NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

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 one prior chemotherapy regimen [ID1072]

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 one prior chemotherapy regimen

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

1

Key decision points

Clinical effectiveness

- What are the current treatment options? Is there high unmet need?
- Is capecitabine the most appropriate comparator?
- Are the people in study 301 generalizable to patients in England for whom eribulin would be considered?
- Do the results show eribulin is effective compared with capecitabine?
- What is the committee's view of the relationship between progression-free and overall survival?

Cost effectiveness

- Is it appropriate to model a progression-free survival benefit?
- Is the survival benefit likely to be pre- or post-progression?
- Which are the most plausible utility values for progressive disease? The company's or ERG's?
- Are treatment costs realistic? Is the 8 month cap on primary and secondary treatment duration appropriate?
- What is the most plausible ICER? Does eribulin meet the end of life criteria?

2

Background

- Eribulin for treating locally advanced or metastatic breast cancer **after two** prior chemotherapy regimens in the advanced setting (subgroup 2 in the company submission) was appraised separately last year as a review of Technology Appraisal 250 (2012), and was subsequently recommended in Technology Appraisal 423 (published December 2016)
- Subgroup 1 in the company submission included a subgroup analysis of patients with HER2-negative disease that had progressed **after one prior chemotherapy regimen** in the advanced setting which is the focus of this appraisal.
- The company were given opportunity to submit new evidence / an updated analysis for this appraisal, but declined
- Consultees and commentators given opportunity to update or replace their statements, but no revised statements have been received

3

HER, human epidermal growth factor receptor

Locally advanced or metastatic breast cancer

- Breast cancer arises from the tissues of the ducts or lobules of the breast. 'Locally advanced' describes tumours larger than 5cm that may have grown into the skin or muscle of the chest or nearby lymph nodes
- 'Metastatic' describes disease that has spread to another part of the body, such as bones, liver or lungs
- 46,417 people diagnosed with breast cancer in England in 2014
- Approximately 9,600 deaths from breast cancer in 2015
- Approximately 13% of people with invasive breast cancer have locally advanced or metastatic disease at diagnosis
- Around 35% of those with early or locally advanced disease will progress to metastatic breast cancer
- 5-year survival rate for metastatic breast cancer in England is 15%
- Company estimate there are approximately 2,660 patients with locally advanced or metastatic breast cancer that has progressed after one prior chemotherapeutic regimen for advanced disease

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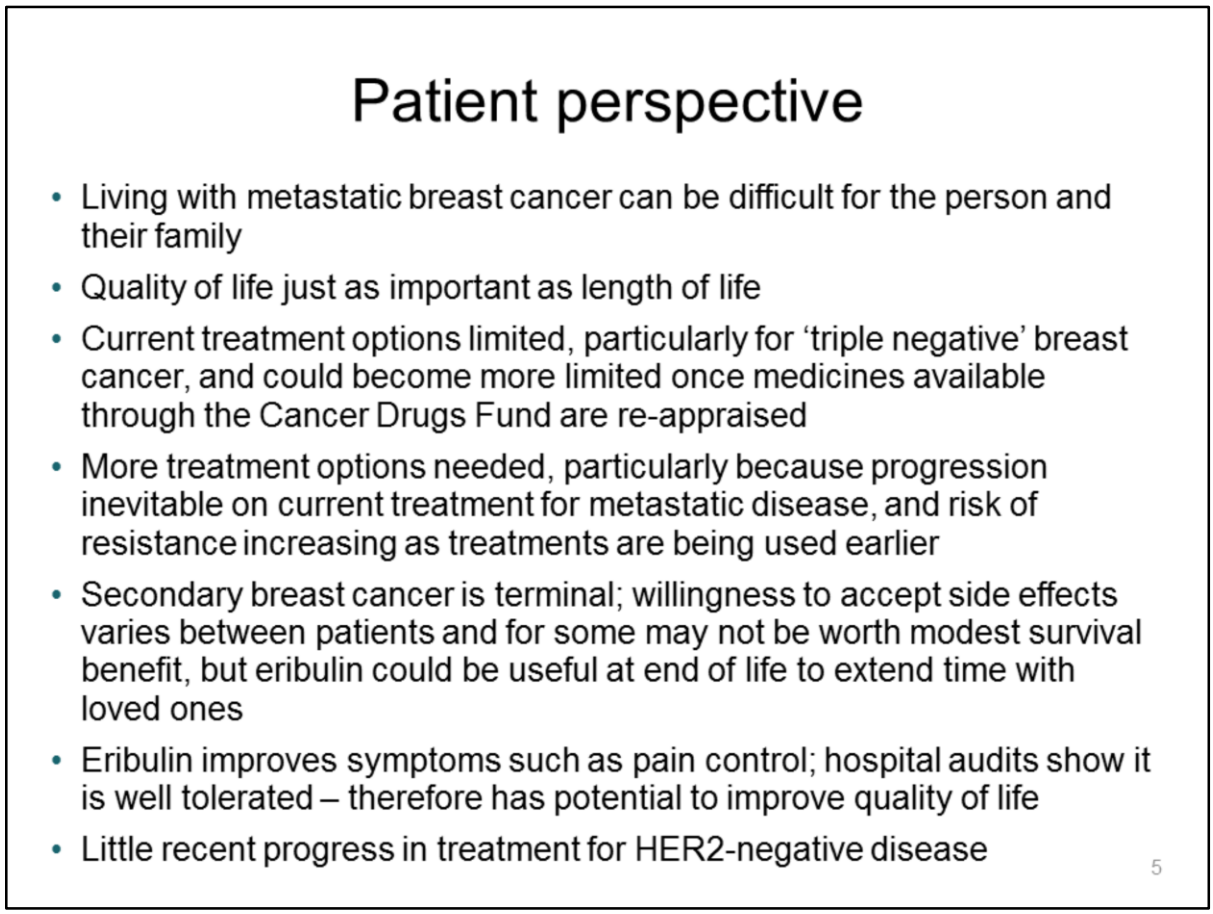
Source: NICE scope (with statistics updated where appropriate, using data from Cancer Research UK and Office for National Statistics)
Source: Company submission: section 6 (page 199)



Source: Breast Cancer Now submission

ER, oestrogen receptor; HER, human epidermal growth factor receptor; PR, progesterone receptor

Triple negative breast cancer is where the tumour is ER-, HER2- and PR-, so the cancer has no receptors and therefore no targeted medicines

Audits undertaken at UK hospitals in over 200 patients receiving eribulin through the Cancer Drugs Fund (after 2 prior chemotherapy regimens)

Eribulin (Halaven)
Eisai

Mechanism of action	Synthetic analogue of halichondrin.B, which inhibits tubulin polymerisation. This disrupts the assembly and formation of microtubules, stopping cancer cell division.
Marketing authorisation	For the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least 1 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.
Administration	Intravenously, over 2 to 5 minutes on days 1 and 8 of 21-day cycle
Dose	1.23 mg/m^2 (ready made solution)
Stopping	Anticipated number of repeat courses of treatment: 6 Dose delay or reduction for grade 3 or 4 adverse events
Cost (list price)	£361 per 2 ml vial (eribulin mesilate equivalent to 0.88 mg eribulin), £541.50 per 3 ml vial (1.32 mg) Patient access scheme approved by Department of Health, which provides simple discount to list price

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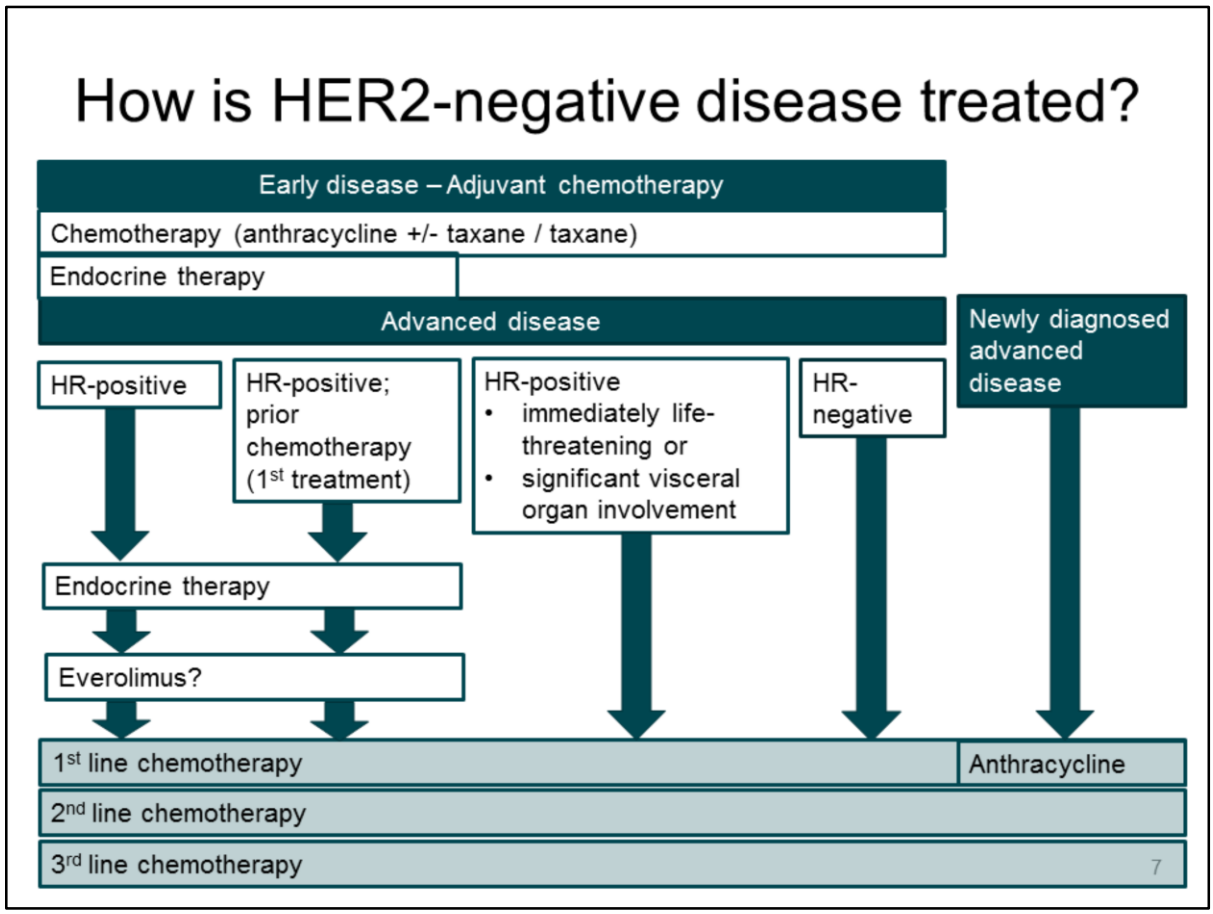
Source: Company submission: section 2.2 (page 26); Table 4 (page 28)

Eribulin was first granted a marketing authorisation for the treatment of 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). This was extended in 2014 to include treatment after one prior therapy.

