriately. • In addition to the PFS analyses as detailed in the SAP, following unblinding, discussion surrounding the interpretation of the "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" led to the formulation of a new set of PFS rules for censoring/progression. As such, this approach represents a post hoc analysis, as the methods used to define and interpret the results were not part of the pre-specified analysis. This analysis is based upon the Independent review of the radiological assessments. For details of this analysis please see the SAP. The main difference from this analysis as opposed to the PFS detailed in the SAP is that it takes into account progressions from non-target lesions (i.e. unequivocal progressions) in addition to new lesion and target lesion progression events. However, the company do not present the results for these post-hoc analyses or critique them in the CS, therefore the ERG is satisfied that these post-hoc analyses are not a cause for concern
Sensitivity analyses for OS	The ERG is satisfied that the results of the sensitivity analysis (primary OS analysis adjusted for number of prior chemotherapy regimens and ER status) is provided in the CSR
Subgroup analyses for OS	A total of 17 subgroup analyses were pre-specified in the CSR. The ERG is satisfied that the results of all pre-specified subgroup analyses are provided in the CSR and notes one of these includes Subgroup 2 on which the company focusses the CS. The ERG also notes that some post-hoc subgroup analysis results are also provided in the CSR which should be interpreted with caution
Adverse events	Safety was assessed through summaries of all AEs, SAEs, deaths, treatment-related AEs and discontinuation due to AEs. The ERG is satisfied that the results of all the AE data analyses are provided in both the primary analysis and final analysis CSRs

AE=adverse event; CSR=clinical study report; EORTC QLQ-BR23=European Organisation for Research and Treatment of Cancer quality of life questionnaire with breast module; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire 30; ER=oestrogen receptor; HER2=human epidermal growth factor receptor 2; IVRS=interactive voice recognition system; OS=overall survival; PFS=progression-free survival; SAE=serious adverse event; SAP=statistical analysis plan; TPC=Treatment of Physician's Choice
Source: CS, CSR, updated CSR and ERG comment

4.5 Patient populations relevant to the current appraisal

As noted in Section 1.1, the company presents evidence for all patients receiving ≥3 chemotherapy regimens for LABC/MBC (the ITT population) and for a subgroup of this population, Subgroup 2. As noted in Sections 4.2 and 4.3, HRQoL data from Study 301 have been provided. The different populations are summarised in Table 10.

Table 10 Summary of populations referred to in the evidence for clinical effectiveness

Trial/ population	Description	Relevant population in decision problem	Relevant outcomes
EMBRACE trial ITT population	All patients who had received at least two prior chemotherapy regimens for LABC/MBC who were randomised, irrespective of whether or not they actually received study treatment or whether they received the medication they were randomised to	All patients receiving ≥3 chemotherapy regimens for LABC/MBC (Original indication for eribulin)	OS PFS ORR
EMBRACE trial safety population	All patients who had received at least two prior chemotherapy regimens for LABC/MBC who were randomised and who received at least a partial dose of study treatment. The population was based on the actual treatment received	All patients receiving ≥3 chemotherapy regimens for LABC/MBC (Original indication for eribulin)	AEs
EMBRACE trial 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) This comprises 73.4% of the EMBRACE ITT population and 73.3% of the EMBRACE safety population	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)	Subgroup of ITT population: • OS • PFS • ORR Subgroup of safety population: • AEs
Study 301 third-line patients	Patients with LABC/MBC whose disease has progressed after two prior chemotherapy regimens for advanced disease which excludes capecitabine	A subgroup of the ITT population	HRQoL

AEs=adverse events; HRQoL=health related quality o of life; ITT=intention-to-treat; LABC/MBC=locally advanced breast cancer/metastatic breast cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

4.6 Patient characteristics of the studies included in the systematic review

4.6.1 Patient disposition

All patients in the EMBRACE trial at the time of the most recent data-cut (after 95% of patients had died). At the time of the primary analysis, when 55% of patients had died, 33 (4.3%) patients were still on study treatment.

Reasons for discontinuing treatment were provided by the company for the ITT population after 55% of patients had died and for Subgroup 2 patients after 95% of patients had died. Despite the analyses being carried out at different time points the reasons appear similar in both populations (see Table 11). The most common reason for discontinuing treatment was disease progression.

Table 11 Patient disposition* in the EMBRACE trial – safety population and Subgroup 2*

Reason for treatment discontinuation	Overall trial population				Subgroup 2			
	Eribulin (N=508)		TPC (N=254)		Eribulin (n=370)		TPC (n=189)	
Patients randomised (ITT population)	508		254		370		189	
Patients who withdrew prior to receiving any treatment	-6		-6		-4		-5	
Patients who were treated on the opposite treatment arm	+1		-1		+1		-1	
Patient who received at least some study treatment (Safety population)	503	(100.0)	247	(100.0)	367	(100.0)	183	(100.0)
Progressive disease, n (%)	335	(66.6)	152	(61.5)	263	(71.7)	118	(64.5)
Clinical progression, n (%)	60	(11.9)	36	(14.6)	46	(12.5)	23	(12.6)
Adverse event, n (%)	49	(9.7)	24	(9.7)	34	(9.3)	21	(11.5)
Physician decision, n (%)	18	(3.6)	11	(4.5)	14	(3.8)	9	(4.9)
Withdrawal by subject, n (%)	9	(1.8)	5	(2.0)	5	(1.4)	5	(2.7)
Death, n (%)	3	(0.6)	2	(0.8)	2	(0.5)	2	(1.1)
Other, n (%)	5	(1.0)	8	(3.2)	3	(0.8)	5	(2.7)
On treatment, n (%)	24	(4.8)	9	(3.6)	0	(0.0)	0	(0.0)

*Patient disposition reported in the CS for the ITT population (when 55% of patients had died) and, for the Subgroup 2 population when 95% of patients had died

Source: CS, adapted from Figure 7 and company response to ERG clarification letter (question A1)

4.6.2 Baseline characteristics

Of the 762 patients recruited to the EMBRACE trial, 51 were from UK centres. The ERG is satisfied that a sufficient number of patients in the trial were from European Union countries that implement care pathways similar to those found in the UK, meaning that findings from the EMBRACE trial can be considered generalisable to NHS clinical practice.

Demographic data, baseline disease, and tumour characteristics are provided in the CS for each treatment arm of the EMBRACE trial for the ITT population and the Subgroup 2 population. These data are reproduced in the Appendices to this ERG report (Section 11.1, Table 39). The ERG considers that the presented data suggest that patient characteristics are well balanced across treatment groups. In summary:

- the majority of patients were Caucasian (>90%)
- the median age of patients was 55 years
- approximately three quarters of women were post-menopausal
- the majority of patients had ER-positive (≥70%) and/or HER2-negative (≥82%) LABC/MBC
- the majority of patients had ECOG PS 0 (≥42%) or ECOG PS 1 (≥48%)
- the most common sites for metastases were bone (>60%) and liver (>60%)
- the median time since diagnosis was just over 5 years.

The ERG notes that in the CS (Appendix 3), the company observes that disease stage at diagnosis differs by trial arm. Information in the CSR, suggests that the main difference between arms is that, at diagnosis, [redacted] of patients treated with eribulin had Stage II disease and [redacted] had Stage IV disease. In contrast, at diagnosis, [redacted] of patients treated with TPC had Stage II disease and [redacted] had Stage IV disease.

The majority of patients (59.4%) in the EMBRACE trial were treated with one of the chemotherapy regimens specified in the final scope issued by NICE and company's decision problem, i.e. vinorelbine, capecitabine or gemcitabine. As noted in Section 2.6 of this ERG report, NICE recommends both capecitabine and vinorelbine as second- or third-line treatments (CG81).[8] Gemcitabine is also a NICE recommended treatment but only in combination with paclitaxel (TA116).[33] It is, however, apparent from Table 12 that only one patient who received gemcitabine also received paclitaxel. Clinical advice to the ERG is that the use of gemcitabine monotherapy is not uncommon for more heavily pre-treated patients. The ERG considers that the TPC agents supplied to EMBRACE trial participants mostly reflect those that are prescribed in NHS clinical practice.

Importantly, 73% of patients in the EMBRACE trial had previously received treatment with capecitabine. These patients were those that constitute Subgroup 2. The characteristics of the Subgroup 2 population are broadly similar to those of the ITT population. The main exceptions are:

- approximately 64% of Subgroup 2 patients had received four or more prior chemotherapy regimens (in any setting) compared with approximately 53% of all patients in the ITT population
- approximately 65% of Subgroup 2 patients had received three or more prior chemotherapy regimens in the LABC/MBC setting compared with approximately 57% of all patients in the ITT population.

The ERG considers that the line of treatment differences are not unexpected since patients in Subgroup 2 had also received prior capecitabine in addition to an anthracycline and taxane. In addition, as approximately 70% of Subgroup 2 patients were from region 1 (North America, Western Europe and Australia) compared with approximately 64% in ITT population, the ERG considers that differences in capecitabine use across the countries in each region may account for these marginal differences between the ITT and Subgroup 2 populations.

Table 12 EMBRACE trial Treatment of Physician's Choice (ITT and Subgroup 2 populations)

TPC agent	ITT population		Subgroup 2	
	N	%	n	%
Chemotherapy	238	93.7	174	92.1
• Vinorelbine	61	24.0	54	28.6
• Gemcitabine*	46	18.1	38	20.1
• Capecitabine	44	17.3	4§	2.1§
• Taxanes	38	15.0	37	19.6
o Paclitaxel†	25	9.8	25	13.2
o Docetaxel	10	3.9	9	4.8
o Ixabepilone	3	1.2	3	1.6
• Anthracyclines	24	9.5	22	11.6
o Doxorubicin‡	23	9.1	21	11.1
o Mitoxantrone	1	0.4	1	0.5
• Other chemotherapy	25	9.8	19	10.1
Hormonal therapy	9	3.6	9	4.8
Other¥	7	2.8	6	3.2
TOTAL*	254	100.0	189	100.0

ITT=intention-to-treat; TPC=Treatment of Physician's Choice.
* One patient (included in both the ITT population and Subgroup 2) received gemcitabine and paclitaxel and is included in the gemcitabine group only
§ Four patients in the TPC arm received capecitabine in the EMBRACE trial even though they had been previously treated with capecitabine prior to entry into the trial
† Paclitaxel includes paclitaxel and nab-paclitaxel
‡ Doxorubicin includes doxorubicin and liposomal doxorubicin

¥ Patients were discontinued prior to treatment initiation or received eribulin instead of the planned TPC
Source: CS, adapted from Table 15 and company response to further ERG clarification

The company states that patients could have been treated with trastuzumab in centres where trastuzumab was available. However, at the time of the EMBRACE trial, trastuzumab was not commonly used and so was not actually employed as part of TPC. The ERG does not consider this to be a limitation of the EMBRACE trial since trastuzumab is only an option for patients with HER2-positive disease (17.8% of ITT population) and, for these patients, trastuzumab would be a treatment option much earlier in the treatment pathway.

4.7 Quality assessment of the RCTs included in the systematic review

The CS includes an assessment of the risk of bias for the EMBRACE trial. This is reproduced in Table 13. The company has also provided an assessment of the risk of bias for Study 301. As data from Study 301 were used to provide information about HRQoL for the current STA, the ERG has also reproduced this assessment in Table 13. Additional information is provided in the appendices to this ERG report (Section 11.4). Overall, the ERG considers that both the EMBRACE trial and Study 301 were generally well designed and well conducted and the ERG agrees with the company's conclusion that both trials have at a low risk of bias.

Table 13 Company's assessment of risk of bias for the EMBRACE trial and Study 301

Study question	Company assessment		ERG Comment
	EMBRACE	Study 301	
Was randomisation carried out appropriately?	Yes	Yes	Agree
Was the concealment of treatment allocation adequate?	NA	NA	As randomisation was conducted centrally, using an IVRS in both trials ensured that a patient's allocation to a particular treatment arm could not be predicted or influenced. In the EMBRACE trial, the use of an IVRS also ensured that each TPC treatment was independently randomised against eribulin to support the conduct and results of subgroup analyses
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	NA	NA	The primary outcome of the EMBRACE trial (OS) was not dependent on subjective assessment. All other relevant efficacy outcomes in EMBRACE were dependent on subjective assessment (PFS and ORR) but blinded review was also conducted in addition to investigator assessment for these outcomes, enabling a comparison to be made to assess risk of bias. Safety data in EMBRACE were also reviewed by the independent DMC. HRQoL data were not blinded in Study 301
Were there any unexpected imbalances in drop-outs between groups?	No	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	Agree, all outcomes were reported in the relevant CSRs. Note, for this STA, OS, PFS, ORR and safety are relevant outcomes from EMBRACE and HRQoL is the only relevant outcome from 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	Yes	Agree

CSR=clinical study report; DMC=data monitoring committee; HRQoL=health-related quality of life; NA=not applicable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; STA=single technology appraisal; TPC=Treatment of Physician's Choice; IVRS=interactive voice response system
Source: CS, adapted from Table 22 and Appendix 3

4.8 Results from the studies included in the systematic review

OS analyses of EMBRACE trial data were conducted at three points in time: primary analysis after 55% of patients had died, updated analysis after 77% of patients had died and the most recent analysis, after 95% of patients had died. PFS analyses were conducted at the primary analysis (after 55% of patients had died) and most recent analysis (after 95% of patients had died). The company also provides ORR results and safety data from the primary analysis. As HRQoL data were not collected as part of the EMBRACE trial, the company has presented data for this outcome from Study 301.

The company only presents OS and PFS results for Subgroup 2 patients. These were calculated using data from the most recent data-cut, i.e. after 95% of patients had died. As a result of a clarification request (question A9), the company also provided some safety data for Subgroup 2 patients.

4.8.1 Overall survival

The ERG cautions that the company's OS HR (but not median OS) result calculated from Subgroup 2 population data may be unreliable. This is because the approach taken to calculate relies on the assumption that the OS K-M data from the intervention and comparator arms of a trial are proportional to one another. Analyses undertaken by the ERG indicate that while the ITT population OS K-M data are proportional the Subgroup 2 OS K-M data are not proportional (see Table 14).

The ITT and Subgroup 2 OS results generated using the latest data-cut (i.e. after 95% of patients had died) were very similar, with median OS for patients treated with eribulin being ≥13 months (Table 14). Improvements versus TPC of between 2.7 and 2.9 months were observed in the ITT population and Subgroup 2 patients, respectively. This improvement was found to be statistically significant for both the ITT population and the Subgroup 2 population; however, as the log rank test also relies on the assumption of proportional hazards, the results of this test should be interpreted with caution when considering the OS data from Subgroup 2 patients.

Table 14 EMBRACE trial overall survival after 95% of patients had died (ITT population and Subgroup 2 populations)

Parameter	ITT population		Subgroup 2	
	Eribulin (N=508)	TPC (N=254)	Eribulin (n=370)	TPC (n=189)
Number of patients who died, n (%)	485 (95.5)	242 (95.3)	356 (96.2)	183 (96.8)
OS, months				
Median (95% CI)	13.24 (12.06 to 14.4)	10.55 (9.23 to 12)	13.0 (11.7 to 13.8)	10.1 (7.7 to 11.4)
Difference in medians (95% CI)	2.7 (1 to 4.4)		2.9 (NA)	
Stratified log-rank test	p=0.011		p=0.008	
Hazard ratio (95% CI)	0.815 (0.696 to 0.955)		0.78 (0.65 to 0.94)	

CI=confidence interval; NA=not available; TPC=treatment of physician choice
Source: Company response to ERG clarification letter, adapted from Table A1

The median OS results for the ITT population which were calculated from the latest data-cut are similar to the median OS reported at both the previous data-cuts, at which points statistically significant improvement in the eribulin arm were also reported (median OS, eribulin versus TPC, primary analysis: 13.1 versus 10.6 months, p=0.041; updated analysis: 13.2 versus 10.6 months, p=0.014). The company's updated analysis demonstrates that the survival curves separate early and remain separated for the duration of the analysis period.

Any treatment given to patients following disease progression has the potential to impact on OS and, as part of the clarification process, the ERG requested details of any post-progression treatments given to patients in both arms of the EMBRACE trial. Details relating to these treatments are summarised in (Table 15). Overall, more patients in the eribulin arm appear to have received more treatment on progression. In particular, it is noticeable that the five most common treatments prescribed post-progression are the five most common agents administered in the TPC arm of the EMBRACE trial. During the previous appraisal of eribulin (TA250), the ERG noted (p24):

> *"The post-progression treatments given appear to be similar in number and type across both arms of the trial thereby minimising the likelihood of affecting the OS results."*[34]

This conclusion was based on data provided by the company for a previous data-cut. Since then, the proportion of patients receiving additional treatment has increased to a greater extent in the eribulin arm than in the TPC arm. However, given that the OS results remain similar, it appears that rather than the additional treatments being an important contributory factor to OS, they simply reflect the fact that patients in the eribulin arm are living longer and so have more time to receive additional treatments.

Table 15 Subsequent treatment received on disease progression (EMBRACE trial ITT and Subgroup 2 populations)

Treatment on disease progression	ITT population		Subgroup 2	
	Eribulin (N=508)	TPC (N=254)	Eribulin (n=370)	TPC (n=189)
Any, n (%)	394 (77.6)	164 (64.6)	290 (78.4)	123 (56.1)
Most common* treatments				
• Capecitabine	58 (11.4)	6 (2.4)	8 (2.2)	0 (0.0)
• Vinorelbine	49 (9.7)	17 (6.7)	41 (11.1)	9 (4.8)
• Gemcitabine	34 (6.7)	24 (9.5)	29 (7.9)	17 (9.0)
• Paclitaxel	42 (8.3)	15 (5.9)	39 (10.5)	12 (6.4)
• Doxorubicin	40 (7.9)	7 (2.8)	31 (8.4)	4 (2.1)
• Cyclophosphamide	22 (4.3)	10 (3.9)	21 (5.7)	9 (4.8)

* >5% in any arm
Source: Company response to ERG clarification letter, adapted from response to A8

4.8.2 Progression-free survival

Analyses carried out using EMBRACE trial data from the latest data cut (after 95% of patients had died) show that ITT and Subgroup 2 population results for median PFS are very similar (Table 16), with PFS for patients treated with eribulin being approximately 3.6 months and improvements versus TPC of between 1.4 and 1.5 months (ITT and Subgroup 2 populations respectively). These results are similar to the primary analysis median PFS results for both trial arms.

Table 16 EMBRACE trial progression-free survival (investigator assessment) using the latest data cut (after 95% of patients had died), ITT and Subgroup 2 populations

Parameter	ITT population		Subgroup 2	
	Eribulin (N=508)	TPC (N=254)	Eribulin (n=370)	TPC (n=189)
Number of patients who progressed or died to n (%)	453 (89.2)	217 (85.4)	334 (90.2)	161 (85.1)
PFS to months				
Median (95% CI)	3.61 (3.29 to 3.75)	2.17 (1.97 to 2.76)	3.6 (3.3 to 3.8)	2.1 (1.9 to 2.2)
Difference in medians (95% CI)	1.4 (NA)		1.5 (NA)	
Stratified log-rank test	p=0.002		p<0.001	
Hazard ratio (95% CI)	0.771 (0.651 to 0.913)		0.68 (0.56 to 0.83)	

CI=confidence interval; NA=not available; PFS=progression-free survival; TPC=treatment of physician choice
Source: Company response to ERG clarification letter, adapted from Table A1

At the time of the primary analysis, the company also reported PFS by independent review for the ITT population. At that time median PFS was similar in both the eribulin and TPC arms of the trial irrespective of whether assessed by the investigator (3.6 months for patients treated with eribulin versus 2.2 months for patients treated with TPCy) or by independent review (3.7 months for patients treated with eribulin versus 2.2 months for patients treated with TPC). The ERG considers that the similarity of the investigator and independent assessed PFS from the primary analysis, and the similarity of the findings to the investigator assessed PFS reported at the most recent data cut (after 95% of patients had died [3.61 versus 2.17 months]) suggests the PFS findings are robust and reliable for the overall population.

Overall, the ERG considers that the findings from the EMBRACE trial demonstrate an improvement in PFS for patients treated with eribulin versus those treated with TPC. This is true for the ITT population and for the Subgroup 2 population. However, the ERG cautions that the company's ITT and Subgroup 2 PFS hazard ratio (but not median PFS) results may be unreliable as the approach taken to calculate these values is only valid if the relevant PFS K-M data are proportional to one another and analyses carried out by the ERG indicate that, for both patient populations, the data are not proportional (see Table 8).