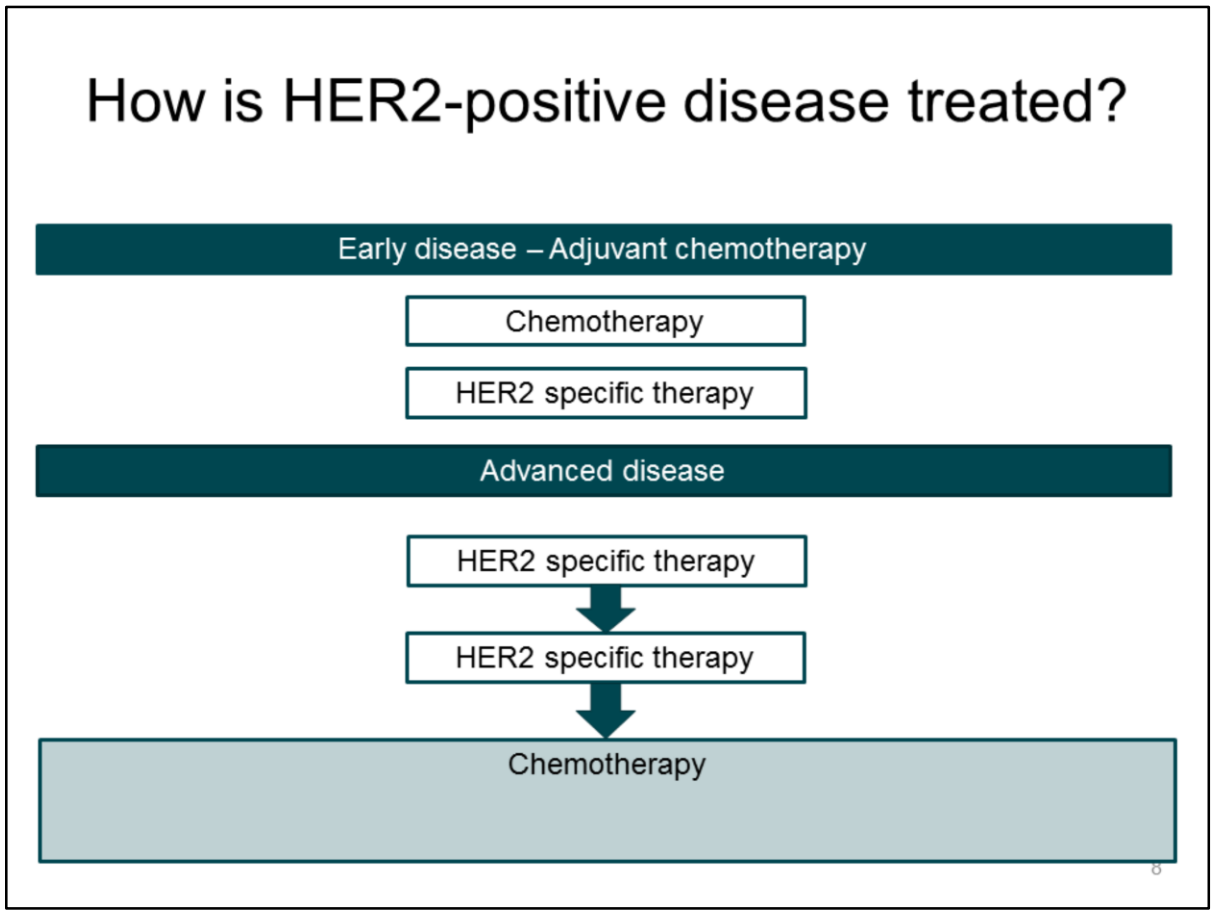
The anticipated number of repeat courses of treatment is based on the median number of cycles of treatment in the trial (6 months in Study 301)

Lower doses recommended for patients with impaired liver function.



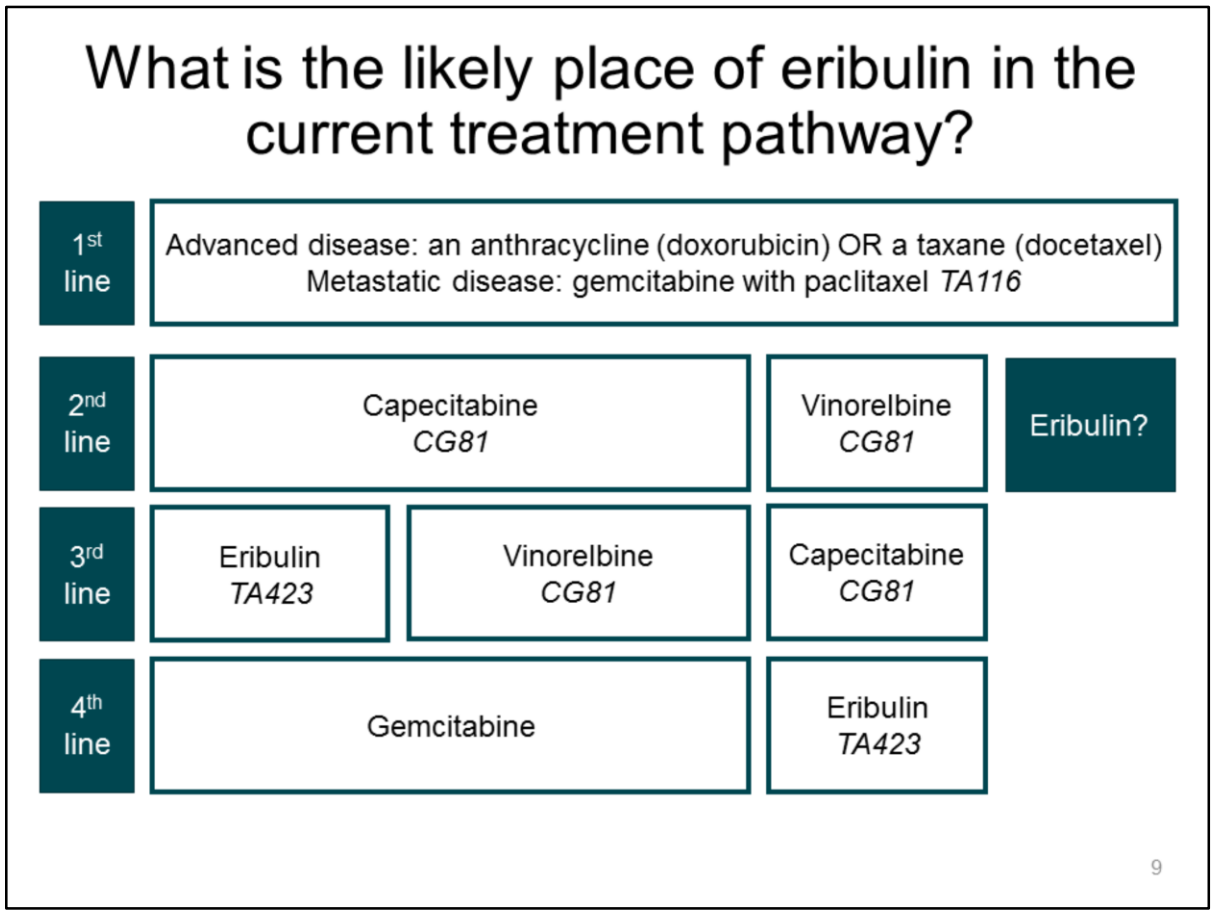
Source: NICE clinical guideline 81: Advanced breast cancer: diagnosis and treatment (Last updated 2017)

HR, hormone receptor; HER, human epidermal growth factor receptor



Source: NICE clinical guideline 81: Advanced breast cancer: diagnosis and treatment (Last updated 2017)

HR, hormone receptor; HER, human epidermal growth factor receptor



Source: NICE Technology Appraisal 423: Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (2016)
Source: NICE clinical guideline 81: Advanced breast cancer: diagnosis and treatment (Last updated 2017)

A taxane is offered if an anthracycline is contraindicated or has been received at an earlier stage in the treatment pathway.

Eribulin was available through the Cancer Drugs Fund for locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens, before being recommended in Technology Appraisal 423.

Decision problem

Comparison of NICE scope and company submission

NICE scope	Company submission
Population Adults with locally advanced or metastatic breast cancer that has progressed after 1 prior chemotherapeutic regimen for advanced disease (anthracycline and a taxane, unless these treatments were not suitable)	**Population** HER2-negative patients with locally advanced or metastatic breast cancer, whose disease has progressed after 1 prior chemotherapy regimen in the advanced setting. Company: 85% locally advanced/metastatic breast cancer is HER2-negative; pre-treated HER2-negative disease not eligible for targeted therapies so unmet clinical need; eribulin most effective in this group ERG agrees
Comparators • Capecitabine • Vinorelbine • Gemcitabine	**Comparators** • Capecitabine ERG agrees main comparator • Vinorelbine included in sensitivity analysis • Gemcitabine not included: not recommended (CG81) and not routinely used ERG agrees
Outcomes: Overall survival; Progression-free survival; Response rate; Adverse effects of treatment; Health-related quality of life	

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Source: NICE scope; Company submission: section 1.1, Table 1 (pages 13-17); Company's clarification response: A2(a) (pages 2-3); ERG report: section 3.1 (pages 24-25), 3.3 (page 26)

While the ERG accepts the arguments about the relevance of the subgroup of patients with HER2-negative disease, it notes advice from clinicians that they would not want to limit treatment with eribulin to patients with HER2-negative disease.
It also notes that the company did not present evidence according to ER status; clinical advice is that patients with HER2-negative and ER-positive disease may also represent a difficult to treat population. *Source: ERG report: section 3.6 (page 27)*

Note: the small proportion of patients with HER2-positive disease in the trial may also have been eligible for trastuzumab emtansine at 2nd line.

Clinical-effectiveness evidence

Company submission, section 4

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Key trial
Study 301

Design	Phase III, open-label, multi-centre, randomised controlled trial
Population	**1,102** patients with locally advanced or metastatic breast cancer that have received **up to 3 prior chemotherapy regimens** (≤2 for advanced disease) including an anthracycline and a taxane **but not capecitabine**
Intervention	Eribulin (as per licensed dosing regimen) **n=554**
Comparator	Capecitabine **n=548**
Primary outcomes	• Overall survival • Progression-free survival
Secondary outcomes	• Objective response rate • Health-related quality of life • Adverse effects
Follow-up	5 years
Subgroups	• HER2 status and geographical region
Subgroup 1	The remit of this appraisal is people who have progressed after **one prior chemotherapy** regimen in the advanced setting. The **company base case is the HER2-negative subgroup only** [12]

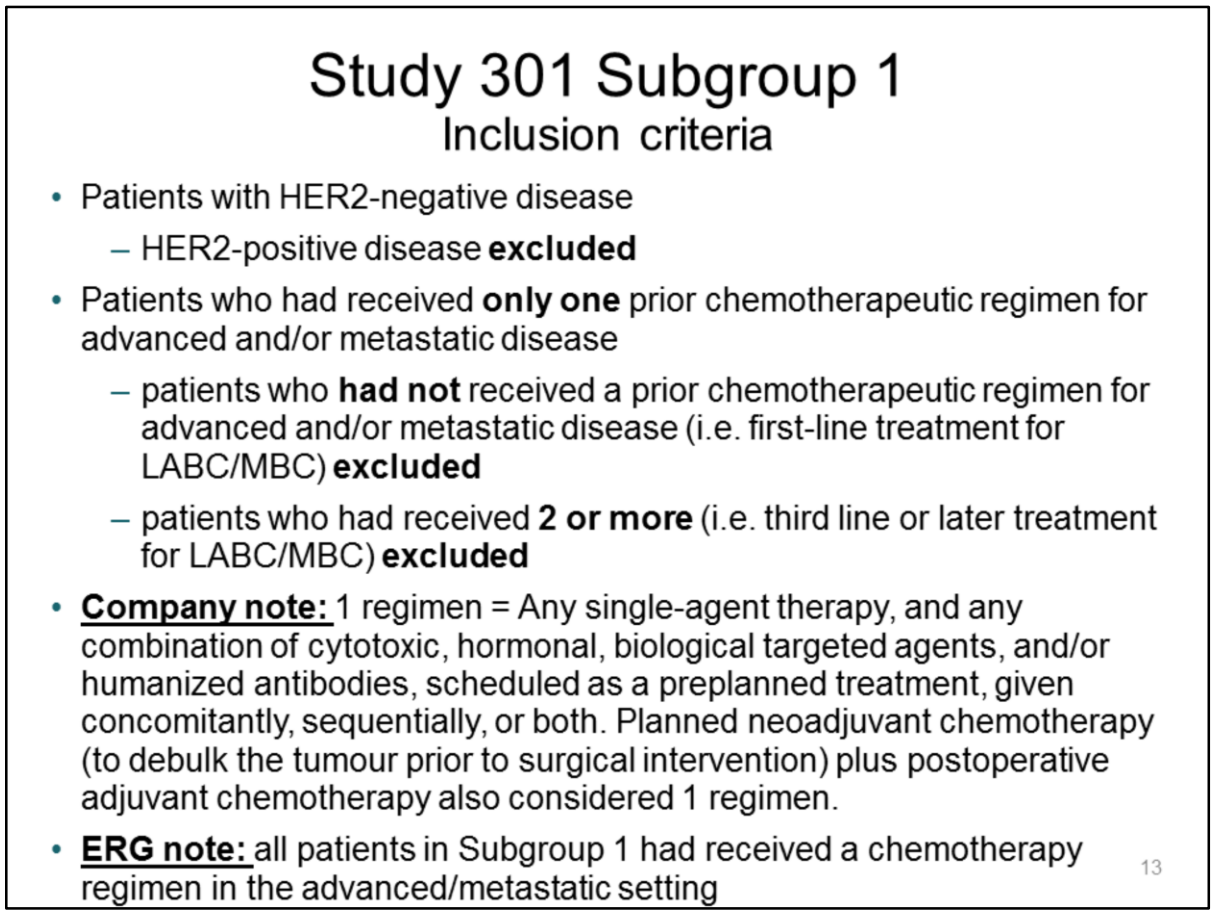
Source: Company submission: section 4.2, Table 7 (pages 48-49); section 4.3 (pages 50-51, 55)

Company rationale for choosing a subgroup of patients with HER2-negative disease within the subgroup of patients having had 1 prior chemotherapy is that:

- approximately 85% patients with locally advanced or metastatic breast cancer have HER2-negative disease,
- there is unmet clinical need for patients with HER2-negative disease because they are not eligible for targeted treatments, and
- eribulin is most effective in this group.

Numbers of patients in the Study 301 subgroups:

	Eribulin	Capecitabine
Patients with 1 prior therapy	280 50.5% total patients	293 53.5% total patients
Patients with 1 prior therapy and HER2-negative disease	186 66.4% patients with 1 prior therapy	206 70.3% patients with 1 prior therapy



Source: Company submission: section 4.3, Table 8 (pages 52-53)

LABC, locally advanced breast cancer; MBC, metastatic breast cancer

Note: MA is for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least 1 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.

ERG: It is unclear how many patients also received a chemotherapy regimen in the adjuvant setting from the company submission but according to the CSR (Table 12), for the overall trial population, [redacted] patients had received no prior adjuvant regimens

It is unclear how many patients had received prior hormonal therapy from the company submission but according to the CSR (Table 12), for the overall trial population, [redacted] had received prior hormonal therapy (537 [48.7%] patients were deemed to be ER-positive in the overall trial population with ER status unknown for 178 [10.5%])

Patient characteristics

Subgroup 1 (HER2-negative disease; 1 prior therapy)

	Eribulin (n=186)	Capecitabine (n=206)
Median age (range)	55 years (31 to 74 years)	52 years (30 to 80 years)
Geographic region		
North America, Western Europe, Asia	46 (24.7%)	56 (26.9%)
Eastern Europe	99 (53.2%)	112 (54.4%)
Latin America, South Africa	41 (22.0%)	38 (18.4%)
ER status		
Positive	104 (55.9%)	116 (56.3%)
Negative	82 (44.1%)	87 (42.2%)
Unknown	0 (0.0%)	3 (1.5%)
Triple negative (ER/PR/HER2)	73 (39.2%)	72 (35.0%)
Number of organs involved		
1	37 (19.9%)	27 (13.1%)
2	59 (31.7%)	62 (30.1%)
≥3	90 (48.4%)	117 (56.8%)

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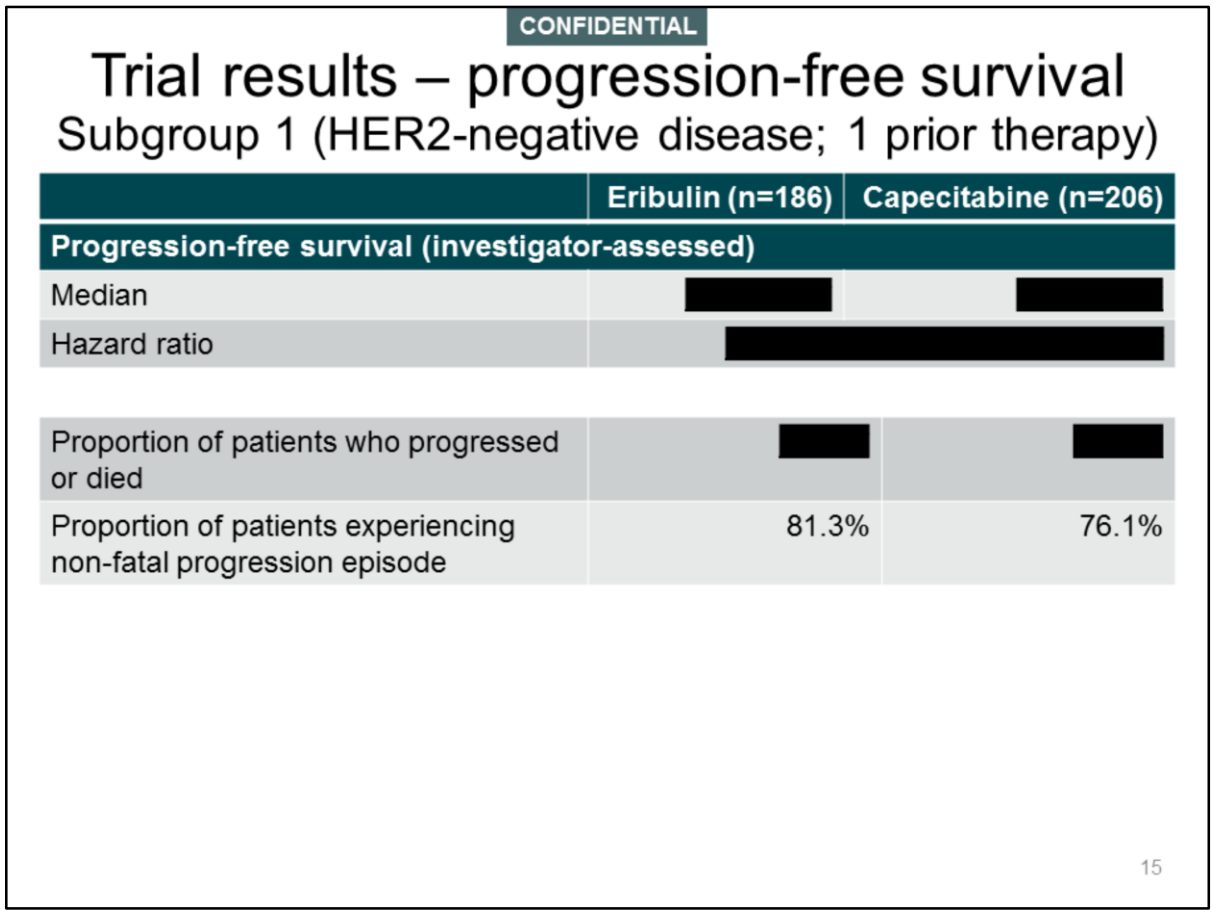
Source: Company submission: section 4.8, Table 30 (page 104); Company's clarification response: Table 3 (page 9)

LABC, locally advanced breast cancer; MBC, metastatic breast cancer; ER, oestrogen receptor; HER, human epidermal growth factor receptor; PR, progesterone receptor



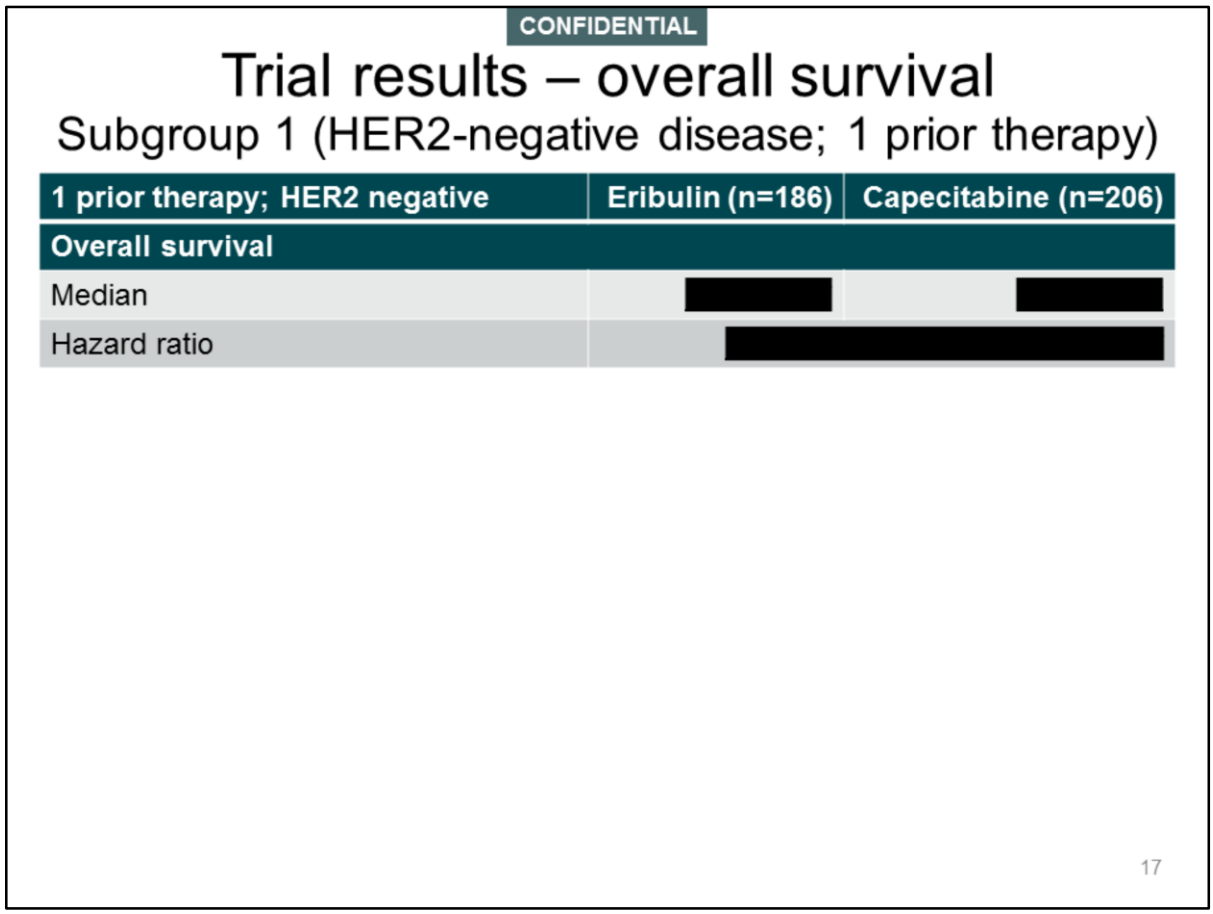
Source: Company submission: section 4.8 (page 105); ERG report: section 4.4.1 (page 33); ERG report: section 5.4.2 (page 73)

ERG notes subgroup 1 is a post-hoc subgroup analysis and therefore has reduced statistical power.