4.8.3 Objective response rate

The company has only reported the primary analysis ORR for the ITT population. The ORR was statistically significantly different in favour of eribulin compared with TPC for both independent-based (12.2% [95% CI 9.4 to 15.5] versus 4.7% [95%CI 2.3 to 8.4] p=0.002) and investigator-based assessments (13.2% [95% CI 10.3 to 16.7] versus 7.5% [95% CI 4.3 to 11.9] p=0.028). The ERG agrees with the company that the magnitude of the ORR should be considered in the context of the population enrolled in the EMBRACE trial as all patients had received at least two previous chemotherapies for LABC/MBC.

4.8.4 Safety

EMBRACE trial primary analysis (after 55% of patients had died) AEs are reported in the CS. Information about AEs experienced by Subgroup 2 patients is not reported in the CS. However, during the clarification process, the company confirmed that the AE data available for Subgroup 2 patients indicate that there are no notable differences between the AE experience of the overall safety population and that of the Subgroup 2 population (response to ERG clarification letter, A9). The company supported this statement by providing data on the most commonly reported AEs for Subgroup 2 patients in each arm of the EMBRACE trial (>10% in either arm). Based on the provided data, the ERG agrees with the company that, in terms of AE experience, there are no notable differences between the EMBRACE trial safety population and the Subgroup 2 population.

A comparison of safety between treatment with eribulin and treatment with TPC is subject to the following caveats:

- as a group, patients in the TPC arm received a wide range of treatments, each of which has a distinct safety profile
- the number of patients receiving each type of TPC was relatively small
- in the EMBRACE trial, overall exposure to study treatment was longer in the eribulin arm compared in the TPC arm (median 3.9 months versus 2.1 months [chemotherapy] and 1 month [hormonal], respectively)

These factors mean that reliable conclusions cannot easily be drawn when comparing incidences of specific AEs in the two arms of the trial.

The overall incidence of AEs experienced by patients participating in the EMBRACE trial is presented in Table 33 of the CS. This table includes details about any AEs, SAEs (including fatal SAEs) and severe AEs. Key points include:

- **Any AE**: most patients experienced at least one AE (98.8% of patients in the eribulin arm and 93.1% in the TPC arm)
- **Severe AEs** (Grade ≥3): these occurred more frequently in the eribulin arm than in the TPC arm (90.7% versus 59.5%). The company (CS, p120) notes that the most common Grade ≥3 AE for patients treated with eribulin was neutropenia (49.7%); however, the most common Grade ≥3 AEs for patients treated with TPC agents are not reported
- **Any SAE**: the incidence of SAEs was similar in both arms of the trial (eribulin: 25.0%, TPC: 25.9%). The company (CS, p113) notes that the most frequently reported SAEs in the eribulin arm were febrile neutropenia (4.2%) and neutropenia (1.8%); the most frequently reported events in the TPC arm were dyspnoea (3.6%) and asthenia (2.4%)
- **Fatal SAEs**: There were fewer fatal AEs in the eribulin arm (4.0%) than in the TPC arm (7.3%). Fatal AEs were more noticeable with capecitabine (9.1%) and gemcitabine (8.7%) compared with eribulin (4.0%).

Most commonly reported adverse events

Details relating to the most frequently reported all-Grade AEs (>10% patients in each arm) in the EMBRACE trial are provided in Table 34 of the CS. The most frequently reported AEs occurring in patients treated with eribulin are reported to be asthenia/fatigue (53.7%), neutropenia (51.7%), alopecia (44.5%), peripheral neuropathy (34.6%) and nausea (34.6%). From Table 34 of the CS it is, however, evident that similar incidences of asthenia/fatigue (50.8%) and neutropenia (49.2%) were seen in patients treated with vinorelbine. For patients treated with TPC the most common AEs were asthenia/fatigue (39.7%), neutropenia (29.6%), nausea (28.3%), anaemia (22.7%) and constipation (20.6%). Only the incidences of anaemia and constipation are higher in the TPC arm than in the eribulin arm (18.7% and 24.7% respectively in patients treated with eribulin).

Treatment related adverse events

In total, 94.2% of patients reported AEs that were considered by the investigator to be treatment-related in the eribulin arm compared with 77.7% in the TPC arm (CS, Table 33). The company notes (CS, p113) that the open-label nature of the trial means that these figures may be subject to bias against the investigational agent (eribulin).

Adverse events leading to treatment discontinuation

The company states that discontinuations due to AEs were lower in the eribulin arm (13.3%) than in the TPC arm (15.4%). However, the ERG observes that discontinuations due to AEs were all marginally lower for patients treated with vinorelbine (11.5%), capecitabine (10.9%) and gemcitabine (10.9%) than for patients treated with eribulin, suggesting that the apparently higher treatment discontinuation rate in the TPC arm can be attributed to the other agents that constituted TPC. Indeed, information in the CSR (Table 23) shows that this was a particular issue for patients treated with taxanes [redacted].

Real world evidence

The company reports (CS, p118) that recently published data from audits undertaken in England, Spain and France/Switzerland have shown that eribulin is well tolerated in a routine clinical practice setting and reflect that patients are not impacted greatly by the side effect profile of eribulin (see Section 4.9). The company concludes that eribulin has a well characterised and manageable safety profile.

Superseded by Erratum

4.8.5 Exposure to study drugs

In the EMBRACE trial, overall exposure to study treatment was longer in the eribulin arm than in the TPC arm. This was observed for all patients in the EMBRACE trial (safety population) and Subgroup 2 patients (Table 17). The median number of cycles of eribulin received by patients was reported in the CS to be between five and six. It is reported in the CS that patients in the eribulin arm received the study drug for almost twice as long as those in the TPC arm. The company considers that the longer duration of therapy demonstrates the superior efficacy and tolerability of eribulin compared with TPC, since therapy was discontinued on disease progression and PFS was longer for patients in the eribulin arm than it was for those receiving TPC. The company further states that evidence from the EMBRACE trial highlights the positive safety and tolerability profile associated with treatment with eribulin.

Table 17 EMBRACE trial exposure to study drugs (safety and Subgroup 2 populations, 95% data-cut)

Parameter	Overall safety population			Subgroup 2	
	Eribulin (N=503)	TPC (Chemotherapy) (N=238)	TPC (Hormonal) (N=9)	Eribulin (n=367)	TPC (n=183)
Duration of exposure, median days (min, max)	118 (21, 1241)	70.0 (1, 1578)	30.0 (25, 188)	119 (21, 1241)	55 (1, 1578)
Number of cycles completed on study, n (%)					
1 to 2	81 (16.1%)	NA	NA	57 (15.5%)	NA
3 to 4	127 (25.2%)			91 (24.8%)	
5 to 6	110 (21.9%)			86 (23.4%)	
> 6	185 (36.8%)			133 (36.2%)	
Range	1 to 55 cycles			1 to 55 cycles	
Dose intensity, median mg/m^2/week (min, max)	0.84 (0.2, 1.0)	NA	NA	0.84 (0.2, 1.0)	NA
Relative dose intensity, % (min, max)	91% (30, 110)	NA	NA	90% (30, 110)	NA
Patients with dose interruption, n (%)	29 (5.8%)	22 (9.2%)	2 (22.2%)	26 (7.1 %)	14 (7.7%)
Patients with dose delay, n (%)	253 (50.3%)	100 (42.0%)	0 (0.0%)	188 (51.2%)	75 (41.0%)
Patients with dose reduction, n (%)	146 (29.0%)	63 (26.5%)	0 (0.0%)	109 (29.7%)	46 (25.1%)

NA=not applicable; TPC=treatment of physician choice
Source: Company response to ERG clarification letter, A4

4.8.6 Health-related quality of life

HRQoL data were not collected as part of the EMBRACE trial but were collected during Study 301. In Study 301 change in HRQoL was a secondary endpoint. The ERG notes that no patient in Study 301 had received more than two lines of treatment and no patient had received prior capecitabine. The ERG cautions, therefore, that the HRQoL findings presented in the CS may only be representative of a fitter subgroup of the EMBRACE trial ITT population and may not be representative of the experience of Subgroup 2 patients.

HRQoL data were collected using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life (QoL) questionnaire[35] and the breast module QLQ-BR23.[36] The EORTC-C30 questionnaire is a validated instrument commonly used in oncology trials.

Data were collected at baseline in clinic before randomisation and then at 6 weeks and 3, 6, 12, 18 and 24 months (or disease progression/treatment change) and at unscheduled visits. Questionnaires were completed prior to any study-related procedures for that visit and before tumour assessment results were communicated to the patient. Patients were asked to complete questionnaires at each clinic visit, even if they had declined previously. Compliance for completing the EORTC QLQ-C30 questionnaires during the study was ≥85% until 12 months, but thereafter sample sizes decreased due to study attrition. The company cautions that, due to the smaller sample sizes, analyses after 6 months should be interpreted with caution.

The principal pre-specified HRQoL outcome in Study 301 was overall global health status (GHS)/quality of life (QoL) at week 6. However, the results reported in the CS are based on additional post-hoc analyses of the study data.

Only data from a subgroup of patients in Study 301 were relevant to all patients receiving ≥3 chemotherapy regimens for LABC/MBC, namely a proportion (28%) of those who had received third-line treatment (n=309). No patient had previously received capecitabine.

The only results reported in the CS for all patients receiving ≥3 chemotherapy regimens for LABC/MBC are scores for GHS. The ERG highlights that HRQoL appears to improve over time (CS, Figure 18 with scores reproduced in Table 18). The baseline GHS score is identical for patients receiving eribulin as a third-line treatment and for patients receiving capecitabine as a third-line treatment (55.2). The score for patients in the eribulin arm rose to 83.3 at 24 months and for patients receiving capecitabine it rose to 68.1, indicating that improvement was greatest in patients treated with eribulin. However, as mentioned previously, the data must be treated with caution due to the low number of patients completing the questionnaire at 24 months (primarily due to most patients having progressed

or having changed treatment by this stage; only 11 patients completed a questionnaire at 24 months).

Table 18 Global health status scores for third-line patients participating in Study 301

Arm	Baseline	6 weeks	Months				
			3	6	12	18	24
Eribulin third-line (n=158)	55.2 (n=148)	57.4 (n=118)	60.9 (n=86)	59.8 (n=46)	64.2 (n=17)	70.8 (n=6)	83.3 (n=5)
Capecitabine third-line (n=151)	55.2 (n-147)	61.4 (n=122)	61.0 (n=75)	62.1 (n=44)	60.8 (n=17)	66.7 (n=9)	68.1 (n=6)

Source: CS, adapted from Figure 18 and company response to ERG clarification letter, A10

While no other HRQoL data that specifically relate to the third-line population are reported, the company states results from the third-line Study 301 patients are "consistent with those in the overall population" (CS, p102). The results for the overall population are presented on pp94 to 100 of the CS and summarised in the Appendices to this ERG report (Section 11.5, Table 40). Without equivalent data being presented for the third-line population, the ERG is unable to comment further on the HRQoL data.

No data for Subgroup 2 patients are available. Nevertheless, the QLQ-C30 results from Study 301 were converted into EQ-5D utility scores and used in the company's economic analysis (see Section 5.5.9).

4.9 Supporting safety data from observational studies

Since April 2011, eribulin has been made available to more than 2300 patients in England via the CDF. Therefore, in addition to the studies identified by its systematic review, the company were also able to present non-RCT, 'real world' evidence to support the assessment of the safety of eribulin. International studies were also identified. The company does not specify how these sources of observational data were identified or selected. The sources of supporting safety data supplied are:

- An audit of 108 patients treated with eribulin at the Royal Marsden Hospital in London, prospectively registered in a database between November 2011 and December 2013 (conference abstract and slides presentation)[37]
- An audit of 75 patients treated with eribulin via the North West CDF from August 2011 to March 2013 (conference abstract)[38]
- An audit of 25 patients treated at 22 centres with eribulin in London via the London CDF between September 2011 and February 2013 (published paper)[39]
- The EUFORIA-1 observational, transversal, retrospective, national study of 104 patients from 19 Spanish hospitals (13 public, 6 private) who were treated between April 2011 and March 2012 (poster presentation)[40]
- The ERIBEX retrospective, international, multi-centre study of 258 patients with LABC/MBC treated at three centres in France and one centre in Switzerland between 28 March 2011 and 15 January 2014 (published paper).[41]

The ERG has summarised data from these studies in Table 19. Patients included in the CDF audits had, on average, received ≥3 prior lines of chemotherapy for LABC/MBC whilst patients in the international studies had received four or five prior lines of chemotherapy for LABC/MBC. In all studies, ≥80% received previous treatment with capecitabine. Overall, the incidences of the most commonly reported key AEs were consistent with the incidences reported in the EMBRACE trial (see Section 4.4.2). In fact, in most cases, the frequencies of these key AEs in each study were lower than those reported for patients participating in the EMBRACE trial.

Table 19 Key safety data from observational studies and the EMBRACE trial

Key study details, safety data and efficacy data	CDF audits (England)			International studies		RCT
	Royal Marsden	North West CDF	London CDF	EUFORIA-1	ERIBEX	EMBRACE (ITT population)
Number of patients on eribulin	108	75	25	104	258	508
Median age, years	54	53	58	57	59	55
Cycles						
• Median	5	6	4	4	5	5 to 6
• Range	1 to 14	NR	1 to 15	1 to 14	1 to 19	1 to 55
• ≥5 cycles, %	57	52	NR	42.3	NR	58.6
Previous lines of chemotherapy for LABC/MBC						
• Median	3	NR	3	NR	4	NR
• Range	1 to 7	0 to 6 ≤3: 70%	1 to 4	NR ≥5: 50.9%	1 to 9	NR ≥3: 86.6%
Patients who previously received capecitabine, %	93	85	80	80.8	85	72.8
Asthenia/fatigue, %						
• All Grade	65	55	8	44.2	60.9	53.7
• Grade ≥3	7	NR	NR	NR	NR	8.7
Neutropenia, %						
• All Grade	45	17	32	25	38.4	51.7
• Grade ≥3	32	NR	0	NR	20.9	45.1
Alopecia, %						
• All Grade	35	NR	NR	17.3	19.4	44.5
• Grade ≥3	NR	NR	NR	NR	NR	0
Peripheral Neuropathy, %						
• All Grade	28¥	33	20	NR	43.0	34.6
• Grade ≥3	2¥	NR	4	NR	3.9	8.2
Nausea, %						
• All Grade	NR	32	12	10.6	10.5	34.6
• Grade ≥3	NR	NR	NR	NR	NR	1.2

AEs=Adverse events; CDF=Cancer Drugs Fund; ITT=intention-to-treat; NR=Not reported
†Reports data comparing patients where re-challenged with an anthracycline or a taxane versus those who were not *Time to treatment progression ¥Neurotoxicity
Source: CS, adapted from Table 35 and p119; additional data extracted from original sources

4.10 Conclusions of the clinical effectiveness section

The company has reported evidence for the clinical effectiveness of two populations relevant to the review of TA250:

- All patients receiving ≥3 chemotherapy regimens for LABC/MBC (ITT population of the EMBRACE trial): patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease. Prior treatment includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable
- 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). Prior treatment also includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable.

Both populations are subgroups of the population for which eribulin is now licensed (as from 2014), namely: patients with LABC/MBC whose disease has progressed after at least one prior chemotherapeutic regimen for advanced disease. Prior treatment includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable. However, the ITT population addressed is the same as that for which eribulin was initially licensed (in 2011) and both populations are identical to the populations that were the focus of the TA250 FAD. The ERG considers this to be appropriate for a review of TA250.

Although the populations considered by the company are identical to those addressed during TA250, the comparator for Subgroup 2 patients is now TPC whereas, previously, the comparator on which the AC finally focussed was vinorelbine. The ERG agrees with the company's view that TPC is a pragmatic comparator for all patients receiving ≥3 chemotherapy regimens for LABC/MBC, including the Subgroup 2 population.

The primary clinical evidence source for this appraisal is the EMBRACE trial. This was a good-quality, multi-centre, phase III, open-label RCT that compared treatment with eribulin versus TPC. The trial population comprised 762 patients, most of whom had been heavily pre-treated (having received ≥3 previous regimens for LABC/MBC; ≥73% received previous treatment with capecitabine). Compared with TPC, this trial has demonstrated an improvement in median OS and median PFS for patients treated with eribulin in the ITT and Subgroup 2 populations. The ERG considers the primary and secondary outcome results to be robust. However, the company's OS hazard ratio for Subgroup 2 patients and the PFS hazard ratios for both the ITT and Subgroup 2 populations should be viewed with caution as the approach taken to calculate these values is only valid if the relevant K-M data are proportional to one another. Analyses carried out by the ERG suggest that the ITT

population PFS K-M data, the Subgroup 2 OS K-M data and the Subgroup 2 PFS K-M data are not proportional.

EMBRACE trial safety data and data from five supporting observational studies of heavily pre-treated patients (≥3 prior lines of chemotherapy for LABC/MBC; ≥80% received previous treatment with capecitabine) indicate that eribulin has an acceptable safety profile and is well tolerated (number of median cycles in the EMBRACE trial was reported to be between five and six and in the observational studies it was between four and six). There were no notable differences between the frequencies of AEs in the EMBRACE trial safety population and the frequencies in the Subgroup 2 population. The ERG considers that the EMBRACE trial and observational studies are likely to be generaliseable to NHS clinical practice.

HRQoL data are not available from the EMBRACE trial. The company has presented data from Study 301 for all patients and third-line patients. No patient received later lines of treatment and no patient had received previous treatment with capecitabine. Therefore, the generalisability of HRQoL data from Study 301 to the ITT population or Subgroup 2 patients may be questioned.

5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of prescribing eribulin for the treatment of LABC/MBC for patients whose disease has progressed following at least two prior chemotherapy regimens for advanced disease and includes capecitabine (if indicated), i.e. the group of patients labelled Subgroup 2 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. The company has also provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 Objective of cost effectiveness review

The company conducted a systematic review of published cost effectiveness studies relevant to the decision problem for Subgroup 2 patients 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 and 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 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.

5.1.2 Eligibility criteria used in study selection

The inclusion/exclusion criteria used by the company to facilitate study selection are reproduced in Table 20.

Table 20 Eligibility criteria used in company economics search strategy

Parameter	Inclusion	Exclusion
Population	Adult patients AND [MBC OR Advanced breast cancer (ABC)] AND 3rd line plus	Non-human OR Children OR Adolescents OR Males OR First- and second-line
Intervention	Eribulin (monotherapy)	All other treatments
Comparator	Any	
Outcomes	All	
Study design	Cost OR Budget OR Budget impact OR Expenditure OR Utilization OR Cost effectiveness OR Cost utility OR Cost benefit OR Cost Minimization OR Cost/Burden of illness studies OR Resource utilisation	Editorials OR Notes OR Comments OR Letters OR Reviews OR Abstracts without full paper available
Language	English	Non-English studies

MBC=metastatic breast cancer
Source: CS, Table 38

5.1.3 Included and excluded studies

The company did not identify any cost effectiveness studies conducted from a UK perspective that were relevant to the Subgroup 2 population. Five cost effectiveness studies[42-45] were initially identified, including two from the grey literature. However, none of these five studies was considered by the company to fall within the final scope issued by NICE. Four studies were conducted outside of the UK (Tremblay,[39] Lopes,[40] Jones[41] and Dranitsaris[42]) and the fifth was the ERG's summary of NICE TA250.[29] The ERG agrees that the summary of NICE TA250[29] could be justifiably excluded from the review since the focus of the paper was not the Subgroup 2 population/comparator. The authors of this paper[29] do however note that: "A supplementary evidence submission from the manufacturer was considered" (p147), and the ERG considers that this evidence[46] is relevant to the Subgroup 2 analysis. There is therefore an argument for including this supplementary evidence submission[46] (and ERG critique of this evidence[47]) even though the clinical data are derived from an earlier data-cut from the EMBRACE trial than are now available.

5.1.4 Findings from cost effectiveness review

None. The company's literature search did not identify any cost effectiveness studies to support the use of eribulin for the treatment of LABC/MBC for patients whose disease has progressed following at least two prior chemotherapy regimens for advanced disease and includes capecitabine (if indicated).

5.2 ERG critique of the company's literature review

The ERG is satisfied with the company's search strategy and is confident that there are no published cost effectiveness studies that fully meet the company's inclusion criteria. The databases searched and search terms used appear to be reasonable.