Note: Results from Subgroup 2 used in TA423 (eribulin after 2 prior chemotherapies):

	Eribulin n=370	TPC n=189
Median overall survival	13.0 months	10.1 months
Hazard ratio	0.78 (95% CI 0.65, 0.94) p=0.008	
Median progression-free survival	3.6 months	2.1 months
Hazard ratio	0.68 (95% CI 0.56, 0.83) p=0.001	

Source: Company submission: section 4.8, Figure 20 (page 105)



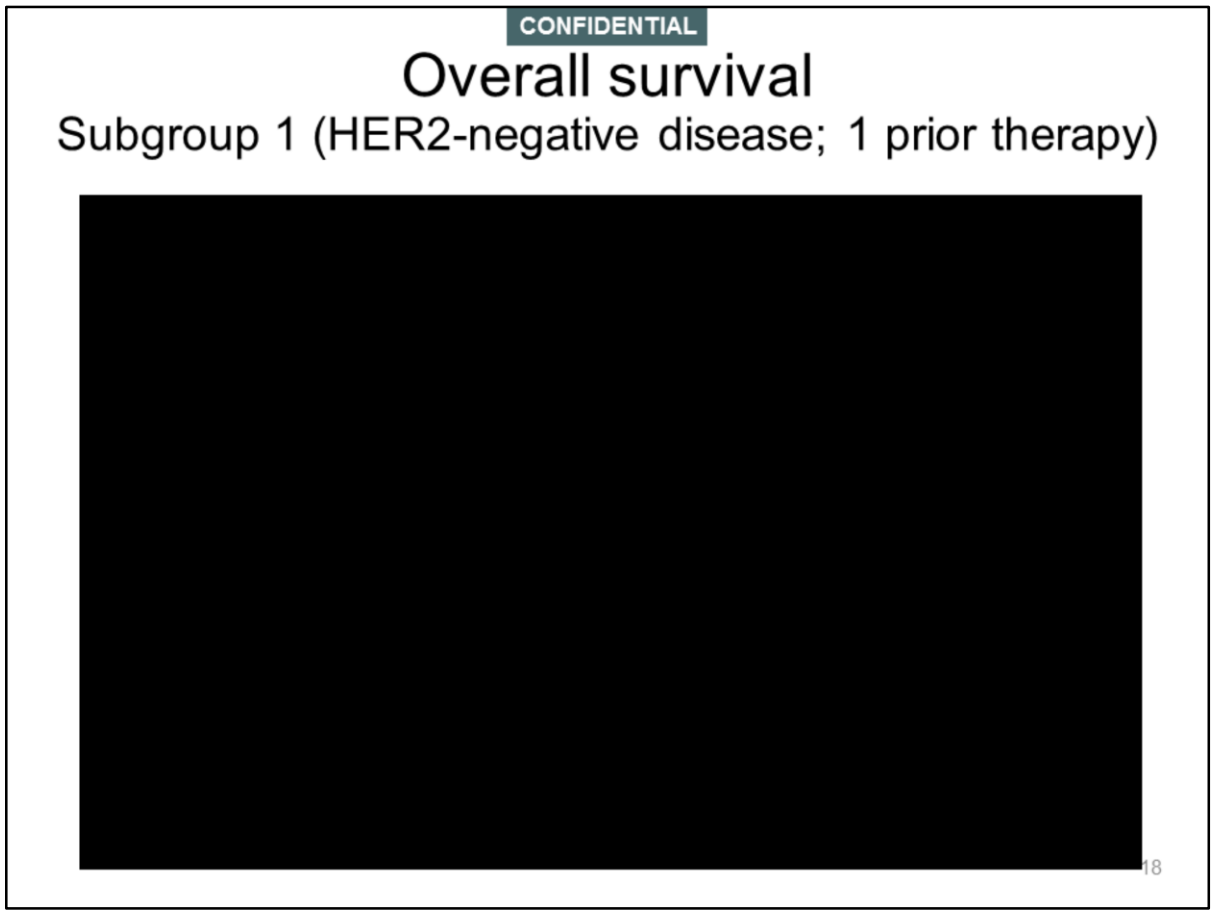
Source: Company submission: section 4.8 (pages 104-105); ERG report: section 4.4.1 (page 33)

ERG notes subgroup 1 is a post-hoc subgroup analysis and therefore has reduced statistical power.

Results from the intention-to-treat population not presented because they are not relevant to the decision problem (some patients have had more than 1 prior chemotherapy regimen). For information, they can be found in the *company submission: section 4.7, Table 24 (page 87); Table 26 (page 91)*.

Note: Results from Subgroup 2 used in TA423 (eribulin after 2 prior chemotherapies):

	Eribulin n=370	TPC n=189
Median overall survival	13.0 months	10.1 months
Hazard ratio	0.78 (95% CI 0.65, 0.94) p=0.008	
Median progression-free survival	3.6 months	2.1 months
Hazard ratio	0.68 (95% CI 0.56, 0.83) p=0.001	



Source: Company submission: section 4.8, Figure 19 (page 105)

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Trial results

Additional subgroup analyses

HER2 -ve; 1 prior therapy (company BC)	Eribulin n=186	Capecitabine n=206
Progression-free survival		
Median	[redacted]	[redacted]
Hazard ratio	[redacted]	
Overall survival		
Median	[redacted]	[redacted]
Hazard ratio	[redacted]	
HER2 -ve; at least 1 prior therapy	**Eribulin n=290**	**Capecitabine n=305**
Progression-free survival		
Median	4.1 months	3.9 months
Hazard ratio	0.93 (95% CI 0.78 to 1.12) p=0.461	
Overall survival		
Median	15.9 months	13.4 months
Hazard ratio	0.84 (95% CI 0.70, 1.00) p=0.048	

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Source: ERG report: section 4.7 (page 45), Table 9 (page 46)

The ERG's literature review identified 2 additional studies that were published since the company had run its evidence searches. 1 was a pooled analysis of data from Study 301 and Study 305, which was considered of little value to the appraisal because the only patients with just 1 prior chemotherapy were those from Study 301, only a few patients in Study 305 had capecitabine and many had received prior capecitabine. The other was Twelves et al. (2016), published subgroup analyses of Study 301 whose results are presented here. *Source: ERG report: section 4.2 (page 30)*

ERG notes that no overall survival benefit is shown for patients with HER2-positive disease, but that the number of patients in this subgroup may be too small to detect at statistically significant difference. *Source: ERG report: section 4.7 (page 45)*

Adverse effects
Study 301

General (safety population)	Eribulin (n=544)	Capecitabine (n=546)
Any adverse event	512 (94.1%)	494 (90.5%)
Any treatment-related adverse event	460 (84.6%)	421 (77.1%)
Any serious adverse event	95 (17.5%)	115 (21.1%)
Fatal serious adverse event	26 (4.8%)	36 (6.6%)
Any treatment-related serious adverse event	7.7%	8.1%
Adverse event leading to discontinuation	43 (7.9%)	57 (10.4%)
Adverse event leading to dose interruption	10 (1.8%)	1 (0.2%)
Common adverse events (subgroup 1)	**Eribulin (n=184)**	**Capecitabine (n=205)**
Neutropenia	98 (53.3%)	30 (14.6%)
Alopecia	64 (34.8%)	6 (2.9%)
Asthenia/fatigue	58 (31.5%)	52 (25.4%)
Nausea	38 (20.7%)	43 (21.0%)
Peripheral neuropathy	30 (16.3%)	10 (4.9%)

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Source: Company submission: section 4.12, Table 33 (page 115), Table 34 (page 116); Company's clarification response: Table 1 (pages 4-5)

The company's clarification response states that there are no notable differences in adverse events experienced in subgroup 1 compared with the overall safety population of Study 301.

Symptom burden; Quality of life

- Adverse events more common with eribulin compared with capecitabine: neutropenia; leucopenia; pyrexia; peripheral neuropathy; alopecia
- Adverse events more common with capecitabine compared with eribulin: diarrhoea; palmar-plantar syndrome
- Health-related quality of life assessed in Study 301 using EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire)
- Results available for all patients with HER2-negative disease but not specifically for Subgroup 1
- Median Global Health Status/Quality of Life scores similar in both arms
- Improved symptoms for those having eribulin compared with capecitabine: diarrhoea; nausea and vomiting; fatigue; appetite loss; insommnia
- Improved symptoms for those having capecitabine compared with eribulin: pain; dyspnoea; financial difficulties; constipation

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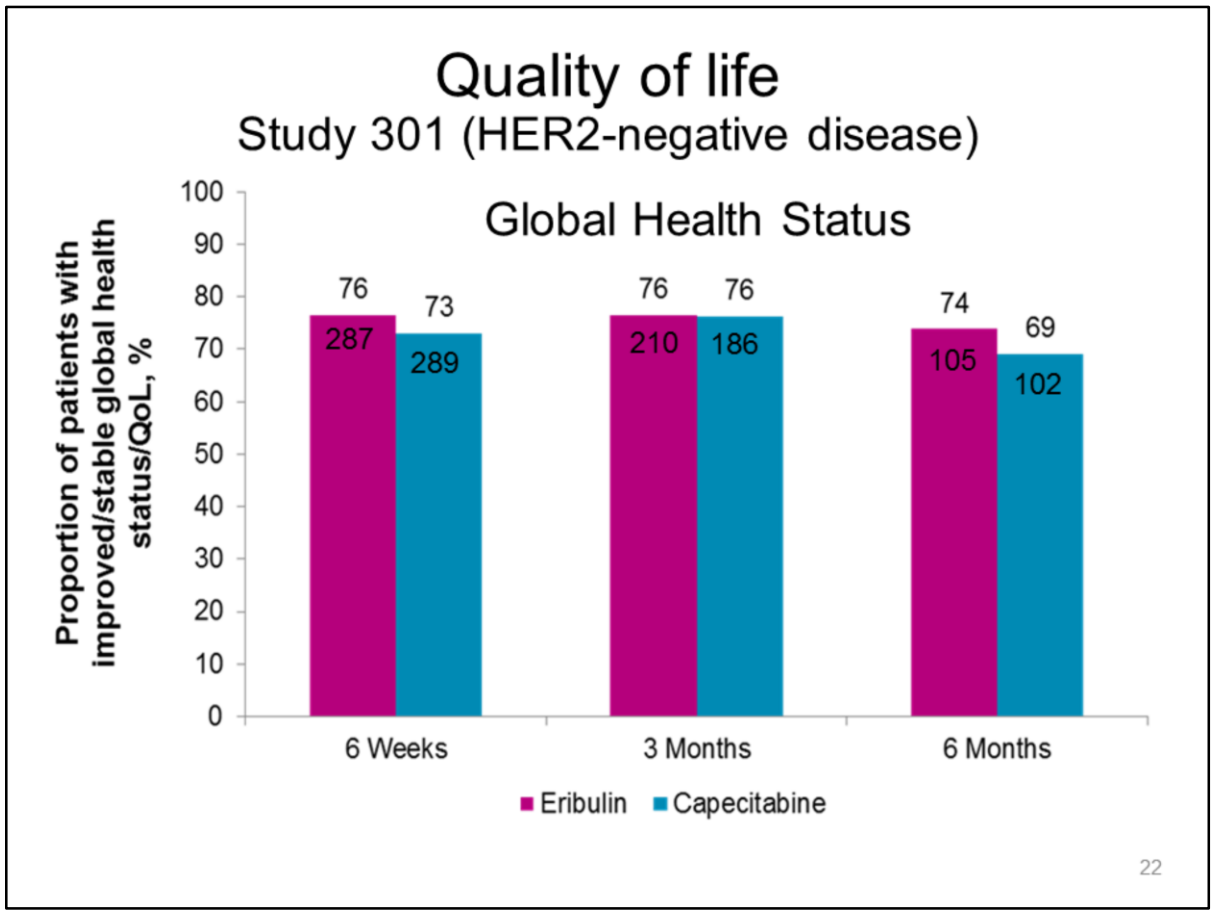
Source: Company submission: section 4.7 (pages 94-102); *Company's clarification response: B3. (page 16); ERG report: section 4.6.2 (page 41), section 4.6.3 (pages 43-44)*



Source: Company submission: section 4.3, Table 9 (page 57); section 4.7, Figure 16 (page 101), section 5.4, Figure 40 (page 151); Company's clarification response: A8 (pages 12-13)

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 Global Health Status/QoL scale.
3 functional scales (physical, emotional, social) and 4 symptom scales (constipation, diarrhoea, pain, sleep) are converted to EQ-5D for use in the economic model.