5.3 Summary of the company's submitted economic evaluation

The company has developed a de novo economic model to allow the comparison of the cost effectiveness of two treatment regimens for patients in Subgroup 2: eribulin and TPC (vinorelbine, gemcitabine, anthracyclines [doxorubicin] and taxanes [paclitaxel and docetaxel]). All patients in Subgroup 2 are assumed to have received prior treatment with capecitabine; therefore, TPC for Subgroup 2 patients excludes capecitabine.

5.3.1 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.

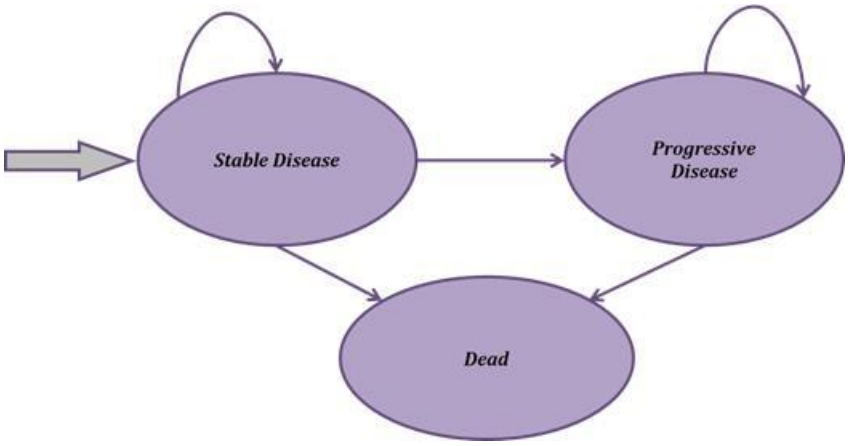

Figure 1 Company model structure

Source: CS, Figure 26

The PFS data represent the frontier between the health states of stable and progressive disease, whilst the OS data represent the frontier between the progressive disease and dead health states. Estimates of OS and PFS are based on K-M data from the EMBRACE trial. 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 vary depending on therapy) or until disease progression, whichever comes first.

5.3.2 Population

The population reflected in the company model is patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease and includes capecitabine (if indicated), i.e. Subgroup 2. All patients in the company model have previously received capecitabine.

5.3.3 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 TPC. The proportions of the different therapeutic options constituting TPC are taken from the ITT population in the EMBRACE trial, excluding capecitabine and any treatments that were used as initial treatment in less than 10% of the TPC arm. The proportions are therefore calculated on a subset of the TPC group. The treatment proportions for TPC are shown in Table 21 and these are used for both primary and subsequent lines of treatment.

The ERG received data on the actual initial treatments received by Subgroup 2 patients in the TPC arm during the clarification process. As these data were not sufficiently different to the proportions used in the base case analysis, no changes were made to the economic model.

The dosing of TPC depends on the chosen treatment. Investigators followed the instructions on the package insert, or local practice for drugs used off-label where the package instructions did not contain the relevant information.

Table 21 Proportions of Treatment of Physician's Choice

Drug name	Number of patients	Proportion	
		ITT population	Subgroup 2
Vinorelbine	61	24.00%	36.75%
Gemcitabine	46	18.10%	27.71%
Paclitaxel	26	10.20%	15.66%
Doxorubicin	23	9.10%	13.86%
Docetaxel	10	3.90%	6.02%
Total	166	65.30%	100.00%

ITT=intention-to-treat
Source: CS, Table 43 and The EMBRACE trial clinical study report, Table 10

In a scenario analysis, the company also considered a comparator arm in which patients, rather than being treated with TPC, were treated with either vinorelbine monotherapy (57%) or gemcitabine monotherapy (43%). In this scenario the relative treatment proportions were those observed in the ITT population of the EMBRACE trial.

Secondary treatments

Patients transitioning from the stable to progressive health states are assumed to receive secondary chemotherapy treatments in the proportions given in Table 21.

Treatment duration

In the base case, the maximum treatment duration in the model for patients in Subgroup 2 is set at 6 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 either eribulin or TPC is therefore linked to the duration of the primary treatment in the stable health state. An alternative scenario is also presented 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 45 of the CS.

Dose intensity

Dose reductions and delays due to AEs are included in the model using a dose intensity modifier. Dose intensity for patients treated with eribulin is 0.84, based on the mean dose intensity observed for patients treated with eribulin in the ITT population of the EMBRACE trial. For simplicity, dose intensity for patients treated with TPC is assumed to be the same as that for patients treated with eribulin.

Superseded by Erratum

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)[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 waste. A patient whose required eribulin dose is 1.86mg will receive their full dose from three 0.88mg packs and 0.78mg is wasted.

5.3.4 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 and lost productivity derived costs. 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.

5.3.5 Treatment effectiveness and extrapolation

The primary data source for the economic model is patient-level data from the EMBRACE trial. The data from this trial were very mature, with only 3% of the Subgroup 2 population in either arm still alive at the time of the 95% OS data cut for the ITT population (June 2013). Given the maturity of the available survival data, the company was able to use the K-M data directly to model OS and PFS for both eribulin and TPC in the base case using a 5-year time horizon.

For the 10- and 20-year time horizon scenario analyses, the company projected PFS and OS beyond the available K-M data 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.

Alternative comparator (vinorelbine/gemcitabine monotherapy) scenario

K-M survival data for this subgroup of the Subgroup 2 patients who participated in the TPC arm of the EMBRACE trial were identified. These data were used to represent transitions between health states in the 5-year base case. To model survival in this population for the 10 and 20 year scenarios, the 5-year K-M data were appended with either an exponential or Weibull distribution.

5.3.6 Health-related quality of life

HRQoL data were not collected as part of the EMBRACE trial and the company therefore conducted a literature search in order to identify HRQoL data relevant to the decision problem (details of which are provided in Appendix 2 to the CS and summarised in Appendices to this ERG report, Section 11.1). The model uses HRQoL data collected in Study 301 identified by this search. This phase III study was designed to compare the effectiveness of treatment with eribulin versus capecitabine in patients with LABC/MBC previously treated with an anthracycline and a taxane. HRQoL was assessed in Study 301 using the EORTC QLQ-C30 and mapped to EQ-5D derived utility scores using a published regression algorithm.[48] The EQ-5D utilities were constructed using the original UK tariff.[49]

The mapped utility values from patients on eribulin in Study 301 are used to represent the equivalent health states in this analysis. The aggregated utility value for the whole Study 301 population is used as the 'progressive' health state for both eribulin and TPC. The 'baseline' and 'tumour response' values for eribulin and TPC groups are considered separately and are adjusted in order to take into account differing rates of tumour response and AEs (see Table 22).

Table 22 Health state utility values

Health state	Eribulin	TPC*
Baseline	0.704	0.704
Tumour response	0.708	0.708
Incremental utility of response	0.076	0.076
Tumour response rate	12.2%	4.7%
Disutility of AEs	-0.0071	-0.0066
Stable disease	0.706	0.701
Progressive disease	0.679	0.679

AEs=adverse events; TPC=Treatment of Physician's Choice;
*TPC assumed equal to eribulin for baseline and tumour response utility values
Source: CS, Table 57

A linear mixed-effects model was used to predict the impact of specific AEs on utility scores from the EORTC QLQ-C30 data from Study 301 (see Table 23). Only common AEs (all grades with a prevalence ≥10%) or serious (≥3 with a prevalence ≥2%) are included within the model.

This disutility value 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 TPC (see Table 22).

The linear mixed-effects model estimated an improvement in utility for alopecia; alopecia has a disutility of zero in the model. Alopecia and peripheral neuropathy are not part of the EORTC QLQ-C30 questionnaire and therefore these utility values should be interpreted with caution.

Table 23 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 51

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. The original data sources are difficult to determine within the model.

Superseded by Erratum

5.3.7 Resources and costs

Drug costs

The price of eribulin used in the model is the approved PAS price. The costs for the TPC arm are based on the proportions of each of the individual TPC treatment options used during the EMBRACE trial (Table 21). These proportions are replaced by a 50:50 weighting of the costs of vinorelbine and gemcitabine monotherapies in a scenario analysis.

Table 24 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[50]
		10 capsules x 30mg	£659.80	
		10 capsules x 80mg	£1,759.20	
Vinorelbine (IV)	Solution vial	10mg	£5.04	eMIT[51]
		50mg	£18.24	
Capecitabine	Tablets	60 tablets x 150mg	£7.73	eMIT[51]
		120 tablets x 500mg	£29.59	
Gemcitabine	Powder vial	200mg	£3.99	eMIT[51]
		1000mg	£30.89	
		2000mg	£21.39	
Docetaxel	Solution vial	20mg	£4.92	eMIT[51]
		80mg	£12.47	
		160mg	£34.83	
Paclitaxel	Solution vial	30mg	£3.41	eMIT[51]
		100mg	£8.50	
		150mg	£11.50	
		300mg	£21.48	
Doxorubicin	Solution vial	10mg	£1.53	eMIT[51]
		50mg	£4.04	
		200mg	£20.30	

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

The subsequent treatment costs following disease progression are the same as the TPC initial treatment costs for both arms of the trial.

Administration costs

Administration costs for eribulin and each of the TPC treatment options are shown in Table 25. 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 25 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[52]
Eribulin, gemcitabine, docetaxel & doxorubicin	Deliver simple parenteral chemotherapy at first attendance	SB12Z	£239.12	NHS Reference Costs 2014/15[52]
Paclitaxel	Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance	SB14Z	£389.41	NHS Reference Costs 2014/15[52]

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 26. Supportive palliative care costs are assumed to be necessary in the final 6 months of life. End of life costs are attributable to the 2-week period prior to death and the total cost is weighted according to the proportion of people likely to spend this time in each place of care.

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

Table 26 Direct medical costs

Type of cost	Health state	Cost	Usage	Source
Stable and progressive disease costs				
Medical oncologist – follow-up	Stable & progressive disease	£158.54		NHS Reference Costs 2014/15[52]
GP contact		£44.00		PSSRU 2015[53]
CT scan		£92.03	33% usage assumed	NHS Reference Costs 2014/15[52]
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[52]
GP home visit		£44.00		PSSRU 2015[53]
Clinical nurse specialist		£88.00		
Community nurse home visit		£58.00		
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,[53] The hospital & community health services (HCHS) index for 2014, Table 16.3 (Pay + prices); [a] Actual source not stated in CS

Adverse event costs

The costs of AEs are detailed in Table 27.

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 is included in the CS.

Table 27 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	127.7	XD25Z	Neutropenia drugs band 1
Febrile neutropenia†	6060	PA45Z (2012-2013)	Febrile neutropenia with malignancy
Alopecia (all-Grade)	0		Assumption - no cost
Leukopenia	127.7	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	N/A	1hr 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	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 to5 (non-elective inpatient short stay)

CC=with complications; HRG=Healthcare Resource Group
†Inflated to 2014-2015 using PSSRU 2015,[53] The hospital & community health services (HCHS) index for 2014, table 16.3 (Pay + prices)
Source: CS, Table 66

5.3.8 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 TPC are shown in Table 28. In the base case, eribulin generates more benefits than TPC [redacted] LYG and +[redacted] QALYs) at an increased cost of [redacted]. The company base case incremental cost effectiveness ratio (ICER) for eribulin versus TPC is £35,624 per QALY gained.

Table 28 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]	£35,624
TPC	[redacted]	[redacted]	[redacted]				

TPC=Treatment of Physicians' Choice; LYG=life years gained; QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio
Source: CS, Table 72

A summary of the predicted drug, drug administration and direct medical costs is presented in Table 29. Just over 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 TPC).

Table 29 Summary of predicted resource use by category of cost

Item	Therapy		Increment	Absolute increment (£)	Absolute increment (%)
	Eribulin	TPC			
Drug and administration costs					
Primary therapy	[redacted]	[redacted]	[redacted]	[redacted]	76.79%
Secondary therapy (TPC)	[redacted]	[redacted]	[redacted]	[redacted]	0.04%
Administration	[redacted]	[redacted]	[redacted]	[redacted]	9.75%
[redacted]					
Medical	[redacted]	[redacted]	[redacted]	[redacted]	10.44%
Palliative care	[redacted]	[redacted]	[redacted]	[redacted]	1.37%
End of life	[redacted]	[redacted]	[redacted]	[redacted]	2.31%
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	3.91%
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	**100.00%**

TPC=Treatment of Physicians' Choice
Source: CS, Table 78

5.3.9 Sensitivity analyses

Deterministic sensitivity analyses

Cost effectiveness results from nine different scenarios are presented in the CS and summarised in Table 30. These results are also displayed in a Tornado diagram (see Figure 2). The resultant ICERs range from £31,226 to £46,912 per QALY gained, i.e. ranging from £4,398 less than the base case to £11,288 greater than the base case.

Table 30 Results of deterministic sensitivity analysis

Scenario	Parameter	ICER per QALY gained	
		Lower value	Upper value
Base case			£35,624
1	Benefits discount rate (0% and 6%)	£33,326	£37,225
2	Costs discount rate (0% and 6%)	£35,037	£36,518
3	Costs and benefits discount rate (0% and 6%)	£34,162	£36,641
4	Eribulin price (±20%)	£31,226	£40,022
5	Comparator price (±20%)	£35,401	£35,848
6	Administration costs (±20%)	£34,930	£36,319
7	Direct healthcare costs (±20%)	£34,947	£36,302
8	Prevalence of AEs (±20%)	£35,346	£35,903
9	HRG costs of AEs (±20%)	£34,447	£46,912

AE=Adverse event; HRG=Healthcare Resource Group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: CS p191 and Table 82

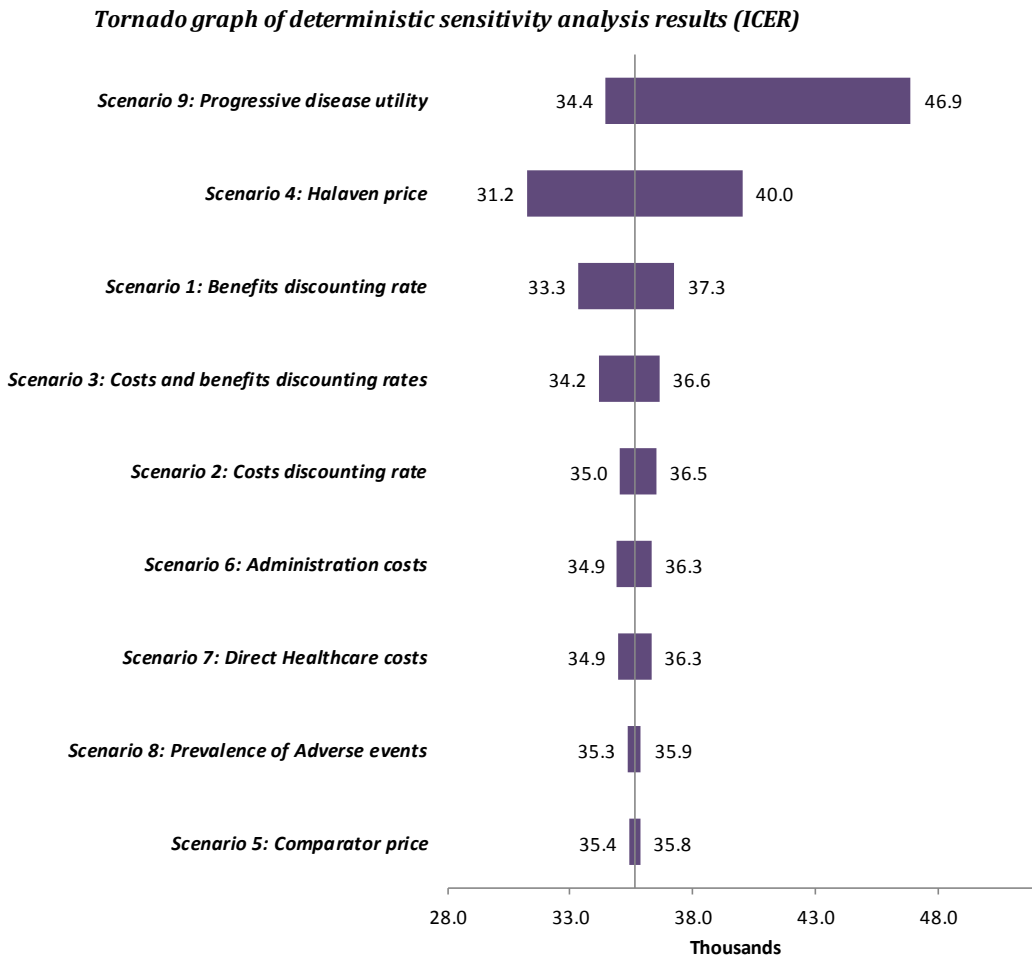

Figure 2 Deterministic sensitivity analysis results displayed in a tornado diagram

Source: CS, Figure 48

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 Subgroup 2 patients are displayed in the CS and reproduced in Figure 3 and Figure 4 respectively. Results from the company's PSA show that, for Subgroup 2 patients, for the comparison of eribulin versus TPC, the ICERs per QALY gained range from between £20,000 to £60,000. Results also show that, for this treatment comparison, there is a 30% probability of treatment with eribulin being cost effective at a threshold of £30,000 per QALY gained and a 72% probability of eribulin being cost effective at a threshold of £50,000 per QALY gained.

Figure 3 Cost effectiveness plane

Source: Company model

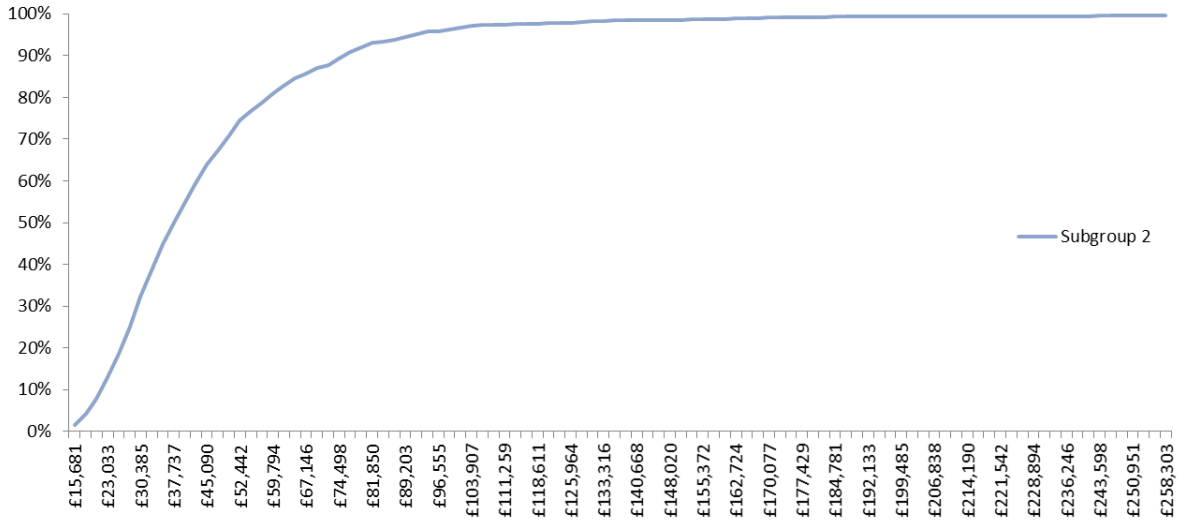

Figure 4 Cost effectiveness acceptability curve

Source: Company model

5.3.10 Scenario analyses

The company carried out six scenario analyses. Results from these analyses are presented in Table 31. The biggest effect on the company's base case cost effective result occurred when the cost of wastage was excluded from the company's base case calculations. This lowered the ICER per QALY gained for the comparison of eribulin versus TPC to £16,053 per QALY gained (a 54% reduction in the base case result).

Table 31 Scenario analysis results

Scenario	Incremental			ICER per QALY gained
	LYG	QALY	Cost	
Base case	[redacted]	[redacted]	[redacted]	£35,624
Maximum treatment duration threshold of 12 months	[redacted]	[redacted]	[redacted]	£39,164
Excluding wastage	[redacted]	[redacted]	[redacted]	£16,053
Vinorelbine and gemcitabine as comparator	[redacted]	[redacted]	[redacted]	£23,931
Prevalence of AEs Grade ≥3	[redacted]	[redacted]	[redacted]	£35,964
Time horizon 10 years	[redacted]	[redacted]	[redacted]	£32,362
Time horizon 20 years	[redacted]	[redacted]	[redacted]	£32,282

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

5.3.11 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[42] decision making criteria (which are based on the NICE Decision Support Unit document on survival extrapolations[54]) to select approaches to extrapolate the available trial survival data
- Costs were primarily based on the NICE Advanced Breast Cancer guidelines[8] and the most recent NHS Reference Costs (2014 to2015)[52]
- 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.