ERG's critique
Clinical effectiveness

- Capecitabine is the most appropriate comparator
- Study 301 generally well designed and conducted with low risk of bias
- Post-hoc subgroup analyses have reduced statistical power
- Health-related quality of life data should be treated with caution because of small proportion of patients completing the questionnaire
- Trial results show:
  - Statistically significant overall survival benefit for eribulin compared with capecitabine in HER2-negative disease after 1 prior therapy
  - Trend towards overall survival benefit for eribulin compared with capecitabine in HER2-negative disease after at least 1 prior therapy
  - No statistically significant difference in progression-free survival for eribulin compared with capecitabine in HER2-negative disease after 1 prior therapy or after at least 1 prior therapy

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Source: ERG report: sections 3.3 (page 26), 4.2 (page 30), 4.3 (page 31), 4.6.3 (pages 43-44), 4.8 (page 48)

Cost-effectiveness evidence

Company submission, section 5

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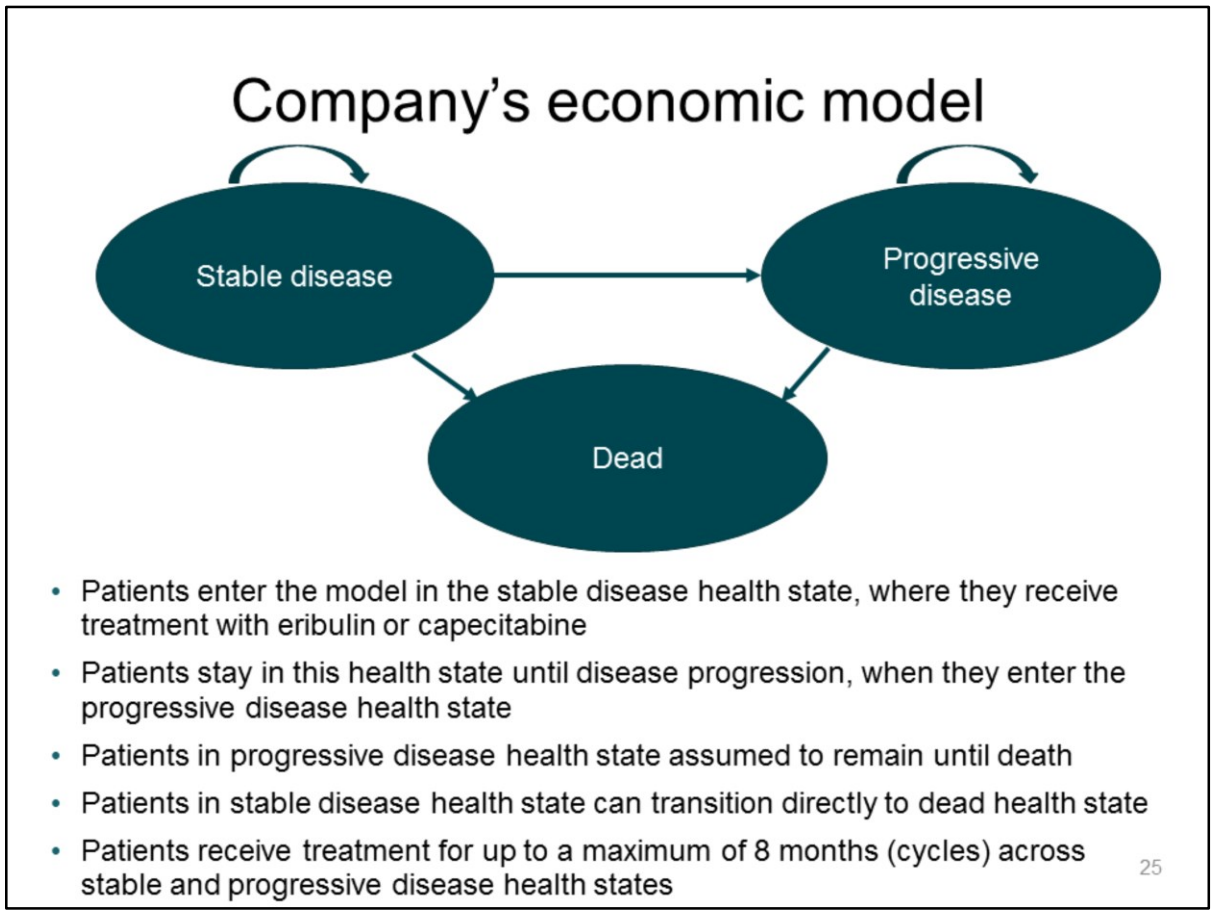


Source: Company submission: section 5.2, Figure 26 (page 134)

Company's economic model

Structure

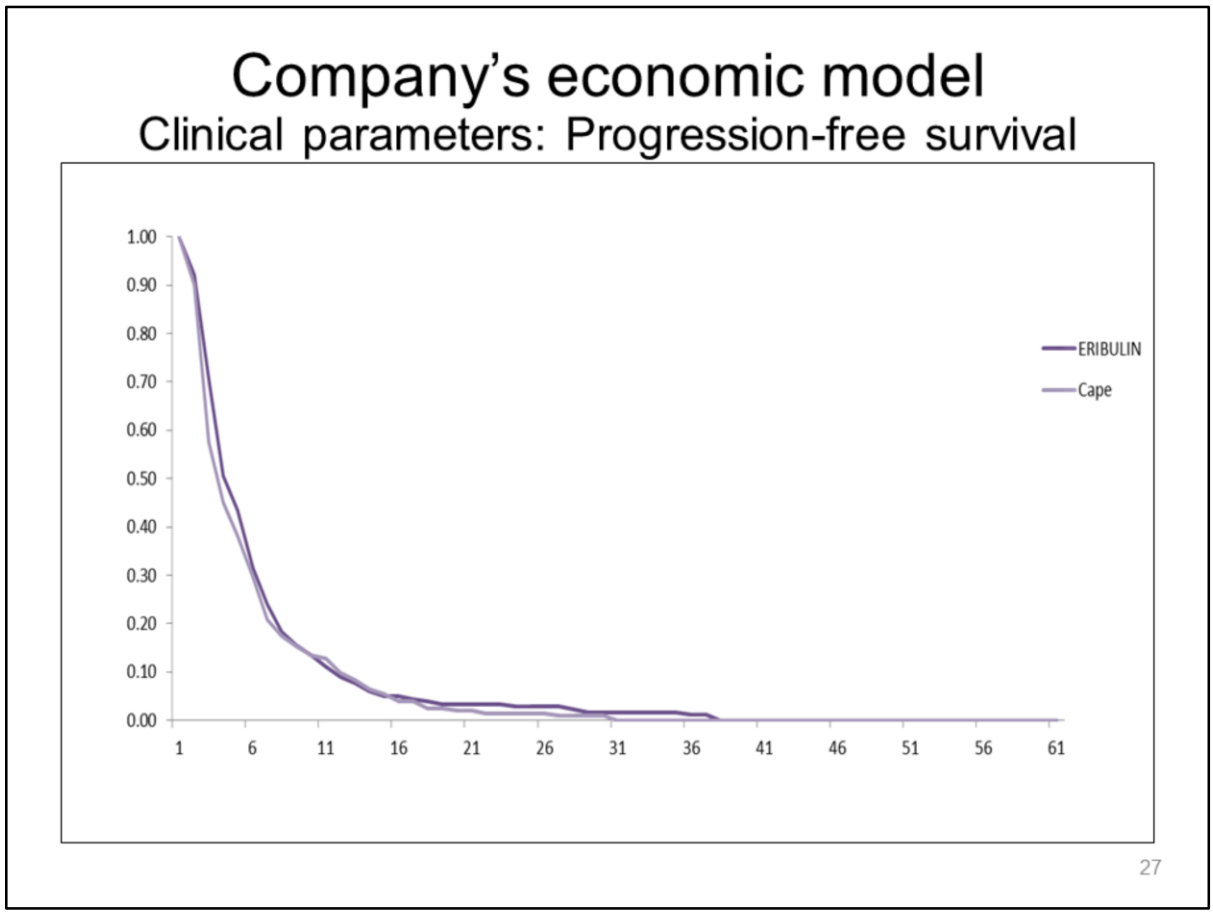
Type	Partition survival
Population	HER2-negative patients with locally advanced or metastatic breast cancer whose disease has progressed after 1 prior chemotherapy regimen in advanced setting
Comparator	Capecitabine; *sensitivity analysis explored capecitabine (50%) and vinorelbine (50%)*
Time horizon	5 years *(10 and 20 years explored in sensitivity analysis)*
Cycle length	1 month (maximum treatment duration of 8 months across stable and progressed disease health states, in both arms)
Measure of effects	Quality-adjusted life years
Discounting	3.5%
Perspective	NHS/PSS
Transition probabilities	Derived from Kaplan-Meier curves from Study 301, subgroup 1 results • Progression-free survival • Overall survival

26

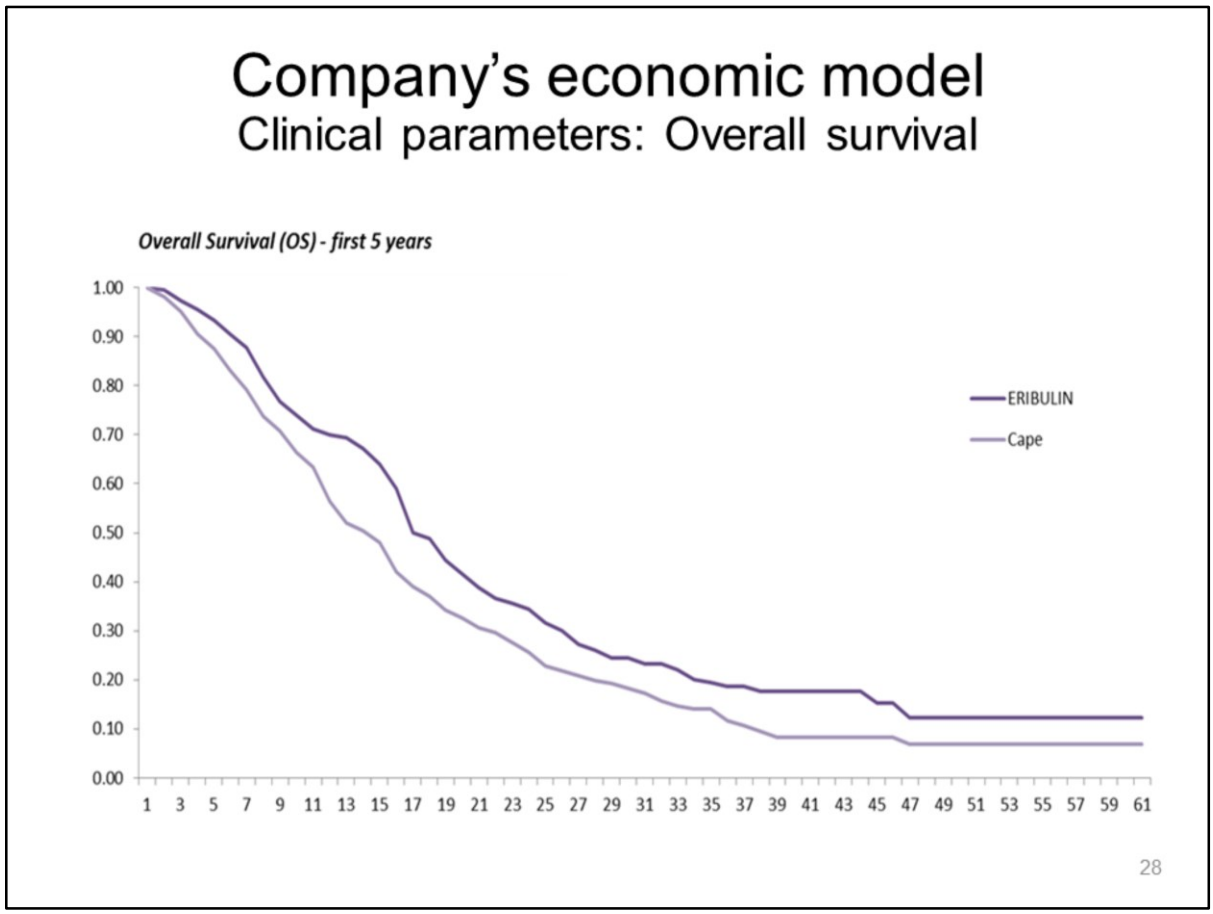
Source: Company submission: section 5.2, Figure 26 (pages 133-135); Table 42 (page 136), (pages 137-138); Company's clarification response: Table 2 (page 8)

Note: The company's model also includes the functionality to model stopping treatment at disease progression.
Note: The Summary of Product Characteristics does not include a stopping rule.

Duration of secondary treatments in progressive disease health state linked to duration of primary treatment in stable disease health state. 8 months derived from Kantar Health study which shows proportion of breast cancer patients progressing between lines of therapy from 1st to 5th. Aggregated average number of cycles after 1 prior chemotherapy and onwards estimated to be 7.3494 months.
Source: Company submission: section 5.2 (pages 137), Table 43 (page 138); Company's clarification response: Table 4 (page 11)



Source: Company submission: section 5.3, Figure 27 (page 140)



Source: Company submission: section 5.3, (page 140), Figure 28 (page 141)

Company: The study was initiated 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. 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, 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.

Company's economic model

Health utility values

- Health-related quality of life data from Study 301 (EORTC QLQ-C30) mapped to EQ-5D utility scores using regression algorithm
- Algorithm developed using data from people with locally advanced breast cancer and good baseline health status (Crott and Briggs, 2010)
- Disutility values associated with adverse events calculated using data from Study 301 (grade 3 or 4 adverse events occurring in >2% patients, plus alopecia [in response to feedback during TA250])
- Stable disease utility scores adjusted for tumour response and disutility
- For progressive disease health state, both arms assigned aggregate utility values of the total study population

Health state	Eribulin	Capecitabine
Stable disease	0.705	0.697
Progressive disease	0.679	0.679

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Source: Company submission: section 5.4, Figure 40 (page 151), pages 160-164, Table 56 (page 164), Table 58 (page 166)
EORTC: European Organisation for Research and Treatment of Cancer
QLQ: Quality of Life Questionnaire

Relevant studies from systematic literature review related to Study 301 data. Health utility values specific to subgroup 1 from Study 301 are not available *(see Company's clarification response: B3. (page 16)*

TA250: Committee noted that alopecia is an important consideration for patients at this stage of treatment because they may already have experienced hair loss earlier in the treatment pathway, and so disutility associated with alopecia should be included in the model.

Note: In TA423 committee agreed the small decrease between stable and progressive disease that was obtained from Crott and Briggs was not plausible. Lloyd et al. values were considered more relevant; resulted in ~20% decline from stable to progressive disease; considered high by clinical experts. Committee concluded most plausible value likely to be in between. Using the Lloyd et al. utility values for progressive disease increased the company's ICER by about £11,000.

Company's economic model

Resource use and costs

Treatment costs	**Average dose of treatment**: calculated based on average body surface area of 1.74m^2 (CI 1.72, 1.76), derived from UK survey data (Sacco et al., recommended by ERG in TA250) **Drug wastage**: costs included (if more than 10% dose required from next pack, next pack used and remainder accounted for as wasted) **Dose intensity**: 0.87 eribulin; 0.86 capecitabine (mean relative dose intensities from Study 301) **Treatment duration**: capped at 8 months so all treatment costs end after 8 cycles **Subsequent therapies**: comprised vinorelbine, gemcitabine, taxanes, anthracyclines
Medical costs	In progressive health state, additional costs relating to palliative (last 6 months of life) and end of life care (last 2 weeks of life) applied
Adverse events	Grade 3/4 events with >2% prevalence needing treatment and/or hospitalisation, converted to monthly rate

Sources: NHS Reference costs 2014-15; PSSRU Unit Costs of Health and Social Care 2015; eMit electronic market information tool; MIMS; NICE clinical guideline for advanced breast cancer (CG81); TA250 feedback. Validated by expert opinion.

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Source: Company submission: section 5.2, page 135, Table 41 (page 136); section 5.5 (pages 167, 170, 172, 174)

No relevant studies identified from systematic literature review.

Secondary treatments after disease progression comprised treatments from Study 305 (subgroup 2)
Study 305 (EMBRACE) is a study of eribulin in locally advanced or metastatic breast cancer that has progressed after **at least 2** prior therapies in the advanced setting. Secondary treatments comprised the 5 most prevalent in the 'Treatment of Physician's Choice' (comparator) arm of Study 305, excluding capecitabine.

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Company's base case results (with PAS)

	Life years gained	Total		Incremental		ICER
		Costs	QALYs	Costs	QALYs	
Capecitabine	[redacted]	[redacted]	[redacted]			
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£36,244**

Probabilistic sensitivity analysis showed ICERs ranged between £27,000 and £48,000 per QALY gained	
Probability of eribulin being cost effective at £25,000 per QALY	8%
Probability of eribulin being cost effective at £30,000 per QALY	20%
Probability of eribulin being cost effective at £50,000 per QALY	70%
End of life Company made a case for eribulin meeting the end of life criteria:	
Life expectancy <2 years; Extension to life >3 months	

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Source: Company submission: section 5.7, Table 71 (page 184), section 5.8 (pages 187, 189)

Company's economic model
Deterministic sensitivity and scenario analyses

	ICER
Company's base case	£36,244
Deterministic sensitivity analysis	
Progressive disease utility (0.705/0.500)	£35,091 - £47,148
Eribulin price (+/-20%)	£32,095 - £40,394
Administration costs (+/-20%)	£34,879 - £37,610
Healthcare costs (+/-20%)	£35,622 - £36,866
Scenario analyses	
Comparator: 50% capecitabine, 50% vinorelbine (equal efficacy)	£33,654
Time horizon: 10 years	£30,217
Time horizon: 20 years (lifetime)	£29,743
Maximum treatment duration: 12 months (1° and 2° treatments)	£38,175
Drug wastage: excluded	£33,000
Adverse event costs: All grade 3/4 events experienced by >2%	£36,221

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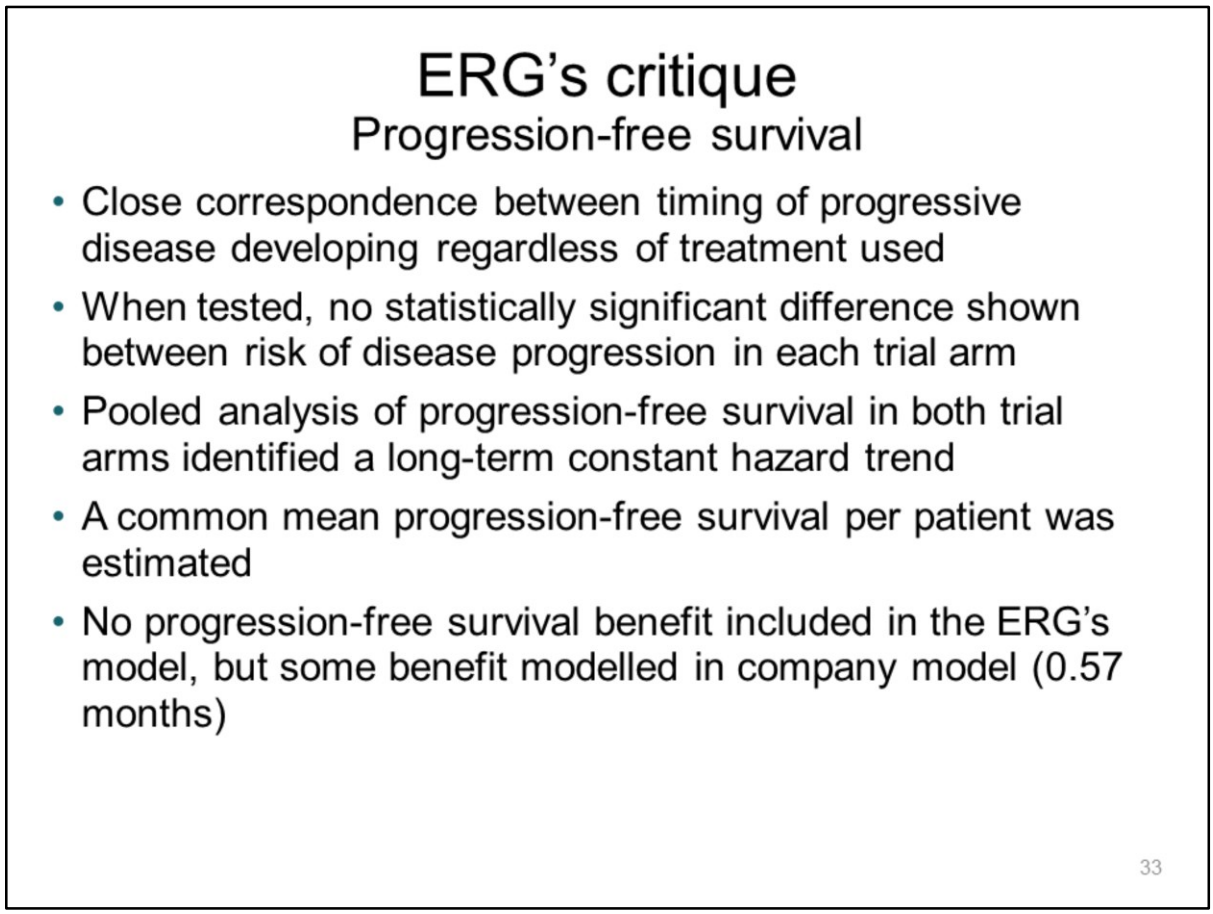
Source: Company submission: section 5.8, Table 80 (page 190), Table 81 (page 191), Table 84 (page 195)