5.4 Model checklists

5.4.1 NICE reference case checklist

Table 32 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 the Institute	Yes
Comparator(s)	Alternative therapies routinely used in the NHS	Treatment of physician's choice (a range of different alternative treatments)
Perspective costs	NHS and Personal Social Services	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	The company uses data from the EMBRACE trial, 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 another trial was converted by a generic mapping algorithm to approximate EQ-5D values
Benefit valuation	Time-trade off or standard gamble	Mapped onto time-trade off scale
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Indirectly
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	PSA lacks the facility to include correlated parameter values

EQ-5D=EuroQol-5 dimension; QALY=quality adjusted life year; PSA=probabilistic sensitivity analysis

5.4.2 Drummond checklist

Table 33 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	The range of currently used alternative therapies is included in the TPC combined comparator
Was the effectiveness of the programme or services established?	Yes	Clear evidence of survival gain in the defined population was established
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 5.6)
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; TPC=Treatment of Physicians' Choice

5.5 Critique of cost effectiveness analyses

5.5.1 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 the treatments included in the model are prescribed on either a weekly or 3-weekly basis. For accuracy, it would have been preferable to employ weekly cycles, but 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 can accumulate over a lifetime horizon.

5.5.2 Patient survival and disease progression

The ERG submitted a clarification request for detailed K-M analysis results for OS, PFS and post-progression survival (PPS) from the EMBRACE trial and the company provided these data. The ERG also requested similar information for time to treatment discontinuation to allow the ERG to employ an alternative approach to estimating treatment costs. Unfortunately, this request was misinterpreted and the ERG could not use the results provided by the company.

Overall survival

The OS K-M data from the EMBRACE trial (Figure 5) indicate that, for patients in both the eribulin and TPC arms, the trial data are nearly complete (only two patients randomised to receive eribulin and one patient randomised to receive TPC were still alive at the time of data cut-off). Re-running the K-M OS analysis indicates that, without any projection of estimated survival in either arm to compensate for the missing follow-up data, the accurate value for the mean OS gain attributable to treatment with eribulin compared to TPC is 3.39 months (95% CI 0.83 to 5.96 months).

The company calibrated exponential projective functions to OS data from each trial arm and applied the results to both arms from month 60 onwards. The ERG has adopted a different approach, 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 – month 35 in the eribulin arm and month 27 in the TPC arm. The ERG then

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applied the calibrated trend lines from the time closest to the final recorded trial death (month 64 for eribulin and month 56 for TPC).

An examination of Figure 5 highlights that, compared with the company's projection, the ERG's method of projection leads to a greater long-term OS advantage for patients treated with eribulin compared with TPC. As a result, implementing the ERG method in the model results in a small reduction of £199 per QALY gained in the size of the estimated ICER.

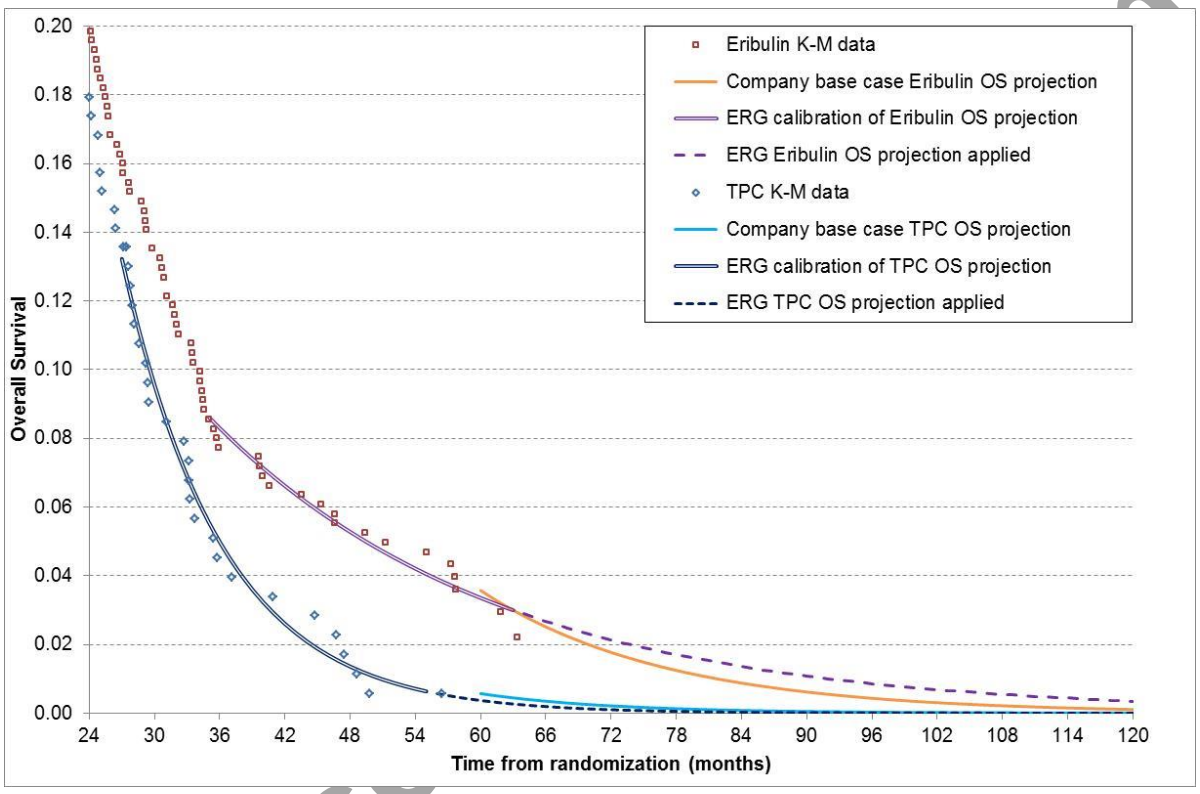

Figure 5 Overall survival Kaplan-Meier data from the EMBRACE trial and two approaches to survival projection

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Progression-free survival

The company has fitted Weibull parametric curves to both sets of trial data, extending non-zero PFS values well beyond the maximum time at which patients were observed to remain progression-free (23 and 25 months), and replaced all of the K-M trial PFS data with the modelled alternative estimates.

Examination of the PFS K-M data from the EMBRACE trial (Figure 6) indicates that the trial data are complete for patients in both arms of the trial. There is, therefore, no need to carry out any projective modelling of PFS and so the ERG has used the K-M data directly. Re-running the K-M PFS analysis indicates that the accurate value for the mean PFS gain attributable to eribulin compared to TPC is 40.4 days (95% CI 13.0 to 67.8 days). However, the company base case results suggest a difference of just 8.2 days. When the ERG replaces the company Weibull curves with the original trial PFS data, the model estimated PFS gain increases to 40.2 days (95% CI 13.0 to 67.8 days).

The main effect of this ERG modification to the company model is to change the balance of treatment costs, so that the incremental cost rises, leading to an increase in the ICER per QALY gained of £1,557.

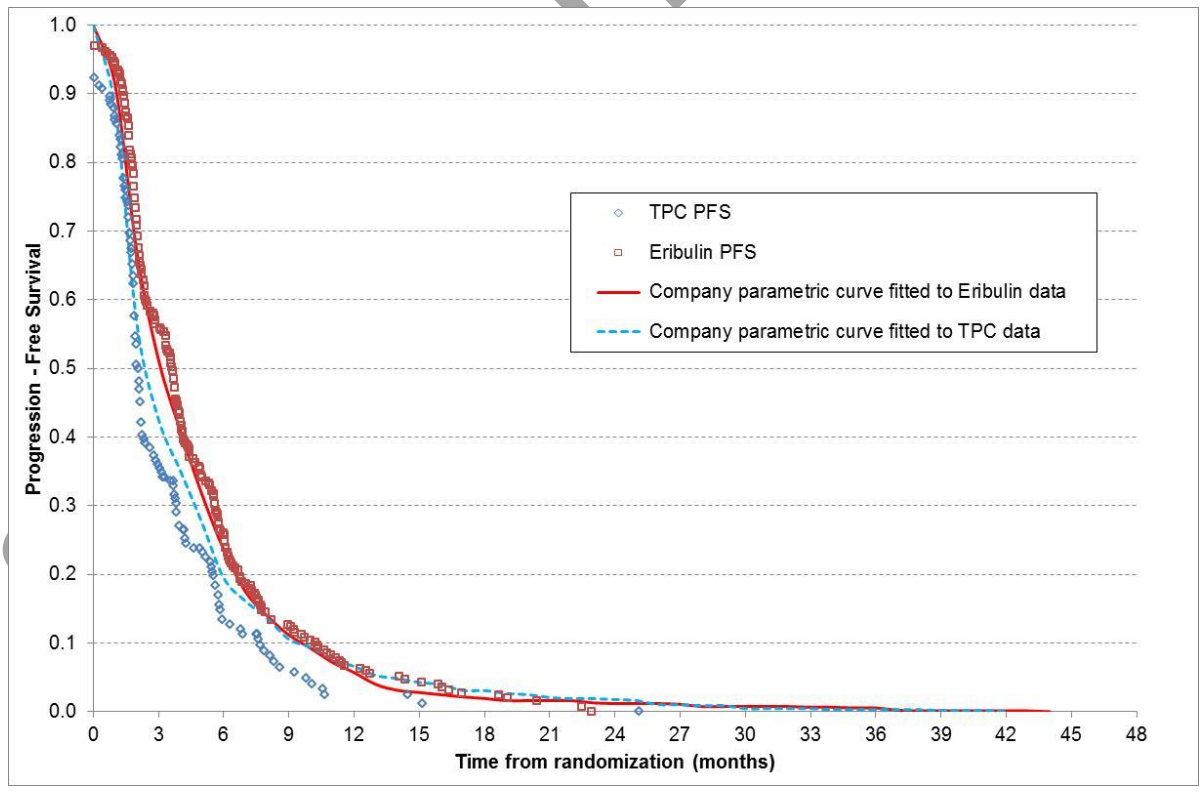

Figure 6 Progression-free survival Kaplan-Meier data from the EMBRACE trial and company Weibull parametric curves

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Post-progression survival

Examination of the PPS K-M data from the EMBRACE trial, which was provided by the company in response to a clarification request, has led the ERG to have serious doubts as to the reliability of the provided data. Post-progression survival analysis includes only those patients whose 'progression event' was a non-fatal progression i.e. excluding any patients who died prior to the time of disease progression. Since the full complement of randomised patients has been included in each trial arm, it is clear that these analyses include patients who died without disease progression. As a result, it is not possible to estimate directly the extent of any survival benefit (or disbenefit) arising after disease progression.

However, the estimates described above for OS and PFS give strong support to a substantial gain in mean survival being experienced by some patients even after recorded disease progression and the cessation of eribulin treatment. This is an important finding, since evidence for many other cancer treatments shows that after progression previous treatments quickly cease to have any bearing on future survival prognosis.

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5.5.3 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 TPC. When this error is corrected, the base case ICER is reduced from £35,624 to £31,276 per QALY gained.

5.5.4 Acquisition cost of chemotherapy

The company has estimated the cost of chemotherapy drugs dosed in terms of BSA using UK BSA estimates from survey data.[55] However, the company modellers have confused standard error and standard deviation when calculating the costs of chemotherapy dosed according to BSA. In addition, no account has been taken of the therapeutic intent of the treatments included in the survey data.[55] This information is included in the full data set, available as a download from the journal web-site.[56] 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 the EMBRACE trial. This yields a slightly higher mean BSA (1.7448) and a standard deviation of 0.1785 (standard error 0.00924). All relevant chemotherapy treatment costs have been re-estimated by the ERG and compared with those used in the company model (Table 34).

The unit cost per dose of chemotherapy has been substantially underestimated for eribulin, oral vinorelbine (after the first cycle) and capecitabine, with smaller differences for all other agents.

Table 34 Unit costs of chemotherapy treatments, comparing ERG estimates to company model parameter values (after the company logic error has been corrected)

Treatment	Unit	Company model	ERG estimate	Difference (ERG vs company model)
Eribulin	Per dose	[redacted]	[redacted]	+£176.65 (+44.2%)
Vinorelbine oral (cycle 1)	Per dose	£242.02	£241.20	-£0.82 (-0.3%)
Vinorelbine oral (cycle 2+)	Per dose	£242.02	£315.84	+£73.82 (+30.5%)
Vinorelbine (IV)	Per dose	£18.24	£18.83	+£0.59 (+3.2%)
Gemcitabine	Per dose	£29.14	£26.20	-£2.96 (-10.1%)
Docetaxel	Per dose	£34.83	£27.90	-£6.93 (-19.9%)
Paclitaxel	Per dose	£21.47	£26.44	+£4.97 (+23.1%)
Doxorubicin	Per dose	£9.62	£11.48	+£1.86 (+19.3%)
Capecitabine	Per cycle	£24.17	£37.01	+£12.84 (+53.1%)

ERG=Evidence Review Group; IV=intravenous

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5.5.5 Dose intensity

The company model features a parameter to represent dose intensity as measured in the EMBRACE trial. However, this does not have any effect on the estimated cost of treatments, nor on the company base case ICER per QALY gained. The cost of treatment is only affected when the company's alternative mode of calculating drug costs (without wastage) is employed.

5.5.6 Dose capping

Within the company model, the number of patients continuing on therapy is estimated using the company's PFS estimate. However, a close examination of the company logic indicates that the long-term PFS data included in the model are set to zero for all time periods after 43 months for the eribulin arm and after 41 months for the comparator arm. This arbitrary measure results in a small bias leading to a slightly higher estimated ICER per QALY gained. Applying the ERG's preferred PFS K-M data removes this bias.

5.5.7 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. However, a PSA ICER per QALY gained calculated by the ERG from the random iteration data is very similar to the deterministic ICER per QALY gained.

5.5.8 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 cost. Correcting this error has the effect of reducing the company base case deterministic ICER per QALY gained by approximately £154.

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5.5.9 Health-related utility values

The company has applied a mapping algorithm, published by Crott and Briggs in 2010,[48] to estimate EQ-5D values from the QLQ-C30 quality of life questionnaire administered to patients in Study 301. The algorithm was based on data made available from an historical clinical trial, which recruited patients from 1999 and compared two chemotherapy regimens. The published trial results[57] 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 the EMBRACE trial and the trial upon which Crott and Briggs[48] based their utility mapping exercise must raise serious questions about the appropriateness of applying this reported algorithm to generate utility values for patients receiving third-line chemotherapy after two prior episodes of disease progression.

The alternative, previously considered by the ERG during TA250, is a utility value set published by Lloyd[30] 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[30] analysis. It is particularly remarkable that the value used in the model for patients with stable disease (but not responding to treatment) is very similar to the value for progressed disease (0.69 versus 0.68), which the ERG considers implausible.

The ERG has tested the effect of substituting the Lloyd[30] progressive disease utility value in place of the company's preferred estimate, and can confirm a resulting increase in the size of the estimated ICER of more than £11,000 per QALY gained.

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5.5.10 Subsequent lines of chemotherapy

The company model offers two options for the estimation of the cost of further lines of chemotherapy beyond eribulin or TPC as third-line therapy:

- Limiting the number of cycles of therapy overall (in the base case to no more than six cycles).
- "Treat to progression", which means that nobody who progresses alive whilst on eribulin or TPC incurs the costs associated with any subsequent chemotherapy (4th, 5th, 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 respond better to third-line treatment will, on average, continue third-line therapy for longer 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 which has been shown to lead to additional mean PPS time and therefore 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 six to 600.
2) The company references a study by Kantar Health[58] 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 £1,600 and an increase in the size of the deterministic ICER of about £9,800 per QALY gained.

5.5.11 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 TPC increases by £670, and the company's base case ICER increases by more than £4,000 per QALY gained.

6 IMPACT ON THE ICER OF ADDITIONAL ERG ANALYSES

To address the points raised in Section 5, the ERG has made the following nine changes to the submitted company model:

- use of ERG preferred PFS estimates (R1)
- use of ERG preferred OS estimates (R2)
- use of annual rather than continuous discounting (R3)
- correction of logic error in costing oral vinorelbine (R4)
- use of ERG revised unit cost of eribulin (R5)
- use of ERG revised unit costs of comparator 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)

The three most influential ERG changes are the choice of utility value for the progressive disease health state (R7), the revised estimate of the cost of eribulin treatment (R5), and the method used to cost subsequent lines of treatment (R8).

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Table 35 Cost effectiveness (eribulin versus TPC): ERG revisions to company base case

Model scenario ERG revision	Eribulin			TPC			Incremental			ICER	ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	Per QALY gained	Change
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£35,624***	**-**
R1) ERG use of K-M PFS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£37,182**	**+£1,557**
R2) ERG use of K-M OS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£35,425**	**-£199**
R3) Annual discounting applied	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£35,471**	**-£154**
R4) Correct logic error on oral vinorelbine costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,276**	**-£4,349**
R5) ERG estimated eribulin unit costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£48,199**	**+£12,575**
R6) ERG estimated comparator unit costs (combined with R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,106**	**-£5,518**
R7) ERG preferred progression utility value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£46,912**	**+£11,288**
R8) ERG alternative method of costing subsequent lines of therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,435**	**+£9,811**
R9) Correct logic error on eribulin administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£39,737**	**+£4,113**
B. ERG revised base case A+R1 to R9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£66,043***	***+£30,418***

Costs and QALYs discounted; life years undiscounted
ERG=Evidence Review Group; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; K-M=Kaplan-Meier; ICER=incremental cost effectiveness ratio

Superseded by Erratum

7 END OF LIFE

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

The K-M analysis of the EMBRACE trial individual patient data allows both these criteria to be considered. The ERG's view is that:

- the mean OS of patients receiving TPC is 13.53 months (95% CI 11.87 to 15.19 months), indicating that survival is much lower than 2 years

- the mean OS gain attributable to treatment with eribulin is at least 3.39 months (95% CI 0.83 to 5.96 months).

8 KEY POINTS FOR DECISION MAKERS

8.1 Clinical effectiveness evidence

Patient population

- The EMA (2014) 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.
- The current STA focuses on patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease, i.e. only a subset of the licensed population.
- Clinical effectiveness evidence from the EMBRACE trial is presented for two populations:
    - All patients receiving ≥3 chemotherapy regimens for LABC/MBC (ITT population): patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease. Prior treatment includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable
    - Subgroup 2: patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease and includes capecitabine (if indicated). Prior treatment also includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable.

Comparators

- The comparators listed in the final scope issued by NICE are vinorelbine, capecitabine and gemcitabine. The company presents evidence for eribulin versus TPC for both the ITT and the Subgroup 2 populations. The ERG considers the use of TPC to be pragmatic and to reflect the likely patient experience in England.
- For the ITT population, options for TPC included vinorelbine, capecitabine and gemcitabine, as well as additional agents which included, but were not limited to, (re-challenge with) anthracyclines and taxanes
- For the Subgroup 2 population, TPC options were the same as the TPC options for the ITT population with the exception that they largely excluded treatment with capecitabine (since all patients in Subgroup 2 had been previously treated with capecitabine).The Subgroup 2 population, therefore, includes some patients who are even more heavily pre-treated than the ITT population. Indeed, approximately 65% of the Subgroup 2 population had received ≥3 prior regimens in the LABC/MBC setting compared with approximately 57% of the ITT population.

Clinical trial evidence

- The majority of evidence is derived from the EMBRACE trial, which is a good quality multi-centre, phase III, open-label, randomised parallel two-arm trial. The majority of patients (73%) had received prior capecitabine and the median number of cycles of eribulin was reported to be between five and six (similar to that reported in audits of eribulin use via the CDF). The findings from the EMBRACE trial show eribulin to be superior to TPC in terms of median OS and median PFS for the ITT population and for patients in Subgroup 2. AE data demonstrate an acceptable safety profile for treatment with eribulin versus TPC.

'Real world' evidence

- The 'real world' evidence provides additional support for the safety of eribulin (median four to six cycles) in relatively heavily pre-treated patients (≥3 previous lines of chemotherapy for LABC/MBC; ≥80% received previous treatment with capecitabine).

Health-related quality of life

- HRQoL data collected via the EORTC QLQ-C30 questionnaire are provided for all patients and third-line patients from Study 301. No patient received later lines of treatment and no patient had received previous treatment with capecitabine. Therefore, the generalisability of HRQoL data from Study 301 to the ITT population or Subgroup 2 patients may be questioned.

8.2 Cost effectiveness evidence

Population

- Cost effectiveness evidence is only presented for the Subgroup 2 population for the comparison of treatment with eribulin versus TPC.