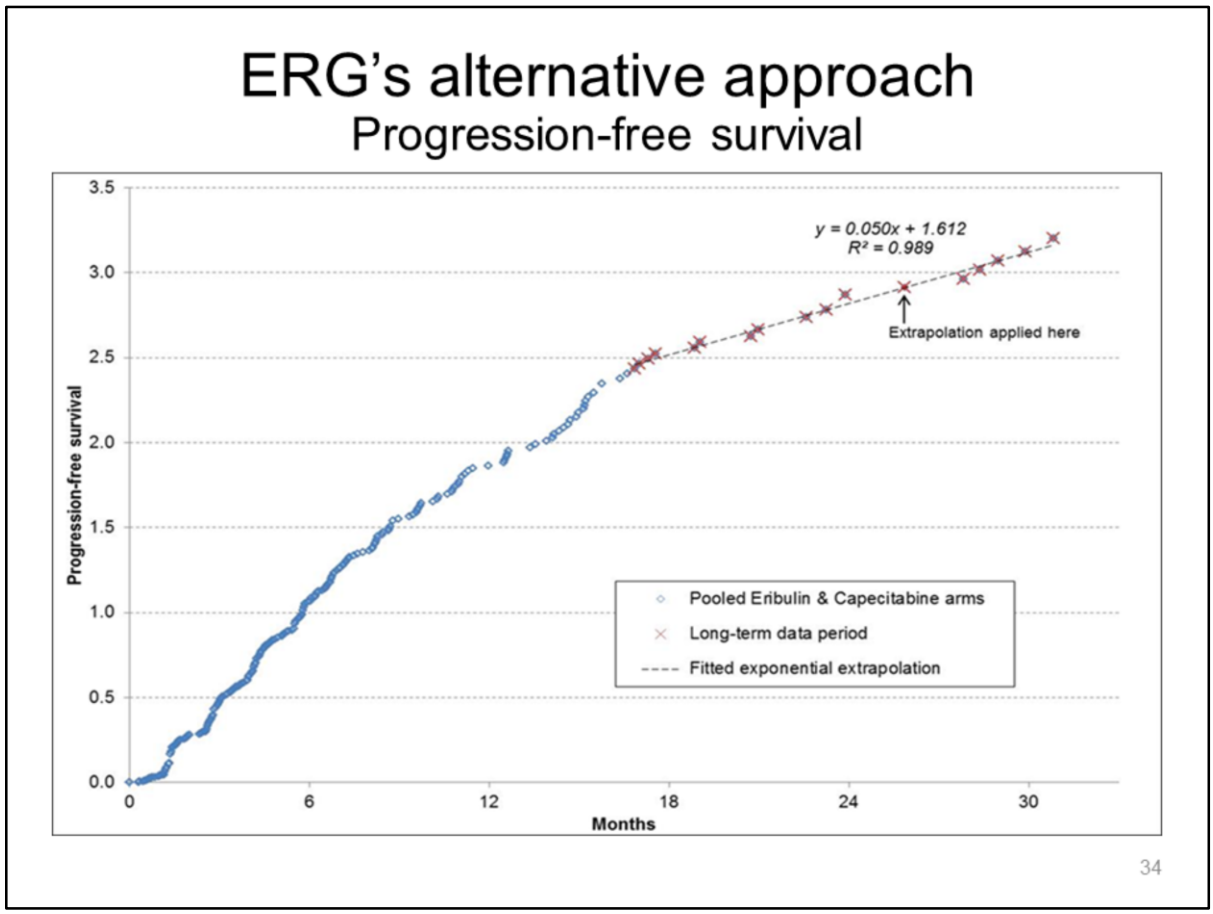
Upper limit of progressive disease utility assumes almost equal value to stable disease; lower limit the lowest value mentioned in previous NICE submissions and used in NICE guidance TA371 for trastuzumab emtansine in HER2-positive, unresectable locally advanced or metastatic breast cancer.

The scenario exploring a 50% capecitabine 50% vinorelbine comparator assumed an equal split of oral and intravenous vinorelbine formulations and that vinorelbine was equal to capecitabine in terms of efficacy, safety and health utility values *Source: Company submission: section 5.6, Table 70 (page 182)*
Note: In TA458 Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane (published July 2017), "[The clinical experts] stated that the precise clinical difference between capecitabine and vinorelbine had not been established in clinical trials, although in their opinion it would be reasonable to assume no difference."

Note: the majority of QALYs are accrued in the progressed disease health state.



Source: ERG report: section 5.4.2 (pages 71-72)



Source: ERG report: section 5.4.2, Figure 7B (page 71)

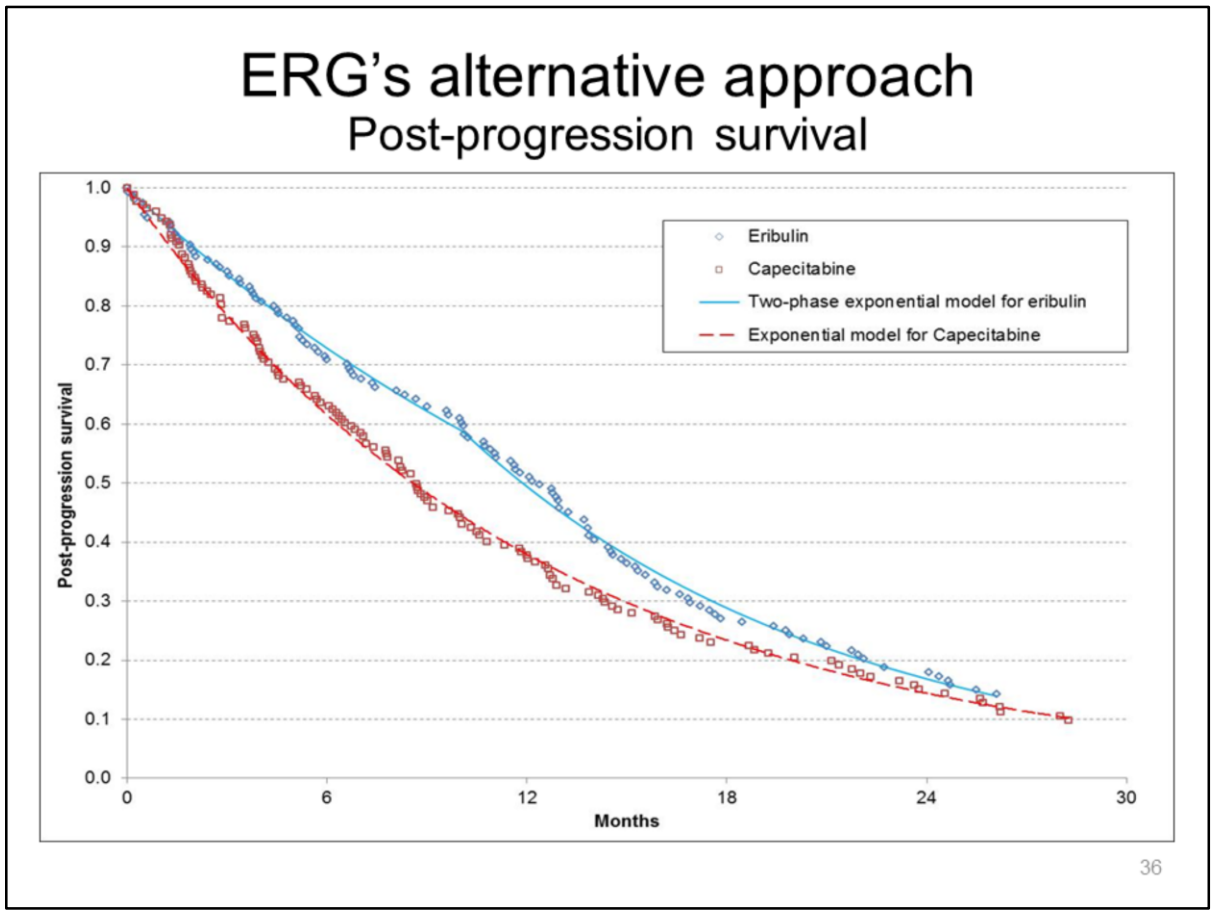
ERG's critique

Post-progression survival

- Exploratory analysis used parametric models fitted to trial data
- Potential for bias in this approach noted:
  - characteristics of patients surviving disease progression may not be well-balanced
  - proportion of non-fatal progression events differed between the 2 arms (eribulin: 81.3%; capecitabine: 76.1%)
- Exploratory analysis showed post-progression survival benefit of 2.21 months, which is less than the OS benefit modelled by the company (4.05 months) and that used in the ERG's base case (5.94 months)
- Comparison of alternative estimates shows uncertainty around additional survival benefit after progression

35

Source: ERG report: section 5.4.2 (page 73)



Source: ERG report: section 5.4.2, Figure 8 (page 73)

ERG's critique

Overall survival

- Trends in cumulative hazard plots of trial data used to identify the time point in each arm where a long-term exponential cumulative hazard trend was established:
  - 25.3 months in eribulin arm
  - 3.2 months in capecitabine arm
- Trend line applied in place of trial data at the time at which the trend line most closely replicated the trial data.
- Exponential extrapolation applied from:
  - 23.72 months in eribulin arm
  - 17.18 months in capecitabine arm
- Modelled benefit greater than company's (5.94 months compared with 4.62 months)

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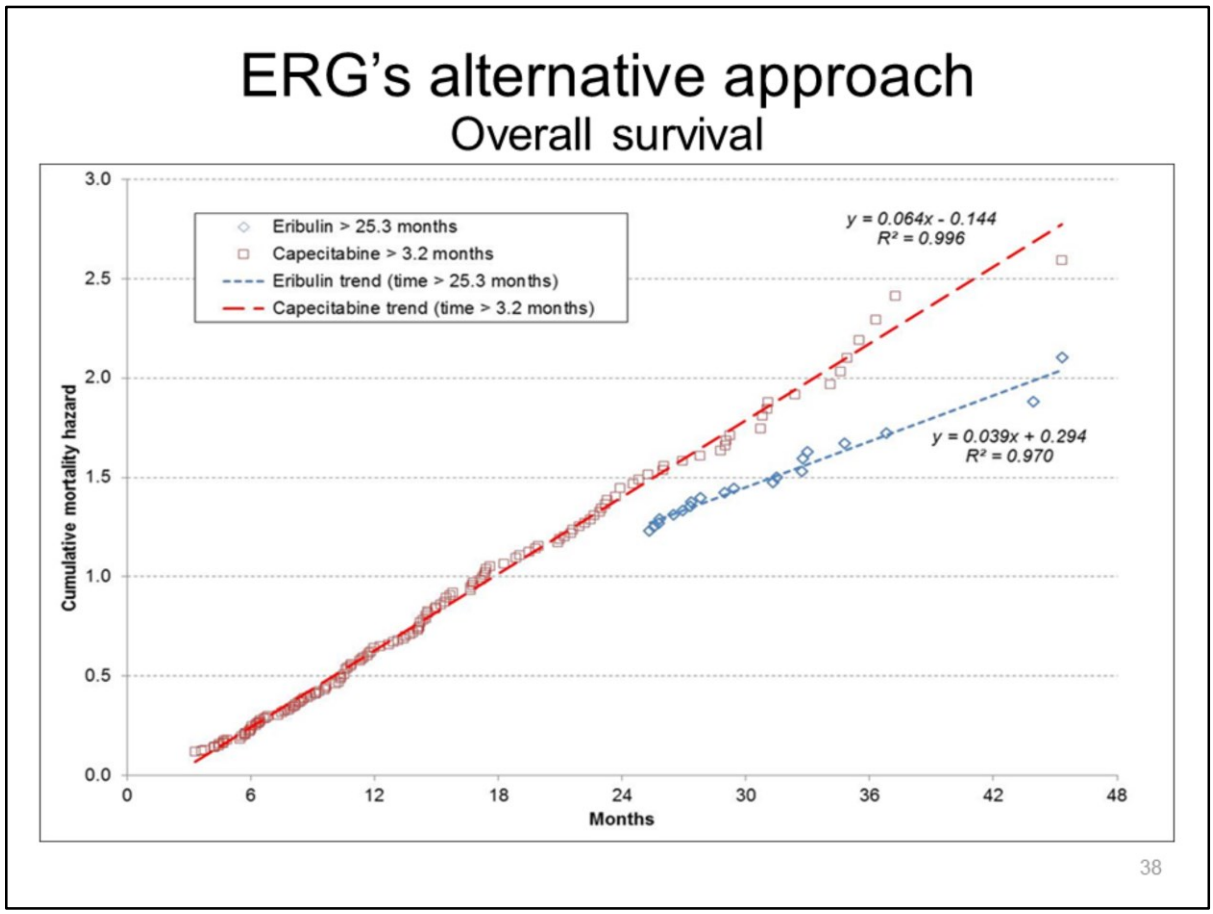
Source: ERG report: section 5.4.2 (page 69)