Model related issues identified by the ERG

- **Survival**: there is a continuing advantage for patients treated with eribulin, even after confirmation of disease progression
- **Costs**:
    - a BSA specific to patients with breast cancer with treatment that is not intended to be neo-adjuvant, adjuvant or palliative, rather than one relating to all women with breast cancer, should have been employed to estimate drug costs. Use of the BSA standard error instead of the standard deviation in the calculations provides underestimates of the cost of treatment
    - the cost of treatment with oral vinorelbine, and thus the cost of the comparator (TPC), is an underestimate
    - the estimation of the cost of further lines of chemotherapy beyond eribulin or TPC as third-line therapy is an underestimate of the true costs to the NHS
    - there is an error in the method used to cap doses
    - variation in dose intensity is not implemented in the company base case and, therefore, has no impact on the company's base case results.
- **HRQoL**: the utility value employed by the company to represent HRQOL in the progressed health state is implausible.
- **Discounting**: continuous, rather than annual, discounting of costs and benefits has been employed by the company.
- **PSA**: the company has not adequately explored the impact of parameter uncertainty.
- **Other issues**: (which have no substantial impact on cost effectiveness results) relate to the use of two different estimates of days in the year (one taking into account leap years), and structuring the model on monthly cycles for treatments that are prescribed weekly or on a 3-weekly basis.

Cost effectiveness results

- The company's base case ICER, for the Subgroup 2 population, for the comparison of the cost effectiveness of treatment with eribulin versus TPC is £35,625 per QALY gained
- Following the implementation of all the ERG's amendments the company's base case ICER increases by £30,418 to £66,043 per QALY gained.

End of life

- The treatment is indicated for patients with a life expectancy of less than 24 months and although the OS gain, experienced by patients in the EMBRACE trial who received eribulin, does not achieve statistical significance, due to the limited number of patients in the trial, the ERG is reasonable confident that eribulin offers an extension to life of at least an additional 3 months compared to current NHS treatment for Subgroup 2 patients.

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9 OVERALL CONCLUSIONS

9.1 Efficacy data

Mature efficacy data from the EMBRACE trial (a good quality multi-centre, phase III, open-label, randomised parallel two-arm trial of 762 patients) show that treatment with eribulin is superior to TPC for the ITT and Subgroup 2 populations. In particular, it appears that treatment with eribulin extends OS for patients who have been heavily pre-treated.

9.2 Safety data

Data from the EMBRACE trial and observational studies also suggest eribulin has an acceptable safety profile in heavily pre-treated patients.

9.3 NHS clinical practice

The median number of cycles with eribulin was reported to be between five and six in the EMBRACE trial (similar to that reported in audits of eribulin use via the CDF). The EMBRACE trial results appear to be generalisable to NHS clinical practice.

9.4 Cost effectiveness

In terms of cost effectiveness, the ERG considers that the company substantially underestimates the size of the most probable base case ICER per QALY gained for eribulin versus TPC in the Subgroup 2 population. The company's base case ICER is £35,624 per QALY gained, which is £30,418 less than the ICER estimated by the ERG (£66,043 per QALY gained).

9.5 Implications for research

All of the apparent survival gain for patients in the EMBRACE trial appears to occur during the post-progression survival period. Further research into whether this is common in other clinical studies and, if so, exploration as to why, may improve current understanding of LABC/MBC.

HRQoL evidence is lacking for the population of patients receiving eribulin as a >3 chemotherapy regimen for LABC/MBC. Further research into HRQoL in more heavily pre-treated patients is warranted.

Superseded by Erratum

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11 APPENDICES

11.1 Literature search for health-related quality of life studies

Full details of the search terms used by the company to locate HRQoL evidence are reported in the CS (Section 5.4 and Appendix 2). The company states that they searched the following two databases: Medline (via PubMed) and Embase (via Scopus). The date of the searches (23 December 2015) and the full date span (1 January 2009 to 30 November 2015) are appropriately reported by the company (CS, Appendix 2).

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). One clinical trial registry (clinicaltrials.gov) was also searched (12 February 2016).

The ERG considers that the search terms used by the company were relevant for the databases searched. The use of free text only was appropriate as the databases that were searched did not have a Medical Subject Headings search function. However, the ERG notes that Scopus does not include all references that are included in Embase. Nonetheless, in general, the ERG is confident that the company's literature search for HRQoL evidence will have identified all relevant HRQoL studies.

The CS provides a detailed report of the inclusion/exclusion criteria applied to the selection of potentially relevant studies. These are described in Table 36. Two reviewers independently undertook study selection in two stages:

- Stage 1 – review of abstracts
- Stage 2 – review of full text papers.

After applying the eligibility criteria to the full texts, all papers meeting the inclusion criteria were retained for data extraction. The methods used for data extraction are not specified in the CS.

Table 36 Inclusion and exclusion criteria for HRQoL evidence for patients receiving ≥3 chemotherapy regimens for LABC/MBC

Parameter	Inclusion	Exclusion
Population	Adult patients AND [MBC OR Advanced breast cancer (ABC)] AND AND 3L+	Non-human OR Children OR Adolescents OR Males OR Studies with a unique focus on patients from outside Europe/USA were excluded
Intervention	Eribulin (monotherapy)	All other treatments or combinations
Comparator	Any	
Outcomes	Utilities/ disutilities/ QALYs for health states of adverse events OR Quality of life assessment including EQ-5D, QLQ-C30, BR-23, FACT, SF-36, SF-6D	All others
Study design	Reports of mapping exercises for any outcome measure to utility OR Reports of utility elicitation exercises OR Reports for utility validation exercises OR Reports of economic evaluations using utility measures elicited during the studies OR Reports of clinical trials assessing HRQOL	Editorials OR Notes OR Comments OR RWE OR Letters OR Other Reviews OR Abstracts without full paper available OR Phase I studies
Language	English	Non-English studies

ABC=advanced breast cancer; MBC=metastatic breast cancer; QALY=quality adjusted life year
Source: CS, Table 53

11.2 Statistical analyses conducted in the EMBRACE trial

The patient populations used for the analysis of the EMBRACE trial outcomes are summarised in Table 37.

Table 37 Patient populations used for the analysis of the EMBRACE trial outcomes

Population	Description
Intention-to-treat (ITT) population	All patients who were randomised, irrespective of whether or not they actually received study treatment or whether they received the medication they were randomised to
Per protocol (PP) population	All patients in the ITT population who met the major inclusion criteria for the study, and who did not have any other major protocol violation. Major violations included patients who were treated on the opposite treatment group than the one to which they were randomised
Response evaluable population	All patients with measurable disease, defined as the presence of at least one measurable lesion, using RECIST criteria. This was identified by independent review
Safety population	All patients who were randomised and who received at least a partial dose of study treatment. The population was based on the actual treatment received

A summary of the statistical analyses performed for the EMBRACE trial efficacy outcomes are provided in Table 38. The primary analysis was planned to occur when 411 deaths had been recorded, although the data cut-off point for the primary analysis was actually after 422 (55%) patients had died (12 May 2009). The company outlines that an updated analysis of OS was conducted at the request of the regulatory authorities, when 77% of deaths had occurred, representing a more mature dataset with longer follow up (3 March 2010 data cut-off point). The most recent OS analysis was performed after 95% of patients had died (17 June 2013), and the company presented data for Subgroup 2 patients using this most recent data cut-off, although the ERG requested that analyses on the ITT population also be performed using this data cut-off point for comparability between Subgroup 2 and the ITT population. The company obliged and results for both the ITT population and Subgroup 2 populations using the most recent data cut-off point are provided in Section 4.8 of this ERG report.

Table 38 Summary of statistical analyses for efficacy outcomes in the EMBRACE trial

	Statistical analysis	Data management, patient withdrawals
Primary outcome (OS)	• Compared between the randomised treatment groups in the ITT population using a two-sided stratified log-rank test at a significance level of 0.049 • Test was stratified by HER2 status, prior capecitabine treatment, and geographical region • Kaplan-Meier survival curves were used to summarise the OS, using 95% limits at selected time points • Kaplan-Meier estimate of the median survival time, and first and third quartiles was presented with 95% CIs • HR was presented based on fitting a Cox regression model and was stratified according to the type of treatment received, HER2 status, prior capecitabine treatment and geographical region • An additional Cox regression model was fitted in which the HR was also adjusted for the number of prior chemotherapy regimens and ER status (covariates)	• Primary analysis of the primary outcome (OS) was compared between the eribulin and TPC groups in the ITT population • These analyses were also performed on the PP population • For patients for whom a date of death was not recorded, i.e., those who were lost to follow-up or who were alive at the date of data cut-off, time to death was censored at the time of last contact
Secondary outcomes	• 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 • Kaplan-Meier plots and the Kaplan-Meier estimates of the medians, and first and third quartiles were presented with the 95% CI for PFS and duration of response • PFS was compared between the treatment groups using a two-sided stratified log-rank test at the 5% significance level • ORR was analysed using exact Pearson Clopper 2-sided 95% confidence limits for the tumour response rates in each treatment group, and was statistically compared between the two treatment groups using a Fisher's Exact Test	• PFS was assessed in both the ITT and PP populations • The response evaluable population was considered the primary population for the analysis of ORR • For the analysis of PFS, patients who had not progressed on the data cut-off date or who were lost to follow-up, were censored at that date

CI=confidence interval; DoR=duration of response; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; ITT=intent-to-treat; K-M=Kaplan-Meier; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PP=per protocol; TPC=Treatment of Physician's Choice
Source: Adapted from Table 13 of the CS

11.3 Baseline characteristics in the EMBRACE trial

During the clarification process, the ERG requested the company present the same baseline characteristics for Subgroup 2 patients as the ITT population, and vice versa. These are summarised below in Table 39. As highlighted in Section 4.6 of this ERG report, the baseline characteristics were distributed evenly across the treatment arms in both the ITT population and Subgroup 2 population, with the exception of cancer staging at diagnosis (data not presented in CS). Furthermore, the baseline characteristics in Subgroup 2 were broadly similar to those of the ITT population. The only exceptions were in terms of geographical region and previous lines of treatment. The latter differences are to be expected since patients had received prior capecitabine. The use of prior capecitabine also likely accounts for the differences in geographical region.

Table 39 Baseline characteristics for the EMBRACE trial - ITT population and Subgroup 2*

Characteristic	ITT population			Subgroup 2		
	Eribulin (N=508)	TPC (N=254)	Total (n = 762)	Eribulin (n = 370)	TPC (n = 189)	Total (n =559)
Median Age (range)	55.0 years (28 to 85)	55.0 years (27 to 81)	55.0 years (27 to 85)	55.0 years (28 to 80)	56.0 years (27 to 78)	55.0 years (28 to 80)
Age distribution, n (%)						
< 40 yrs	34 (6.7)	17 (6.7)	51 (6.7)	24 (6.5)	15 (7.9)	39 (7.0)
≥ 40 – < 65 yrs	380 (74.8)	180 (70.9)	560 (73.5)	280 (75.7)	133 (70.4)	413 (73.9)
≥ 65 yrs	94 (18.5)	57 (22.4)	151 (19.8)	66 (17.8)	41 (21.7)	107 (19.1)
Race, n (%)						
Caucasian	470 (92.5)	233 (91.7)	703 (92.3)	346 (93.5)	174 (92.1)	520 (93.0)
Black	20 (3.9)	14 (5.5)	34 (4.5)	13 (3.5)	10 (5.3)	23 (4.1)
Asian/Pacific Islander	3 (0.6)	2 (0.8)	5 (0.7)	1 (0.3)	2 (1.1)	3 (0.5)
Other	15 (3.0)	5 (2.0)	20 (2.6)	10 (2.7)	3 (1.6)	13 (2.3)
Geographic region, n (%)						
North America, Western Europe, Australia	325 (64.0)	163 (64.2)	488 (64.0)	258 (69.7)	131 (69.3)	389 (69.6)
Eastern Europe	129 (25.4)	64 (25.2)	193 (25.3)	77 (20.8)	40 (21.2)	117 (20.9)
Latin America, South Africa	54 (10.6)	27 (10.6)	81 (10.6)	35 (9.5)	18 (9.5)	53 (9.5)
Reproductive status, n (%)						
Fertile	46 (9.1)	20 (7.9)	66 (8.7)	33 (8.9)	14 (7.4)	47 (8.4)
Post-menopausal	379 (74.6)	199 (78.3)	578 (75.9)	280 (75.7)	150 (79.4)	430 (76.9)
Surgically sterile	78 (15.4)	35 (13.8)	113 (14.8)	53 (14.3)	25 (13.2)	78 (14.0)
Infertile	5 (1.0)	0	5 (0.7)	4 (1.1)	0 (0.0)	4 (0.7)
Median time since original diagnosis (range)	5.4 years (0.1, 37.4)	5.1 years (0.6, 22.9)	5.2 years (0.1, 37.4)	5.7 years (0.1, 37.4)	5.3 years (0.6, 22.9)	5.6 years (0.1, 37.4)
ER Status, n (%)†						
+	336 (70.0)	171 (70.4)	507 (70.1)	257 (72.0)	130 (70.7)	387 (71.5)
–	143 (29.8)	72 (29.6)	215 (29.7)	99 (27.7)	54 (29.3)	153 (28.3)
Unknown	1 (0.2)	0	1 (0.1)	1 (0.3)	0	1 (0.2)

Characteristic	ITT population			Subgroup 2		
	Eribulin (N=508)	TPC (N=254)	Total (n = 762)	Eribulin (n = 370)	TPC (n = 189)	Total (n =559)
PR Status, n (%)†						
+	254 (56.2)	123 (54.7)	377 (55.7)	195 (57.9)	93 (54.4)	288 (56.7)
–	197 (43.6)	102 (45.3)	299 (44.2)	141 (41.8)	78 (45.6)	219 (43.1)
Unknown	1 (0.2)	0	1 (0.1)	1 (0.3)	0	1 (0.2
HER2 status, n (%)†						
+	83 (18.0)	40 (17.2)	123 (17.8)	60 (17.3)	29 (16.3)	89 (17.0)
–	373 (81.1)	192 (82.8)	565 (81.6)	285 (82.4)	149 (83.7)	434 (82.8)
Unknown	4 (0.9)	0	4 (0.6)	1 (0.3)	0	1 (0.2)
Triple negative (ER/PR/HER2-negative), n (%)†	93 (18.3)	51 (20.9)	144 (19.8)	68 (18.4)	38 (20.1)	106 (19.0)
No. of organs involved‡, n (%)						
1	85 (16.7)	35 (13.8)	120 (15.7)	61 (16.5)	25 (13.2)	86 (15.3)
2	172 (33.9)	82 (32.3)	254 (33.3)	128 (34.6)	59 (31.2)	187 (33.4)
3	145 (28.5)	77 (30.3)	222 (29.1)	106 (28.6)	60 (31.7)	166 (29.7)
4	71 (14.0)	37 (14.6)	108 (14.2)	49 (13.2)	29 (15.3)	78 (14.0)
5	24 (4.7)	16 (6.3)	40 (5.2)	18 (4.9)	10 (5.3)	28 (5.0)
≥ 6	9 (1.8)	7 (2.8)	16 (2.1)	6 (1.6)	6 (3.2)	12 (2.1)
Tumour sites in > 10% patients overall, n (%)						
Bone	306 (60.2)	158 (62.2)	464 (60.9)	234 (63.2)	120 (63.5)	354 (63.3)
Liver	296 (58.3)	159 (62.6)	455 (59.7)	225 (60.8)	127 (67.2)	352 (63.0)
Lymph nodes	220 (43.3)	118 (46.5)	338 (44.4)	150 (40.5)	87 (46.0)	237 (42.4)
Lung	197 (38.8)	95 (37.4)	292 (38.3)	138 (37.3)	67 (35.4)	34 (18.0) 205 (36.7)
Pleura	87 (17.1)	42 (16.5)	129 (16.9)	62 (16.8)		96 (17.2)
Breast	54 (10.6)	24 (9.4)	78 (10.2)	30 (8.1)	13 (6.9)	43 (7.7)
ECOG performance status, n (%)						
0	217 (42.7)	103 (40.6)	320 (42.0)	154 (41.6)	80 (42.3)	234 (41.9)
1	244 (48.0)	126 (49.6)	370 (48.6)	179 (48.4)	90 (47.6)	269 (48.1)
2	39 (7.7)	22 (8.7)	61 (8.0)	30 (8.1)	16 (8.5)	46 (8.2)

Characteristic	ITT population			Subgroup 2		
	Eribulin (N=508)	TPC (N=254)	Total (n = 762)	Eribulin (n = 370)	TPC (n = 189)	Total (n =559)
No. of prior chemotherapy regimens (adjuvant and LABC/MBC setting), n (%)						
1	1 (0.2)	0	1 (0.1)	1 (0.3)	0 (0.0)	1 (0.2)
2	65 (12.8)	31 (12.2)	96 (12.6)	17 (4.6)	11 (5.8)	28 (5.0)
3	176 (34.6)	83 (32.7)	259 (34.0)	122 (33.0)	51 (27.0)	173 (30.9)
4	166 (32.7)	79 (31.1)	245 (32.2)	142 (38.4)	69 (36.5)	211 (37.7)
5	85 (16.7)	51 (20.1)	136 (17.8)	74 (20.0)	48 (25.4)	122 (21.8)
≥ 6	13 (2.6)	9 (3.5)	22 (2.9)	13 (3.5)	9 (4.8)	22 (3.9)
No. of prior regimens in LABC/MBC setting, n (%)						
0	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	8 (1.6)	7 (2.8)	15 (2.0)	2 (0.5)	2 (1.1)	4 (0.7)
2	219 (43.1)	90 (35.4)	309 (40.6)	130 (35.1)	53 (28.0)	183 (32.7)
3	163 (32.1)	83 (32.7)	246 (32.3)	132 (35.7)	67 (35.4)	199 (35.6)
4	92 (18.1)	55 (21.7)	147 (19.3)	81 (21.9)	48 (25.4)	129 (23.1)
5	21 (4.1)	13 (5.1)	34 (4.5)	21 (5.7)	13 (6.9)	24 (6.1)
≥ 6	4 (0.8)	5 (2.0)	9 (1.2)	4 (1.1)	5 (2.6)	9 (1.6)
Duration of last chemotherapy (months), Median (min, max)†	3.57 (0.0, 32.0)	3.50 (0.1, 25.3)	3.53 (0.0, 32.0)	3.8 (0.0, 32.0)	3.7 (0.1, 25.3)	3.7 (0.0, 32.0)
No. of patients who previously (adjuvant and LABC/MBC setting) received: n (%)						
Taxanes	503 (99.0)	251 (98.8)	754 (99.0)	365 (98.6)	186 (98.4)	551 (98.6)
Anthracyclines	502 (98.8)	250 (98.4)	752 (98.7)	365 (98.6)	185 (97.9)	550 (98.4)
Capecitabine	370 (72.8)	189 (74.4)	559 (73.4)	370 (100.0)	189 (100.0)	559 (100.0)

ECOG=eastern cooperative oncology group; ER=oestrogen receptor; HER2=human epidermal growth factor receptor 2; ITT=intent-to-treat; LABC=locally advanced breast cancer; PR=progesterone receptor; TPC=treatment of Physician's Choice

*Table excludes missing data for all characteristics

†For the ER, PR, HER2 and triple negative status, the percentages are calculated from the total number of patients tested

‡The number of organs involved was based on the investigator review data

Source: Company response to the ERG clarification letter, Table A2 and company response to further ERG clarification

11.4 Additional ERG observations on the quality assessment of the randomised controlled trials

In both trials, patients and investigators were not blinded to treatment allocation. From a pragmatic point of view, this is reasonable given that the administration and scheduling of agents in the intervention and comparator arms differed in both trials, particularly in the EMBRACE trial where TPC entailed a number of possible treatment options. However, it can be considered a weakness, increasing the risk of bias. However, the ERG notes that for the EMBRACE trial, an independent data monitoring committee (DMC) reviewed the safety of eribulin treatment and assessed the interim efficacy data and the trial sponsor remained blinded to OS data until database lock. In addition to investigator review of outcomes relating to tumour response (PFS and ORR), independent assessment of PFS and ORR were also undertaken. Results of the independent assessments, compared with investigator assessments are summarised in the main body of the report, Section 4.8.2.

For the results of a trial with so many centres to be meaningfully interpreted, the manner in which the protocol is implemented should be clear and similar across all centres. With so many investigators in different countries, general clinical practice will always be an issue and the results of a trial can only be generalisable if it is executed efficiently. The CSR of the EMBRACE trial states that study monitors were responsible for establishing and maintaining regular contact between study centres and the company. Monitors made regular visits to each study centre (maximum time between visits was 6 weeks) to check adherence to the protocol and inform the company of any issues arising. The monitor provided written reports to the company after each contact with the study centre. The ERG is confident that the company made every effort to ensure that the trial procedures were implemented comprehensively across all study centres.

11.5 Health-related quality of life data reported for all patients

The HRQoL findings reported in the CS for all patients in Study 301 are summarised in Table 40. It is important to note that only 28% of these patients received eribulin as a third-line treatment for LABC/MBC and no patient had been previously treated with capecitabine.

Table 40 Health-related quality of life data reported in Study 301 - all patients

Domain	Results summarised in CS*
Global GHS/QoL (QLQ-C30)	Overall, the median global health status (GHS)/ quality of life (QoL) scores were similar between the eribulin and capecitabine groups: Mean scores around 50 suggest significant impact of disease Median time to symptom worsening (TSW) was similar for both arms The majority of patients (≥74%) in both treatment groups maintained or improved their GHS/ QoL versus baseline using minimum important differences (MID) analysis †
Functional	
QLQ-C30: cognitive; emotional; physical; social; role	There were no differences between the two treatment arms in terms of impact on patients' functioning over time, as measured by changes in EORTC QLQ-C30 scores for functional scales Scores on QLQ-C30 functional scales were generally good (mean values around and above 70) 10% to 35% of patients in both treatment arms experienced a clinically significant worsening of their functioning
QLQ-BR23: body image; future perspective; sexual enjoyment; and sexual functioning	Breast-cancer-specific functional scales of the QLQ-BR23 questionnaire showed impact on all domains for eribulin (mean scores 32 to 65), in particular, on sexual functioning (mean score 14) Patients receiving eribulin had comparatively worse scores on the body image ($p<0.001$) and sexual functioning scales ($p<0.05$), measured by QLQ-BR23, than those receiving capecitabine 10% to 35% of patients in both treatment arms experienced a clinically significant worsening of their functioning No statistically significant differences over the course of the study were observed between the treatment groups, except that a higher proportion of patients receiving capecitabine reported a meaningful worsening on the future perspective scale than those receiving eribulin (MID 10; HR=1.173 [95% CI=1.015, 1.356]; $p<0.05$) †
Symptoms	
QLQ-C30: appetite loss; constipation; diarrhoea; dyspnoea; fatigue; financial difficulties; insomnia; nausea and vomiting; pain	Patients receiving capecitabine had comparatively more severe symptoms (that is, higher symptom scores) for nausea and vomiting ($p<0.001$) and diarrhoea ($p<0.001$) and shorter TSW for all these symptoms ($p<0.05$) compared with those treated with eribulin ¥
QLQ-BR23: arm symptoms; breast symptoms; systemic therapy side-effects; and upset by hair loss	Patients receiving eribulin had worse mean scores for other systemic therapy side-effects including dry mouth, different tastes, irritated eyes, feeling ill, hot flushes, headaches, and hair loss (all $p<0.001$), and upset by hair loss ($p<0.05$) and shorter TSW for all these symptoms ($p<0.05$) compared with those treated with capecitabine ¥

*Note: All scores for the EORTC QLQ-C30 and EORTC QLQ-BR23 were transformed to a scale from 0 to 100 as described in the EORTC manual[59]

† MID was defined as smallest difference in scores between groups in the scales of interest, which patients perceived as beneficial; literature-based threshold values for MID were used for scales in the EORTC QLQ-C30[60] and because there are no published MIDs on the QLQ-BR23, a 10-point change was considered consistent with previous estimates[61]

Source: CS, pp94 to 100

¥ TSW was defined as time until clinically meaningful deterioration by a specified threshold for each patient-reported endpoint; TSW was calculated for each HRQoL scale using Kaplan-Meier curves

11.6 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 – 9 (n=2 not used).

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

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ERG Table X2 Row Title	Associated detail	Implementation instructions
R1. ERG PFS estimates (Binary switch Mod_1)	ERG survival estimates for both PFS and OS are included as a new worksheet 'ERG_survival'	In Sheet 'Appendix Partition' **Replace** formula in cell E8 by =IF(Mod_1=1,ERG_survival!D4, INDEX(EXT_data,MATCH($B8,EXT_Cycle,0), MATCH(E$5&E$7&$P$9&$P$8&$W$9,EXT_Key,0))) **Copy** formula in cell E8 to range E9:E248 **Replace** formula in cell F8 by =IF(Mod_1=1,ERG_survival!F4, INDEX(EXT_data,MATCH($B8,EXT_Cycle,0), MATCH(F$5&F$7&$P$9&$P$8&$W$9,EXT_Key,0))) **Copy** formula in cell F8 to range F9:F248
R2. ERG OS estimates (Binary switch Mod_2)	ERG survival estimates for both PFS and OS are included as a new worksheet 'ERG_survival'	In Sheet 'Appendix Partition', **Replace** formula in cell G8 by =IF(Mod_2=1,ERG_survival!E4, INDEX(EXT_data,MATCH($B8,EXT_Cycle,0), MATCH(G$5&G$7&$P$9&$P$8&$W$7,EXT_Key,0))) **Copy** formula in cell G8 to range G9:G248 **Replace** formula in cell H8 by =IF(Mod_2=1,ERG_survival!G4,INDEX(EXT_data, MATCH($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

Superseded by Erratum

ERG Table X2 Row Title	Associated detail	Implementation instructions
		<u>In Sheet 'Appendix Transition',</u> **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
R4. Correct logic error in oral vinorelbine costing (Binary switch Mod_7)	None	<u>In Sheet 'Appendix dose and BSA'</u>, **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$60*Q78) **Copy** cell S78 **Paste** to range S79:S138
R5. ERG estimated eribulin unit costs (Binary switch Mod_5)	ERG_Reworked_Drug_Costs(final).xlsx	<u>In Sheet 'Appendix dose and BSA'</u>, **Replace** formula in cell H75 by =SUMPRODUCT(($D$78:$D$138)*(H$78:H$138))*IF(Mod_5=1,1.441618,1) **Replace** formula in cell I75 by =SUMPRODUCT(($D$78:$D$138)*(I$78:I$138))*IF(Mod_5=1,1.441618,1)

Superseded by Erratum

ERG Table X2 Row Title	Associated detail	Implementation instructions
R6. ERG estimated comparator costs (Binary switch Mod_6)	ERG_Reworked_Drug_Costs(final).xlsx	In Sheet 'Appendix dose and BSA', **Replace** formula in cell M75 by =SUMPRODUCT(($D$78:$D$138)*(M$78:M$138)) *IF(Mod_6=1,1.032214,1) **Replace** formula in cell N75 by =SUMPRODUCT(($D$78:$D$138)*(N$78:N$138)) *IF(Mod_6=1,1.032214,1) **Replace** formula in cell S75 by =SUMPRODUCT(($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$138)) *IF(Mod_6=1,1.53137,1) **Replace** formula in cell Z75 by =SUMPRODUCT(($D$78:$D$138)*(Z$78:Z$138)) *IF(Mod_6=1,1.53137,1) **Replace** formula in cell AF75 by =SUMPRODUCT(($D$78:$D$138)*(AF$78:AF$138)) *IF(Mod_6=1,0.898964,1) **Replace** formula in cell AG75 by =SUMPRODUCT(($D$78:$D$138)*(AG$78:AG$138)) *IF(Mod_6=1,0.898964,1) **Replace** formula in cell AM75 by =SUMPRODUCT(($D$78:$D$138)*(AM$78:AM$138)) *IF(Mod_6=1,0.80107,1) **Replace** formula in cell AN75 by =SUMPRODUCT(($D$78:$D$138)*(AN$78:AN$138)) *IF(Mod_6=1,0.80107,1) **Replace** formula in cell AT75 by =SUMPRODUCT(($D$78:$D$138)*(AT$78:AT$138)) *IF(Mod_6=1,1.231349,1) **Replace** formula in cell AU75 by =SUMPRODUCT(($D$78:$D$138)*(AU$78:AU$138)) *IF(Mod_6=1,1.231349,1) **Replace** formula in cell AZ75 by =SUMPRODUCT(($D$78:$D$138)*(AZ$78:AZ$138)) *IF(Mod_6=1,1.19404,1) **Replace** formula in cell BA75 by =SUMPRODUCT(($D$78:$D$138)*(BA$78:BA$138)) *IF(Mod_6=1,1.19404,1)

Superseded by Erratum

ERG Table X2 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=1,0.96,F11) **Replace** formula in cell H29 by =IF(Mod_8=1,0.496,H11)
R8. ERG alternative option for costing subsequent treatments	'Model parameters':Q13 must be set to "Maximum number of cycles"	In Sheet 'Model parameters', **Replace** formula in cell R17 by =IF(Mod_9=1,600,6) **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 P92 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

Superseded by Erratum

ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Eribulin for treating locally advanced or metastatic breast cancer after chemotherapy [ID964]

Confidential until published

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CONTAINS COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company identified 15 overall issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. Not all were considered by the ERG to be factual inaccuracies but some were considered to require minor changes to the text. The pages of the report affected are presented here. Please note:

- New text added by the ERG is in *italics and underlined*.
- Text deleted completely (as opposed to being re-worded) is struck out.
- Unaltered text which is considered to be of relevant context to that added, amended or deleted (such as headings or sentences preceding or following the added, amended or deleted text) is presented in its original font.
- All other unaltered text is greyed out.

1 SUMMARY

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 (TA250). At that time eribulin was licensed 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. In 2014 the European Medicines Agency licence for treatment with eribulin was broadened to include less heavily treated patients. The new licence is for the treatment of adult patients with LABC/MBC who have progressed after at least **one** chemotherapeutic 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 relating to two different subgroups of the licensed population, one relating to the licence that was valid in 2012 and the other to the 2014 licence. Following discussions between the company, NICE and the ERG, the scope of this STA was amended so that its only focus is a review of TA250. The remainder of this report is therefore only concerned with the evidence submitted by the company for a review of TA250.

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

Clinical effectiveness evidence is derived primarily from the EMBRACE trial and is considered by the company for two populations:

- All patients receiving ≥3 chemotherapy regimens for LABC/MBC: patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease. Prior treatment includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable. This is the EMBRACE trial intention-to-treat (ITT) population.
- Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease and includes capecitabine (if indicated). Prior treatment also includes a previous anthracycline and taxane in either the adjuvant or metastatic setting unless these treatments were not suitable. This is a subgroup (73%) of the EMBRACE trial and is referred to by the company (and within this ERG report) as Subgroup 2.

The company's probabilistic sensitivity analysis (PSA) involved varying only a limited number of parameters. There is a 30% probability of treatment with eribulin being cost effective at a threshold of £30,000 per QALY gained and a 72% probability of it being cost effective at a threshold of £50,000 per QALY gained.

The company carried out six scenario analyses. Excluding the cost of drug wastage had the largest impact and lowered the ICER to £16,053 per QALY gained (a 54% reduction in the base case result).

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

The ERG considers that investigator-assessed PFS data are more reflective of patient experience than independently-assessed data. The ERG has recalibrated the PFS model to use investigator- rather than independently-assessed data from the EMBRACE trial and has remodelled the PFS projections to extrapolate PFS in the time horizon scenario analyses.

The company used K-M data alone to model OS in the base case and appended projective functions from 5 years onwards to model patient OS in the time horizon scenario analyses. 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, but is more pronounced in the time horizon scenario analyses.

The company misinterpreted one of the ERG's clarification questions and has not provided the relevant PPS K-M data. The ERG was therefore unable to estimate directly the extent of any survival benefit (or disbenefit) arising after disease progression. However, OS and PFS estimates give strong support to a substantial gain in mean survival being experienced by some patients even after recorded disease progression and cessation of treatment with eribulin.

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 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 affect 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 QLQ-C30 quality of life 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.

1.6 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:

- Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease which includes capecitabine, have a life expectancy of less than 24 months
- Data from the EMBRACE trial demonstrate that eribulin extends life by more than 3 months compared with TPC.

1.7 ERG commentary on end of life criteria

The ERG agrees with the company that eribulin is a treatment that is indicated in patients with a short life expectancy. The ERG also considers that eribulin is likely to offer an extension to life of at least an additional 3 months compared to current NHS treatment; the ERG estimates a mean OS gain of 3.39 months (95% confidence interval 0.83 to 5.96 months) for patients treated with eribulin compared with patients treated with TPC although this does not achieve statistical significance due to the small trial population.

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

1.8.1 Strengths

Clinical evidence

- The EMBRACE trial compared the efficacy and safety of eribulin with TPC, a comparator arm that reflects the real life choices faced by physicians and patients with an advanced stage of LABC/MBC
- Mature clinical effectiveness data are available (95% of patients have died)
- The EMBRACE trial is the only currently available source of good-quality clinical effectiveness evidence describing the use of treatments available to patients receiving ≥3 chemotherapy regimens for LABC/MBC.

Cost effectiveness evidence

- The availability of mature survival data allows a reliable assessment of the relative effectiveness of treatment with eribulin versus TPC for the Subgroup 2 population.

1.8.2 Weaknesses and areas of uncertainty

Clinical evidence

- HRQoL data were not available from the EMBRACE trial
- Although HRQoL data for third-line patients were available from Study 301, only 28% of all patients in this trial received study treatment as a third-line option for LABC/MBC. The majority of all patients in the ITT population included in the EMBRACE trial (including patients in Subgroup 2) had received a greater number of previous lines of treatment than those participating in Study 301. Study 301 also excluded patients previously treated with capecitabine (unlike the EMBRACE trial). Thus it is unclear if the available HRQoL data are generalisable to all patients receiving ≥3 chemotherapy regimens for LABC/MBC or to Subgroup 2 patients.

Cost effectiveness evidence

- No evidence has been provided to demonstrate the cost effectiveness of treatment with eribulin versus TPC for the ITT population
- *Independently-assessed data have been used rather than investigator-assessed data to model PFS*
- Within the company model, costs and benefits have been discounted continuously rather than annually
- The ERG has identified several issues relating to the methods employed by the company to estimate drug acquisition and administration costs
- The company has used an implausibly high post-progression utility value
- The exploration of parameter uncertainty undertaken by the company is insufficient.

1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG implemented nine individual corrections/modifications to the company's model. When these changes are implemented individually for the comparison of the cost effectiveness of treatment with eribulin versus TPC for the Subgroup 2 population, they both increase and decrease the size of the company's base case ICER per QALY gained. The three most influential ERG changes are the revised estimate of the cost of eribulin treatment (base case ICER change: *+£9,793*), the choice of utility value for the progressive disease health state (base case ICER change: +£11,288), and the method used to cost subsequent lines of treatment (base case ICER change: +£9,811). The combined effect of all of the ERG changes yields an ICER of *£62,672* 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 *£27,047*) for the comparison of treatment with eribulin versus TPC in patients with LABC/MBC whose disease

has progressed after at least two prior chemotherapy regimens for advanced disease and includes capecitabine.

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 final scope issued by NICE is presented in Table 3. Each parameter is discussed in more detail in the text following the table (Section 3.1to Section 3.7). **As noted in Section 2.3 the CS provides information relating to two subgroups of patients; however, this ERG report only considers the information provided by the company that facilitates a review of TA250.**

Table 3 Final NICE scope and company's decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the CS
Population	Adults with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease (anthracycline and a taxane, unless these treatments were not suitable)	Clinical and cost effectiveness evidence is presented for Subgroup 2 patients: patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease which includes capecitabine (if indicated). This was one of two populations on which the Appraisal Committee finally focussed on in TA250 Clinical effectiveness evidence is also presented for the broader population of patients with LABC/MBC whose disease has progressed after at least two prior chemotherapy regimens for advanced disease (but who have not received prior capecitabine). This was the other population on which the Appraisal Committee finally focussed on in TA250
Intervention	Eribulin	As per scope
Comparator (s)	• Vinorelbine • Capecitabine • Gemcitabine	Clinical effectiveness: Treatment of Physician's Choice (TPC), including: • Vinorelbine • Capecitabine • Gemcitabine • Anthracyclines (doxorubicin) • Taxanes (paclitaxel and docetaxel) Clinical effectiveness and base case cost effectiveness: Treatment of Physician's Choice (TPC), including: • Vinorelbine • Gemcitabine • Anthracyclines (doxorubicin) • Taxanes (paclitaxel and docetaxel) Cost effectiveness scenario analysis: *50%* of population received vinorelbine and *50%* received gemcitabine

Parameter	Final scope issued by NICE	Decision problem addressed in the CS
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health related quality of life	As per scope for all patients in the EMBRACE trial Health-related quality of life data are derived from an alternative trial (Study 301) The only endpoints reported for Subgroup 2 patients are: • Overall survival • Progression-free survival • Adverse effects of treatment (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 economic evaluation utilised patient-level data from the EMBRACE trial. 5-year survival data from this trial were very close to being complete and the company therefore set the base case time horizon to 5 years. Cost effectiveness results from scenario analyses considering 10- and 20-year time horizons were also provided Costs were considered from an NHS perspective A Patient Access Scheme for eribulin has been approved by the Department of Health and this cost has been used in the cost effectiveness analyses
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups according to HER2 status, oestrogen receptor and line of treatment 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	Subgroup 2 patients are representative of patients in current clinical practice in England as observed through the usage of eribulin obtained via the Cancer Drugs Fund (CDF). Recently published data from three audits undertaken in England show that 80% or more of patients who had obtained eribulin via the CDF had received prior capecitabine
Other considerations	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.	Since the licence for eribulin has been updated to enable eribulin to be used earlier in the treatment pathway, and since the current STA is a review of TA250, all patients receiving ≥3 chemotherapy regimens for LABC/MBC and Subgroup 2 patients constitute subgroups of the licensed population. For these heavily pre-treated patients, the company considers eribulin should be considered using NICE's end of life criteria

Source: Final scope issued by NICE and CS, adapted from Table 1

Table 6 Summary of the EMBRACE trial and Study 301 characteristics

Parameter	Description	
	EMBRACE trial	**Study 301**
Intervention and comparator	Eribulin (N=508, 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 TPC (N=254, randomised) The selection of the TPC agent took place prior to randomisation	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 2 to 5 chemotherapy regimens, including a taxane and an anthracycline; at least 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	• 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	135 secondary care centres in 19 countries (including UK)	210 secondary care centres in 24 countries
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, any drugs not allowed concomitantly with the selected TPC, according to the relevant package insert	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, ~~any drugs not allowed concomitantly with the selected TPC, according to the relevant package insert~~
Primary outcomes	Overall survival	Overall survival and progression-free survival
Secondary outcomes	Progression-free survival, objective response rate and safety	Objective response rate, safety and health-related quality of life

ECOG=Eastern Cooperative Oncology Group; G-CSF=granulocyte-colony stimulating factor; HER2=human epidermal growth factor receptor 2; HRQoL=health-related quality of life; IV=intravenous; LABC=locally advanced breast cancer; MBC=metastatic breast cancer; PS=performance status; TPC=Treatment of Physician's Choice
Source: CS, adapted from Table 12

Most commonly reported adverse events

Details relating to the most frequently reported all-Grade AEs (>10% patients in each arm) in the EMBRACE trial are provided in Table 34 of the CS. The most frequently reported AEs occurring in patients treated with eribulin are reported to be asthenia/fatigue (53.7%), neutropenia (51.7%), alopecia (44.5%), peripheral neuropathy (34.6%) and nausea (34.6%). From Table 34 of the CS it is, however, evident that similar incidences of asthenia/fatigue (50.8%) and neutropenia (49.2%) were seen in patients treated with vinorelbine. For patients treated with TPC the most common AEs were asthenia/fatigue (39.7%), neutropenia (29.6%), nausea (28.3%), anaemia (22.7%) and constipation (20.6%). Only the incidences of anaemia and constipation are higher in the TPC arm than in the eribulin arm (18.7% and 24.7% respectively in patients treated with eribulin).

Treatment related adverse events

In total, 94.2% of patients reported AEs that were considered by the investigator to be treatment-related in the eribulin arm compared with 77.7% in the TPC arm (CS, Table 33). The company notes (CS, p113) that the open-label nature of the trial means that these figures may be subject to bias against the investigational agent (eribulin).

Adverse events leading to treatment discontinuation

The company states that discontinuations due to AEs were lower in the eribulin arm (13.3%) than in the TPC arm (15.4%). However, the ERG observes that discontinuations due to AEs were all marginally lower for patients treated with vinorelbine (11.5%), capecitabine (*11.4%*) and gemcitabine (10.9%) than for patients treated with eribulin, suggesting that the apparently higher treatment discontinuation rate in the TPC arm can be attributed to the other agents that constituted TPC. Indeed, information in the CSR (Table 23) shows that this was a particular issue for patients treated with taxanes [redacted]

Real world evidence

The company reports (CS, p118) that recently published data from audits undertaken in England, Spain and France/Switzerland have shown that eribulin is well tolerated in a routine clinical practice setting and reflect that patients are not impacted greatly by the side effect profile of eribulin (see Section 4.9). The company concludes that eribulin has a well characterised and manageable safety profile.

Table 21 Proportions of Treatment of Physician's Choice

Drug name	Number of patients	Proportion	
		ITT population	Subgroup 2
Vinorelbine	61	24.00%	36.75%
Gemcitabine	46	18.10%	27.71%
Paclitaxel	26	10.20%	15.66%
Doxorubicin	23	9.10%	13.86%
Docetaxel	10	3.90%	6.02%
Total	119	65.30%	100.00%

ITT=intention-to-treat
Source: CS, Table 43 and The EMBRACE trial clinical study report, Table 10

In a scenario analysis, the company also considered a comparator arm in which patients, rather than being treated with TPC, were treated with either vinorelbine monotherapy (*50%*) or gemcitabine monotherapy (*50%*). ~~In this scenario the relative treatment proportions were those observed in the ITT population of the EMBRACE trial.~~

Secondary treatments

Patients transitioning from the stable to progressive health states are assumed to receive secondary chemotherapy treatments in the proportions given in Table 21.

Treatment duration

In the base case, the maximum treatment duration in the model for patients in Subgroup 2 is set at 6 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 either eribulin or TPC is therefore linked to the duration of the primary treatment in the stable health state. An alternative scenario is also presented 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 45 of the CS.

Dose intensity

Dose reductions and delays due to AEs are included in the model using a dose intensity modifier. Dose intensity for patients treated with eribulin is 0.84, based on the mean dose intensity observed for patients treated with eribulin in the ITT population of the EMBRACE trial. For simplicity, dose intensity for patients treated with TPC is assumed to be the same as that for patients treated with eribulin.

A linear mixed-effects model was used to predict the impact of specific AEs on utility scores from the EORTC QLQ-C30 data from Study 301 (see Table 23). Only common AEs (all grades with a prevalence ≥10%) or serious (≥3 with a prevalence ≥2%) are included within the model.

This disutility value 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 TPC (see Table 22).

The linear mixed-effects model estimated an improvement in utility for alopecia; alopecia has a disutility of zero in the model. Alopecia and peripheral neuropathy are not part of the EORTC QLQ-C30 questionnaire and therefore these utility values should be interpreted with caution.

Table 23 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 51

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. *The original data sources for adverse events were the EMBRACE trial patient level data.*

5.5 Critique of cost effectiveness analyses

5.5.1 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 the treatments included in the model are prescribed on either a weekly or 3-weekly basis. For accuracy, it would have been preferable to employ weekly cycles, but 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 can accumulate over a lifetime horizon.

5.5.2 Patient survival and disease progression

The ERG submitted a clarification request for detailed K-M analysis results for OS, PFS and post-progression survival (PPS) from the EMBRACE trial and the company provided these data. The ERG also requested similar information for time to treatment discontinuation to allow the ERG to employ an alternative approach to estimating treatment costs. Unfortunately, this request was misinterpreted and the ERG could not use the results provided by the company.

Overall survival

The OS K-M data from the EMBRACE trial (*Figure 5*) indicate that, for patients in both the eribulin and TPC arms, the trial data are nearly complete (only two patients randomised to receive eribulin and one patient randomised to receive TPC were still alive at the time of data cut-off). Re-running the K-M OS analysis *using data received from the company during the clarification process* indicates that, without any projection of estimated survival in either arm to compensate for the missing follow-up data, the accurate value for the mean OS gain attributable to treatment with eribulin compared to TPC is 3.39 months (95% CI 0.83 to 5.96 months).

In order 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 – month 35 in the eribulin arm and month 27 in the TPC arm *(Figure 5)*. The ERG then applied the calibrated trend lines from the time closest to the final recorded trial death (month 64 for eribulin and month 56 for TPC). *Since the calibrated trend line for TPC was applied at month 56, before the end of the 5 year base case, the ERG's revised OS in the base case includes 4 months of projected survival for TPC. As a result, implementing the ERG method in the model results in a small reduction of £199 per QALY gained in the size of the estimated ICER for the base case scenario.*

An examination of Figure 5 *also* highlights that, compared with the company's projection, the ERG's method of projection leads to a greater long-term OS advantage for patients treated with eribulin compared with TPC in the time horizon scenarios. ~~As a result, implementing the ERG method in the model results in a small reduction of £199 per QALY gained in the size of the estimated ICER for the base case scenario.~~

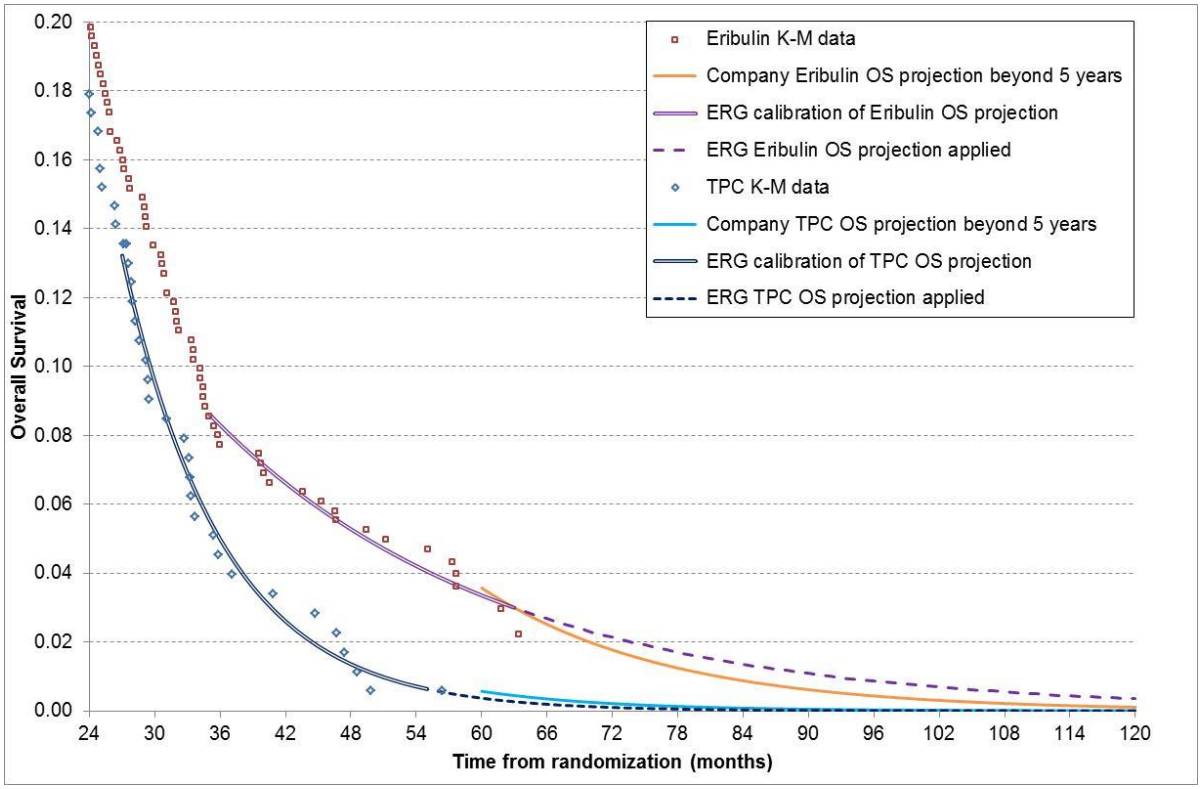

Figure 5 Overall survival Kaplan-Meier data from the EMBRACE trial and two approaches to survival projection

Progression-free survival

For the base case scenario (5 year horizon) the company model uses only the PFS K-M trial data. However, in the extended time horizon scenarios, the company uses fitted Weibull parametric curves to both sets of trial data, extending non-zero PFS values well beyond the maximum time at which patients were observed to remain progression-free (23 and 25 months).

Examination of the latest PFS K-M data from the EMBRACE trial based on the investigator assessment of progression (Figure 1) indicates that the trial data are complete for patients in both arms of the trial. There is, therefore, no need to carry out any projective modelling of PFS and so the ERG has used the K-M data directly. Re-running the K-M PFS analysis indicates that the accurate value for the mean PFS gain attributable to eribulin compared to TPC is 40.4 days (95% CI 13.0 to 67.8 days). However, the company base case results using the independent assessment of progression suggest a difference of just 8.2 days using the original PFS trial data. The ERG considers that investigator-assessed PFS data are more reflective of patient experience than independently-assessed data. When the ERG replaces the company base case PFS curves with the ERG preferred PFS data provided in response to the clarification question, the model estimated PFS gain increases to 40.2 days (95% CI 13.0 to 67.8 days).

The main effect of this ERG modification to the company model is to change the balance of treatment costs, so that the incremental cost rises, leading to an increase in the ICER per QALY gained of £1,557.

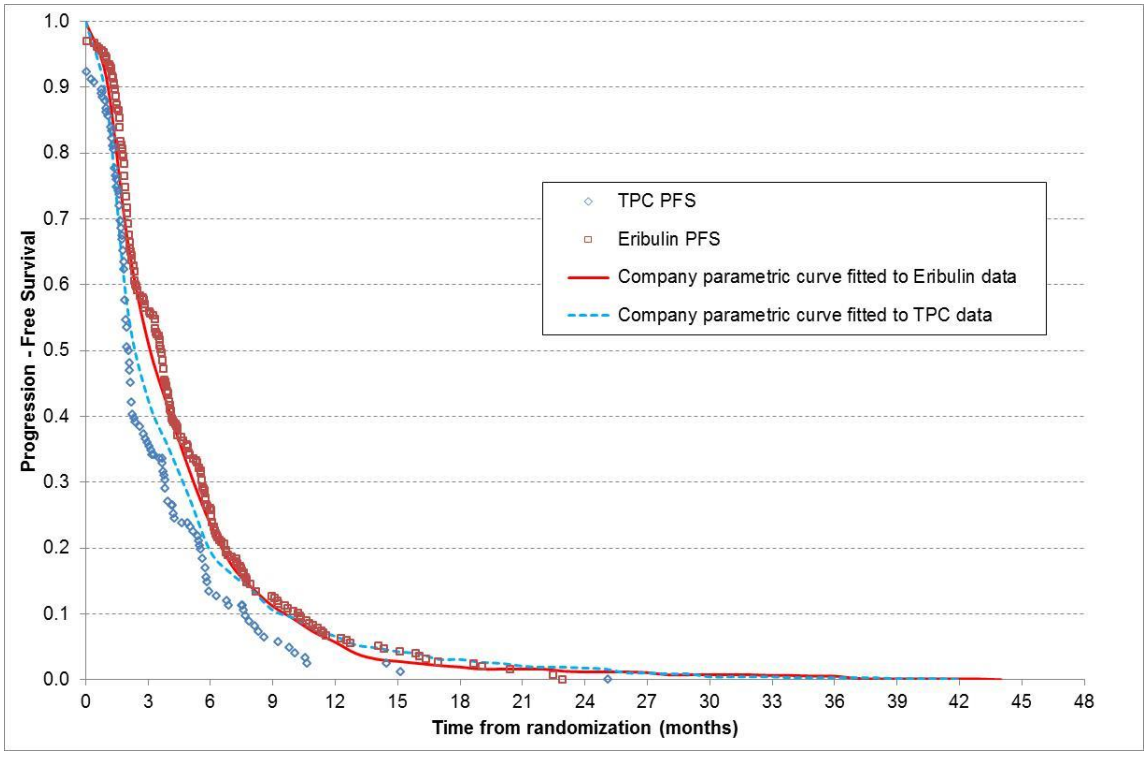

Figure 1 Progression-free survival Kaplan-Meier data from the EMBRACE trial and company Weibull parametric curves

Post-progression survival

Examination of the PPS K-M data from the EMBRACE trial, which was provided by the company in response to a clarification request, has led the ERG to conclude that the company misinterpreted the clarification question and has not provided the relevant data. Post-progression survival analysis includes only those patients whose 'progression event' was a non-fatal progression i.e. excluding any patients who died prior to the time of disease progression. Since the full complement of randomised patients has been included in each trial arm, it is clear that these analyses include patients who died without disease progression. As a result, it is not possible to estimate directly the extent of any survival benefit (or disbenefit) arising after disease progression.

However, the estimates described above for OS and PFS give strong support to a substantial gain in mean survival being experienced by some patients even after recorded disease progression and the cessation of eribulin treatment. This is an important finding, since evidence for many other cancer treatments shows that after progression previous treatments quickly cease to have any bearing on future survival prognosis.

5.5.3 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 TPC. When this error is corrected, the base case ICER is reduced from £35,624 to £31,276 per QALY gained.

5.5.4 Acquisition cost of chemotherapy

The company has estimated the cost of chemotherapy drugs dosed in terms of BSA using UK BSA estimates from survey data.[55] However, the company modellers have confused standard error and standard deviation when calculating the costs of chemotherapy dosed according to BSA *(See Addendum to the ERG Report)*. In addition, no account has been taken of the therapeutic intent of the treatments included in the survey data.[55] This information is included in the full data set, available as a download from the journal web-site.[56] 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 the EMBRACE trial. This yields a slightly higher mean BSA (1.7448) and a standard deviation of 0.1785 (standard error 0.00924). All relevant chemotherapy treatment costs have been re-estimated by the ERG and compared with those used in the company model (Table 34).

The unit cost per dose of chemotherapy has been substantially underestimated for eribulin, oral vinorelbine (after the first cycle) and capecitabine, with smaller differences for all other agents.

Table 34 Unit costs of chemotherapy treatments, comparing ERG estimates to company model parameter values (after the company logic error has been corrected)

Treatment	Unit	Company model	ERG estimate	Difference (ERG vs company model)
Eribulin	Per dose	[redacted]	[redacted]	+£176.65 (+44.2%)
Vinorelbine oral (cycle 1)	Per dose	£242.02	£241.20	-£0.82 (-0.3%)
Vinorelbine oral (cycle 2+)	Per dose	£242.02	£315.84	+£73.82 (+30.5%)
Vinorelbine (IV)	Per dose	£18.24	£18.83	+£0.59 (+3.2%)
Gemcitabine	Per dose	£29.14	£26.20	-£2.96 (-10.1%)
Docetaxel	Per dose	£34.83	£27.90	-£6.93 (-19.9%)
Paclitaxel	Per dose	£21.47	£26.44	+£4.97 (+23.1%)
Doxorubicin	Per dose	£9.62	£11.48	+£1.86 (+19.3%)
Capecitabine	Per cycle	£24.17	£37.01	+£12.84 (+53.1%)

ERG=Evidence Review Group; IV=intravenous

5.5.5 Dose intensity

The company model features a parameter to represent dose intensity as measured in the EMBRACE trial. However, this does not have any effect on the estimated cost of treatments, nor on the company base case ICER per QALY gained. The cost of treatment is only affected when the company's alternative mode of calculating drug costs (without wastage) is employed.

5.5.6 Dose capping

Within the company model, the number of patients continuing on therapy is estimated using the company's PFS estimate. However, a close examination of the company logic indicates that the long-term PFS data included in the model are set to zero for all time periods after 43 months for the eribulin arm and after 41 months for the comparator arm. This mirrors the extent of PFS K-M trial data available for the independent assessment of progression. The ERG has applied the PFS K-M data based on the investigator assessment which indicate shorter treatment periods in both arms (see above).

However, a conflict arises when extended time horizon scenarios are modelled in that parametric extrapolation of OS is then applied to model outcomes, but the corresponding PFS extrapolation is not used in the calculation of treatment costs which remain fixed at the unprojected maximum duration. This has the effect of reducing the estimated cost of both treatments leading to a lower incremental cost of eribulin compared to TPC and a slightly higher estimated ICER per QALY gained.

5.5.7 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. However, a PSA ICER per QALY gained calculated by the ERG from the random iteration data is very similar to the deterministic ICER per QALY gained.

5.5.8 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 cost. Correcting this error has the effect of reducing the company base case deterministic ICER per QALY gained by approximately £154.

5.5.9 Health-related utility values

The company has applied a mapping algorithm, published by Crott and Briggs in 2010,[48] to estimate EQ-5D values from the QLQ-C30 quality of life questionnaire administered to patients in Study 301. The algorithm was based on data made available from an historical clinical trial, which recruited patients from 1999 and compared two chemotherapy regimens. The published trial results[57] 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 the EMBRACE trial and the trial upon which Crott and Briggs[48] based their utility mapping exercise must raise serious questions about the appropriateness of applying this reported algorithm to generate utility values for patients receiving third-line chemotherapy after two prior episodes of disease progression.

The alternative, previously considered by the ERG during TA250, is a utility value set published by Lloyd[30] 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[30] analysis. It is particularly remarkable that the value used in the model for patients with stable disease (but not responding to treatment) is very similar to the value for progressed disease (*0.70* versus 0.68), which the ERG considers implausible.

The ERG has tested the effect of substituting the Lloyd[30] progressive disease utility value in place of the company's preferred estimate, and can confirm a resulting increase in the size of the estimated ICER of more than £11,000 per QALY gained.

6 IMPACT ON THE ICER OF ADDITIONAL ERG ANALYSES

To address the points raised in Section 5, the ERG has made the following nine changes to the submitted company model *(Table 35)*:

- use of ERG preferred PFS estimates (R1)
- use of ERG preferred OS estimates (R2)
- use of annual rather than continuous discounting (R3)
- correction of logic error in costing oral vinorelbine (R4)
- use of ERG revised unit cost of eribulin (R5)
- use of ERG revised unit costs of comparator 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)

The three most influential ERG changes are the choice of utility value for the progressive disease health state (R7), the revised estimate of the cost of eribulin treatment (R5), and the method used to cost subsequent lines of treatment (R8).

Table 35 Cost effectiveness (eribulin versus TPC): ERG revisions to company base case

Model scenario ERG revision	Eribulin			TPC			Incremental			ICER	ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	Per QALY gained	Change
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£35,624***	-
R1) ERG use of K-M PFS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£37,182**	**+£1,557**
R2) ERG use of K-M OS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£35,425**	**-£199**
R3) Annual discounting applied	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£35,471**	**-£154**
R4) Correct logic error on oral vinorelbine costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,276**	**-£4,349**
R5) ERG estimated eribulin unit costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£45,418***	***+£9,793***
R6) ERG estimated comparator unit costs (combined with R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,106**	**-£5,518**
R7) ERG preferred progression utility value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£46,912**	**+£11,288**
R8) ERG alternative method of costing subsequent lines of therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,435**	**+£9,811**
R9) Correct logic error on eribulin administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£39,737**	**+£4,113**
B. ERG revised base case A+R1 to R9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£62,672***	***+£27,047***

Costs and QALYs discounted; life years undiscounted
ERG=Evidence Review Group; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; K-M=Kaplan-Meier; ICER=incremental cost effectiveness ratio

Cost effectiveness results

- The company's base case ICER, for the Subgroup 2 population, for the comparison of the cost effectiveness of treatment with eribulin versus TPC is £35,625 per QALY gained
- Following the implementation of all the ERG's amendments the company's base case ICER increases by *£27,047* to *£62,672* per QALY gained.

End of life

- The treatment is indicated for patients with a life expectancy of less than 24 months and although the OS gain, experienced by patients in the EMBRACE trial who received eribulin, does not achieve statistical significance, due to the limited number of patients in the trial, the ERG is reasonable confident that eribulin offers an extension to life of at least an additional 3 months compared to current NHS treatment for Subgroup 2 patients.

9 OVERALL CONCLUSIONS

9.1 Efficacy data

Mature efficacy data from the EMBRACE trial (a good quality multi-centre, phase III, open-label, randomised parallel two-arm trial of 762 patients) show that treatment with eribulin is superior to TPC for the ITT and Subgroup 2 populations. In particular, it appears that treatment with eribulin extends OS for patients who have been heavily pre-treated.

9.2 Safety data

Data from the EMBRACE trial and observational studies also suggest eribulin has an acceptable safety profile in heavily pre-treated patients.

9.3 NHS clinical practice

The median number of cycles with eribulin was reported to be between five and six in the EMBRACE trial (similar to that reported in audits of eribulin use via the CDF). The EMBRACE trial results appear to be generalisable to NHS clinical practice.

9.4 Cost effectiveness

In terms of cost effectiveness, the ERG considers that the company substantially underestimates the size of the most probable base case ICER per QALY gained for eribulin versus TPC in the Subgroup 2 population. The company's base case ICER is £35,624 per QALY gained, which is *£27,047* less than the ICER estimated by the ERG (*£62,672* per QALY gained).

9.5 Implications for research

All of the apparent survival gain for patients in the EMBRACE trial appears to occur during the post-progression survival period. Further research into whether this is common in other clinical studies and, if so, exploration as to why, may improve current understanding of LABC/MBC.

HRQoL evidence is lacking for the population of patients receiving eribulin as a >3 chemotherapy regimen for LABC/MBC. Further research into HRQoL in more heavily pre-treated patients is warranted.

11.6 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 – 9 (n=2 not used).

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

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ERG Table X2 Row Title	Associated detail	Implementation instructions
R1. ERG PFS estimates (Binary switch Mod_1)	ERG survival estimates for both PFS and OS are included as a new worksheet 'ERG_survival'	In Sheet 'Appendix Partition' **Replace** formula in cell E8 by =IF(Mod_1=1,ERG_survival!D4, INDEX(EXT_data,MATCH($B8,EXT_Cycle,0), MATCH(E$5&E$7&$P$9&$P$8&$W$9,EXT_Key,0))) **Copy** formula in cell E8 to range E9:E248 **Replace** formula in cell F8 by =IF(Mod_1=1,ERG_survival!F4, INDEX(EXT_data,MATCH($B8,EXT_Cycle,0), MATCH(F$5&F$7&$P$9&$P$8&$W$9,EXT_Key,0))) **Copy** formula in cell F8 to range F9:F248
R2. ERG OS estimates (Binary switch Mod_2)	ERG survival estimates for both PFS and OS are included as a new worksheet 'ERG_survival'	In Sheet 'Appendix Partition', **Replace** formula in cell G8 by =IF(Mod_2=1,ERG_survival!E4, INDEX(EXT_data,MATCH($B8,EXT_Cycle,0), MATCH(G$5&G$7&$P$9&$P$8&$W$7,EXT_Key,0))) **Copy** formula in cell G8 to range G9:G248 **Replace** formula in cell H8 by =IF(Mod_2=1,ERG_survival!G4,INDEX(EXT_data, MATCH($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 Table X2 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*
R4. 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$60*Q78) **Copy** cell S78 **Paste** to range S79:S138
R5. ERG estimated eribulin unit costs (Binary switch Mod_5)	ERG_Reworked_Drug_Costs(final).xlsx	In Sheet 'Appendix dose and BSA', **Replace** formula in cell H75 by =SUMPRODUCT(($D$78:$D$138)*(H$78:H$138))*IF(Mod_5=*1.34394*,1) **Replace** formula in cell I75 by =SUMPRODUCT(($D$78:$D$138)*(I$78:I$138))*IF(Mod_5=*1.34394*,1)

ERG Table X2 Row Title	Associated detail	Implementation instructions
R6. ERG estimated comparator costs (Binary switch Mod_6)	ERG_Reworked_Drug_Costs(final).xlsx	In Sheet 'Appendix dose and BSA', **Replace** formula in cell M75 by =SUMPRODUCT(($D$78:$D$138)*(M$78:M$138)) *IF(Mod_6=1,1.032214,1) **Replace** formula in cell N75 by =SUMPRODUCT(($D$78:$D$138)*(N$78:N$138)) *IF(Mod_6=1,1.032214,1) **Replace** formula in cell S75 by =SUMPRODUCT(($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$138)) *IF(Mod_6=1,1.53137,1) **Replace** formula in cell Z75 by =SUMPRODUCT(($D$78:$D$138)*(Z$78:Z$138)) *IF(Mod_6=1,1.53137,1) **Replace** formula in cell AF75 by =SUMPRODUCT(($D$78:$D$138)*(AF$78:AF$138)) *IF(Mod_6=1,0.898964,1) **Replace** formula in cell AG75 by =SUMPRODUCT(($D$78:$D$138)*(AG$78:AG$138)) *IF(Mod_6=1,0.898964,1) **Replace** formula in cell AM75 by =SUMPRODUCT(($D$78:$D$138)*(AM$78:AM$138)) *IF(Mod_6=1,0.80107,1) **Replace** formula in cell AN75 by =SUMPRODUCT(($D$78:$D$138)*(AN$78:AN$138)) *IF(Mod_6=1,0.80107,1) **Replace** formula in cell AT75 by =SUMPRODUCT(($D$78:$D$138)*(AT$78:AT$138)) *IF(Mod_6=1,1.231349,1) **Replace** formula in cell AU75 by =SUMPRODUCT(($D$78:$D$138)*(AU$78:AU$138)) *IF(Mod_6=1,1.231349,1) **Replace** formula in cell AZ75 by =SUMPRODUCT(($D$78:$D$138)*(AZ$78:AZ$138)) *IF(Mod_6=1,1.19404,1) **Replace** formula in cell BA75 by =SUMPRODUCT(($D$78:$D$138)*(BA$78:BA$138)) *IF(Mod_6=1,1.19404,1)

ERG Table X2 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	'Model parameters':Q13 must be set to "Maximum number of cycles"	In Sheet 'Model parameters', **Replace** formula in cell R17 by =IF(Mod_9=1,600,6) **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

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Eribulin for treating locally advanced or metastatic breast cancer after chemotherapy [ID964]

You are asked to check the ERG report from Liverpool reviews and implementation group (Lrig) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Monday 5th September 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Date of company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 7 of the ERG report it is stated: "In **July** 2016 the company submitted evidence relating to two different subgroups of the licensed population, one relating to the licence that was valid in 2012 and the other to the 2014 licence."	In **June** 2016 the company submitted evidence relating to two different subgroups of the licensed population, one relating to the licence that was valid in 2012 and the other to the 2014 licence.	This is a factual inaccuracy and needs correcting as it implies that the company did not meet the evidence submission deadline of the 17th June, which is not correct.	This is a typographical error, text amended

Issue 2 Proportion of patients receiving vinorelbine and gemcitabine in the cost effectiveness scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 23 in Table 3 of the ERG report it is stated: "Cost effectiveness scenario analysis: 57% of population received vinorelbine and 43% received gemcitabine" On page 64 of the ERG report it is stated: "In a scenario analysis, the company also considered a comparator arm in which patients, rather than being treated with TPC, were treated with either vinorelbine monotherapy (57%) or gemcitabine monotherapy (43%)."	Page 23: Cost effectiveness scenario analysis: 50% of population received vinorelbine and 50% received gemcitabine Page 64: In a scenario analysis, the company also considered a comparator arm in which patients, rather than being treated with TPC, were treated with either vinorelbine monotherapy (50%) or gemcitabine monotherapy (50%.	This is a factual inaccuracy. It does not reflect the proportions in the cost effectiveness evidence submitted by the company and therefore needs correcting. In Table 1 (decision problem) on page 15 of the company submission, it states: "Sensitivity analysis scenario comparator - *mix of 50% gemcitabine and 50% vinorelbine (including both oral and IV formulation).* Selected as an alternative set of comparators for subgroup 2 in order to reflect the final scope."	This is a typographical error, text amended

Issue 3 Additional incorrect text in Table 6 of the report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 34 in Table 6 of the ERG report in the Study 301 column it is stated: "Medications disallowed included: other investigational drugs; anti-tumour therapies including chemotherapy, hormone therapy, radiation therapy, gene therapy, biologics, or immunotherapy, any drugs not allowed concomitantly with the selected TPC, according to the relevant package insert "	Medications disallowed included: other investigational drugs; anti-tumour therapies including chemotherapy, hormone therapy, radiation therapy, gene therapy, biologics, or immunotherapy.	This is a factual inaccuracy. The additional text at the end of the sentence is relevant for the EMBRACE trial only. It does not apply to Study 301 and therefore needs to be removed.	This is a typographical error, text amended

Issue 4 Proportion of patients on capecitabine discontinuing due to adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 51 of the ERG report it is stated: "…discontinuations due to AEs were all marginally lower for patients treated with vinorelbine (11.5%), capecitabine (**10.9**%) and gemcitabine (10.9%)…"	…discontinuations due to AEs were all marginally lower for patients treated with vinorelbine (11.5%), capecitabine (**11.4**%) and gemcitabine (10.9%)…	This is a factual inaccuracy. The EMBRACE CSR states that 11.4% of patients on capecitabine discontinued due to adverse events and therefore this needs correcting.	This is a typographical error, text amended

Issue 5 Data sources for adverse event values in model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 67 of the ERG report it is stated: "For costs, an additional criterion of 'AEs that require treatment or hospitalisation' is also applied. **The original data sources are difficult to determine within the model.**"	For costs, an additional criterion of 'AEs that require treatment or hospitalisation' is also applied. The original data sources for adverse events were the EMBRACE patient level data."	This is a factual inaccuracy and needs correcting as it implies that the company has not been clear regarding the source of the data which is not true. It states in the model and on page 174 at the bottom of Table 65 of the company submission that the source is "Study 305 patient level data".	See amended text in Section 5.3.6

Issue 6 Projective functions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 82 of the ERG report in Figure 5 it is stated: "Company base case Eribulin OS projection" "Company base case TPC OS projection" On page 12 of the ERG report, it is stated: "However, the company has used projective functions to model patient OS and PFS experience over the whole model time horizon." On page 14 of the ERG report it is stated: "Projective functions, rather than mature EMBRACE trial survival data, have been used within the company model to reflect patient PFS and OS experience. This has led to inaccurate estimates of the efficacy of eribulin versus TPC "	"Company sensitivity scenario analysis OS projection" "Company sensitivity scenario analysis TPC OS projection" Page 12: As requested by the ERG, as a sensitivity scenario analysis, the company has used projective functions to model patient OS and PFS experience over the whole model." Page 14: This wording needs to be amended to reflect that in the company submission, the 5 year time horizon has been selected as basecase scenario with the model being based exclusively on within trial patient level data with no extrapolation required to reduce uncertainty. The longer time horizons and extrapolation were only included as sensitivity scenario analyses upon ERG request.	This is a factual inaccuracy and needs correcting as it does not accurately reflect the company submission. As stated in the company submission on pages 134 and 135, the 5 year time horizon has been selected as basecase scenario with the model being based exclusively on within trial patient level data with no extrapolation required to reduce uncertainty. The company believes that this timeframe approximates a lifetime projection in the model patient population. The longer time horizons and extrapolation was included in the submission as a sensitivity scenario analysis in response to a specific request from the ERG during the decision problem meeting.	See amended text in Sections 1.5, 1.8.2 and in Section 5.5.2 under the sub heading "Overall survival" (pages 81 to 82) See also amended legend in Figure 5

Issue 7 Progression-free survival extrapolation – company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 83 of the ERG report it is stated: **"Progression-free survival** The company has fitted Weibull parametric curves to both sets of trial data, extending non-zero PFS values well beyond the maximum time at which patients were observed to remain progression-free (23 and 25 months), and replaced all of the K-M trial PFS data with the modelled alternative estimates."	**Progression-free survival** The company has used a time-to-event non-parametric Kaplan-Meier estimator reflecting the curves derived by the Kaplan-Meier survival functions estimated based on patient-level data.	This is a factual inaccuracy and the ERG report text needs to be amended in order to reflect the description of the analysis as mentioned in the manufacturer's submission. As described in the company submission on page 139 in section 5.3, Eisai has used time-to-event non-parametric Kaplan-Meier estimator reflecting the curves derived by the Kaplan-Meier survival functions estimated based on patient-level data.	See amended text in Section 5.5.2 under the sub heading "Progression-free survival"

Issue 8 Progression-free survival extrapolation – ERG modification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 83 of the ERG report it is mentioned: "There is, therefore, no need to carry out any projective modelling of PFS and so the ERG has used the K-M data directly. Re-running the K-M PFS analysis indicates that the accurate value for the mean PFS gain attributable to eribulin compared to TPC is 40.4 days (95% CI 13.0 to 67.8 days). However, the company base case results suggest a difference of just 8.2 days. When the ERG replaces the company Weibull curves with the original trial PFS data, the model estimated PFS gain increases to 40.2 days (95% CI 13.0 to 67.8 days)."	The wording should reflect the proposed amends as a result of issue 7 and the difference between the ERG modification (using investigator review patient level data) and the data the company has used in their submission and model (independent patient level data).	In response to clarification questions, the company provided the ERG with detailed KM analysis results for PFS based on investigator review patient level data. The ERG has therefore rerun PFS K-M curves using investigator review patient-level data. However, as stated in the company submission on page 139, section 5.3, in the cost effectiveness model, a time-to-event non-parametric Kaplan-Meier estimator was developed utilising the PFS patient level data as reported in the independent review. Therefore, the comparison between the two K-M PFS curves is inaccurate and the ERG report needs to be amended accordingly.	See amended text in Section 5.5.2 under the sub heading "Progression-free survival" See also amended text in Sections 1.5 and 1.8.2

Issue 9 Post-progression survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 84 of the ERG report it is stated: "Examination of the PPS K-M data from the EMBRACE trial, which was provided by the company in response to a clarification request, has led the ERG to have serious doubts as to the reliability of the provided data. Post-progression survival analysis includes only those patients whose 'progression event' was a non-fatal progression i.e. excluding any patients who died prior to the time of disease progression." On page 12 of the ERG report it is stated: "The ERG has serious doubts about the reliability of the PPS K-M data provided in response to a clarification request and, therefore, was unable to estimate directly the extent of any survival benefit (or disbenefit) arising after disease progression."	Examination of the PPS K-M data from the EMBRACE trial, which was provided by the company in response to a clarification request, has led the ERG to conclude that the company had misinterpreted the clarification question and had not provided the relevant data. Post-progression survival analysis includes only those patients whose 'progression event' was a non-fatal progression i.e. excluding any patients who died prior to the time of disease progression." Page 12: The company had misinterpreted the ERG clarification question and had not provided the relevant PPS K-M data and, therefore, the ERG was unable to estimate directly the extent of any survival benefit (or disbenefit) arising after disease progression."	This is a factual inaccuracy as the wording is misleading and may be interpreted that Eisai intentionally provided unreliable data. The ERG clarification question B1-c stated: "Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis stratified by treatment arm (eribulin vs TPC)." As indicated by the aforementioned clarification request, insufficient information was given regarding the preferences of the ERG on the analysis to be performed. Thus, it would be inaccurate to doubt the reliability of the provided data since Eisai was not aware of the exact preferences of the ERG group.	This is not a factual inaccuracy. The ERG did not receive any request to further specify what it was asking for in clarification question B1-c and so could only conclude, on analysis, that the data was unreliable. However, the company's proposed amendment still makes the point that the ERG was not able to use the PPS data provided, so the text has been amended. See also amended text in Section 1.5

Issue 10 Commercial in confidence information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 85 of the ERG report, Table 34 includes information on the cost of eribulin which is not highlighted as commercial in confidence information.	Please underline and highlight in blue the costing information on eribulin in Table 34.	This information incorporates a PAS discount and thus needs to be indicated as commercial in confidence in the report.	Data now marked as commercial in confidence information

Issue 11 Dose Intensity

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 86 of the ERG report it is stated: *"**Dose intensity*** The company model features a parameter to represent dose intensity as measured in the EMBRACE trial. However, this does not have any effect on the estimated cost of treatments, nor on the company base case ICER per QALY gained. The cost of treatment is only affected when the company's alternative mode of calculating drug costs (without wastage) is employed*."*	The wording should reflect the fact that dose intensity was intended by the company to be a fixed variable within the model.	The text seems to imply a malfunction in company's model which is not accurate and needs to be amended.	This is not a factual inaccuracy and no changes have been made to the report. The ERG could not find any reference in the CS to the fact that dose intensity was intended to be a fixed variable. Regardless, the ERG would expect the company to include an estimate of uncertainty in all variables, and therefore it is important to mention it in our report.

Issue 12 Dose capping

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 86 of the ERG report it is stated: "**Dose capping** Within the company model, the number of patients continuing on therapy is estimated using the company's PFS estimate. However, a close examination of the company logic indicates that the long-term PFS data included in the model are set to zero for all time periods after 43 months for the eribulin arm and after 41 months for the comparator arm. This arbitrary measure results in a small bias leading to a slightly higher estimated ICER per QALY gained. Applying the ERG's preferred PFS K-M data removes this bias."	The wording should reflect that the company has used time-to-event non-parametric Kaplan-Meier estimator reflecting the curves derived by the Kaplan-Meier survival functions estimated based on patient-level data.	This is a factual inaccuracy and the ERG report text needs to be amended in order to reflect the description of the analysis as mentioned in the manufacturer's submission. As described in the company submission on page 139 in section 5.3, Eisai has used time-to-event non-parametric Kaplan-Meier estimator reflecting the curves derived by the Kaplan-Meier survival functions estimated based on patient-level data.	See amended text in Section 5.5.6

Issue 13 Probabilistic sensitivity analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 86 of the ERG report it is stated: "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." On page 94 of the ERG report it is stated: **"PSA**: the company has not adequately explored the impact of parameter uncertainty."	The wording should reflect the fact that the company provided a stochastic variability PSA utilising distributions around the variables, rather than mentioning that no probabilistic ICER was generated.	This is a factual inaccuracy and the ERG report text needs to be amended in order to reflect the description of the analysis as mentioned in the manufacturer's submission. A stochastic variability PSA was provided in section 5.8 of the company submission (pages 187-189) based on distribution around the variable estimates. ERG's preference over a regression-based PSA could be characterised as fair but the ERG report should not indicate that this was an inadequate exploration of the PSA from the company.	This is not a factual inaccuracy and no changes have been made to the report. Any PSA required by NICE must include the effects of parameter correlations, which frequently reveal important non-linearities in resulting ICERs. The probabilistic distributions shown by the company therefore fail to provide the committee with essential information on the full extent of uncertainty in the model results.

Issue 14 Health-related utility values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 87 of the ERG report it is stated: "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 analysis. It is particularly remarkable that the value used in the model for patients with stable disease (but not responding to treatment) is very similar to the value for progressed disease (0.69 versus 0.68), which the ERG considers implausible." On page 94 of the ERG report it is stated: "**HRQoL**: the utility value employed by the company to represent HRQOL in the progressed health state is implausible."	Page 87 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 analysis. It is particularly remarkable that the value used in the model for patients with stable disease (but not responding to treatment) is very similar to the value for progressed disease (**0.70** versus 0.68). Page 94: **HRQoL:** the utility value used in the model for patients with stable disease is very similar to the value for progressed disease (**0.70** versus 0.68).	Eisai consider the characterisation "implausible" assigned to the progressed disease utility values as inaccurate. In addition, the value reported for stable disease is incorrect and needs to be amended as per the proposed wording. Metastatic Breast Cancer (MBC) patients at these late lines of therapy are very familiar with the concept of progression both from a physical and psychological point of view. Therefore, the small decrement between pre and post progression should not be received at such a great surprise. Moreover, as stated in manufacturer's submission on page 196, Lloyd et al, 2010 utilities were elicited based on preferences from members of the general public through a vignette study. In contrast, utility values used within manufacturer's economic evaluation have been estimated – through a mapping exercise - based on patient-level HRQoL data collected through the study 301 using QLQ-C30 instrument. The preference of using study 301 extracted utility values within the cost utility assessment was due to	This is a typographical error, text amended

		the fact that the aforementioned values are extracted through patient-reported outcomes rather than members of the public and thus are more robust.	

Issue 15 Subsequent lines of chemotherapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 88 of the ERG report it is stated: *"*The company references a study by Kantar Health 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."	Change 60% to 29.5% (mean of the 22%-37% range).	The aforementioned calculations are inaccurate and need to be amended since: • Specific data have been provided from line 3 and onwards. Thus, data from earlier lines should not have been considered. • Table 45 in the manufacturer's submission on page 139 shows that apart from patients dying, there is a great proportion of patients that do not receive the next line of therapy. The percentage of patients transitioning from third to forth and from forth to fifth line ranges between 22%-37%.	This is not a factual inaccuracy and no changes have been made to the report. The ERG has calculated the proportion of surviving patients who go on to the next line of therapy in the Kantar paper, and these yield values clustered around 60% across the different patient subgroups and the different phases of treatment. Therefore the ERG used 60% as an approximation when estimating the costs of subsequent treatment received to the patients surviving at each cycle. Using the unadjusted percentages in the Kantar paper within the model is incorrect.