Source: ERG report: section 5.4.2, Figure 5 (page 70)

Modelled mean survival benefit

Comparison of company's and ERG's results

	Eribulin	Capecitabine	Net gain
Overall survival			
Company's estimates	21.75 months	17.13 months	4.62 months
ERG's estimates	23.72 months	17.78 months	5.94 months
Progression-free survival			
Company's estimates	4.56 months	3.99 months	0.57 months
ERG's estimates	7.65 months	7.65 months	0.00 months
Post-progression survival			
Company's estimates	17.19 months	13.14 months	4.05 months
ERG's estimates (OS - PFS)	16.07 months	10.13 months	5.94 months
ERG's estimates (exploratory)	19.39 months	17.18 months	2.21 months

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Source: ERG report: section 5.4.2 (pages 69-73); Company submission: section 5.3, Figure 29 (page 141)

ERG's critique

Health utility values

- Crott and Briggs (2010) algorithm based on a historical clinical trial including only untreated patients with locally advanced (not metastatic) breast cancer where only neo-adjuvant treatments were administered
- The Crott and Briggs algorithm is not appropriate because of differences in the population between Study 301 and patients in whom the mapping algorithm was developed (disease stage; line of treatment; type of treatment).
- Lloyd et al. (2006) utility values for breast cancer patients having chemotherapy have been used in TA250 and are more appropriate
- Progressive disease utility value used in company's model similar to value for stable disease which is implausible
- ERG preferred utility values in Lloyd et al. for progressive disease
- ERG's alternative utility values:

Health state	Eribulin	Capecitabine
Stable disease	0.705	0.697
Progressive disease	0.496	0.496

Source: ERG report: section 5.4.8 (page 77)

ERG's critique

Resource use and costs

- Treatment costs underestimated because of:
  - Logic errors relating to oral vinorelbine and eribulin administration
  - Method of applying average body surface area data to calculate unit costs of eribulin and other chemotherapies:
    - Range of required doses and scope for wastage is greater than that estimated by company because of calculation error (using standard error instead of standard deviation)
    - Survey data used to estimate average body surface area includes patients having adjuvant, neo-adjuvant and palliative care; these should be excluded to obtain closer match to patients in Study 301
- Treatment costs before progression may be overestimated over time because company uses PFS as a proxy for number of patients on treatment before progression; ERG prefers time to treatment discontinuation which takes account of any discontinuation before progression.

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Source: ERG report: sections 5.4.2 (page 74), 5.4.3, 5.4.4 (page 75), 5.4.5 (page 76), 5.4.10 (page 79)

ERG's critique
Treatment duration

- In the company's model treatment can either stop at progression or be capped at a maximum of 8 months (cycles) across primary and secondary treatments (stable and progressive disease)
- These 2 options both underestimate costs of secondary treatments
- A maximum number of overall treatment cycles does not take account of different responses to 3rd line treatment: patients whose disease responds well are likely to continue treatment for longer and more likely to proceed to further lines of treatment
- Stopping treatment at progression results in no costs incurred for secondary treatments: eribulin is associated with additional post-progression survival so leads to more additional lines of treatment and associated costs
- ERG applies a 3rd option to the company's model which removes the cap on the maximum number of cycles of treatment and includes the costs of secondary treatments for 60% patients with progressed disease in each cycle.

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Source: ERG report: section 5.4.9 (page 78)

The ERG includes costs of secondary treatments for 60% of patients with progressed disease in each cycle, derived from the average proportion of patients with progressed disease who go on to have an extra course of treatment in the Kantar Health data.

ERG's critique
Cost effectiveness

- Availability of an almost fully mature survival dataset allows a reliable assessment of the relative effectiveness of treatment with eribulin compared with capecitabine for the subgroup 1 population
- Probabilistic sensitivity analysis limited and cannot be relied upon to generate meaningful results because:
  - Limited number of parameters varied (survival, utility, primary and secondary treatment costs)
  - Does not account for uncertainty related to correlated values
  - Parameter uncertainty not explored sufficiently (for example, treatment costs only varied +/-10%)
- Adverse event costs may be underestimated (only 1 episode assumed)
- Alternative approaches may be more appropriate for OS and PFS estimates, progressive disease utility values and primary and secondary treatment costs (see previous slides)

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Source: ERG report: sections 1.9.1 (page 15), 1.9.2 (page 16), 5.3.9 (page 59), 5.3.12 (page 65), 5.4.6 (page 76).

ERG's changes to company's base case

	Company	ERG
OS	Direct from KM trial data	Parametric models fitted
PFS	Direct from KM trial data	Common mean PFS per patient
Utilities	Crott & Briggs (2010)	Lloyd et al. (2006)
Costs	• Pre-progression treatment derived from PFS • Logic errors (eribulin administration; oral vinorelbine) • Average BSA calculation error • Average BSA survey data including irrelevant treatments	• Pre-progression treatment derived from TTD • Logic errors corrected • Average BSA error corrected • Average BSA survey data excluding irrelevant treatments
Treatment duration	8 month cap applied across primary and subsequent treatments	No cap (subsequent treatment costs included for 60% patients post-progression)

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OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; TTD, time to treatment discontinuation; BSA, body surface area

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ERG's base case results (with PAS)

	Inc. Cost	Inc. QALY	ICER
Company's base case	[redacted]	[redacted]	**£36,244**
ERG's PFS estimates	[redacted]	[redacted]	**£50,866**
ERG's OS estimates	[redacted]	[redacted]	£37,646
Annual discounting instead of continuous	[redacted]	[redacted]	£36,111
Time to treatment discontinuation used for costs	[redacted]	[redacted]	£39,286
Unit cost: eribulin	[redacted]	[redacted]	£40,630
Unit cost: other chemotherapies	[redacted]	[redacted]	£36,021
Utility value for progressive disease	[redacted]	[redacted]	**£47,148**
Secondary treatment costs	[redacted]	[redacted]	**£47,354**
Logic error: eribulin administration costs	[redacted]	[redacted]	£39,192
Logic error: oral vinorelbine costs	[redacted]	[redacted]	£36,341
ERG's base case	[redacted]	[redacted]	**£82,743**

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Source: ERG report: section 5.5, Table 25 (page 81)

The ERG's changes highlighted in **bold** are those that have the greatest impact on the ICER.

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End of life

Criterion	Study 301 (subgroup 1) trial results	Company's modelled results	ERG's modelled results
Short life expectancy, normally less than 24 months	Mean: 17.13 months Median: [redacted]	Mean: Not presented Median: 13.24 months	Mean: 17.78 months Median: 13.02 months
Extension to life, normally a mean additional 3 months	Mean: 4.62 months Median: [redacted]	Mean: 4.61 months Median: 2.73 months	Mean: 5.94 months Median: >3.00 months

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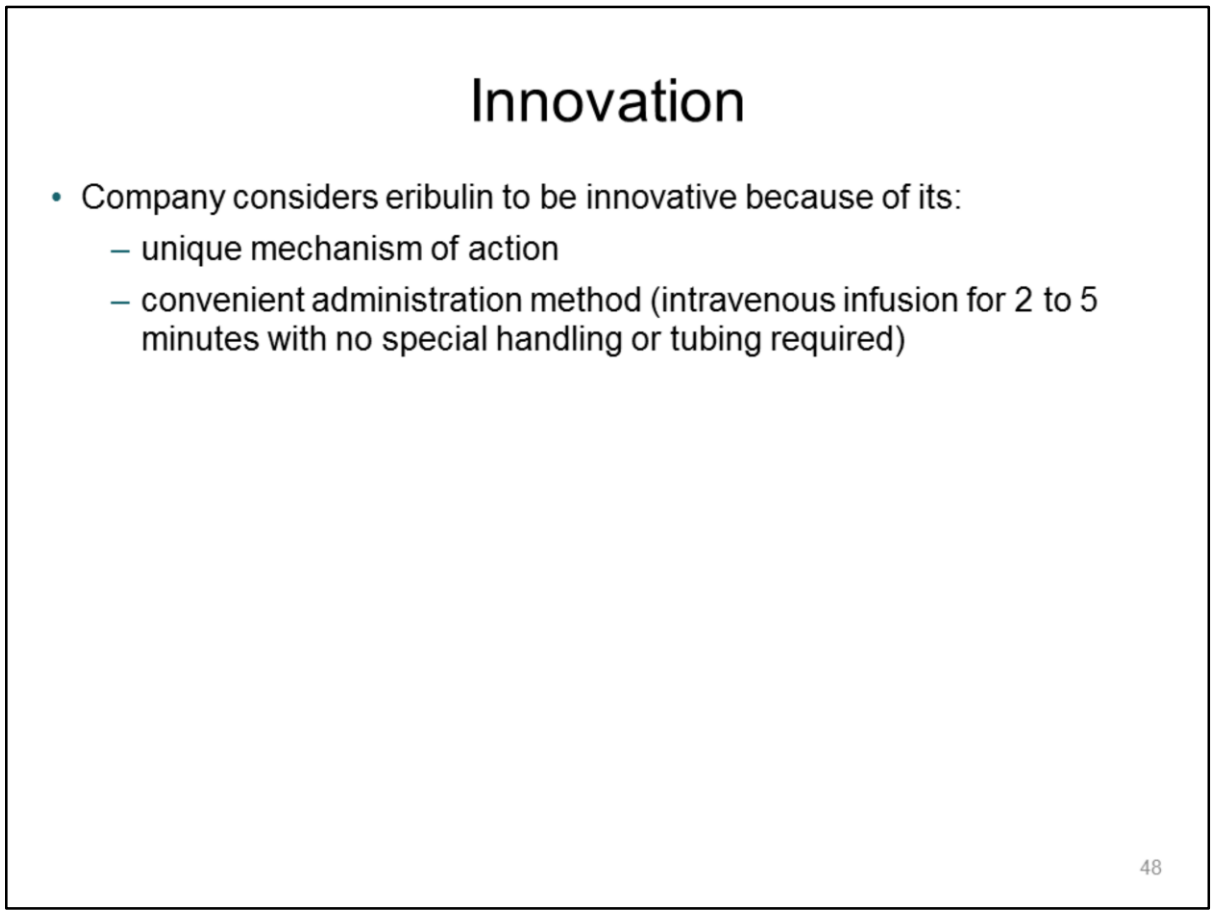
Source: Company submission: section 4.13, Table 36 (page 123); section 5.3, Figure 29 (page 141); section 5.7 (page 185); ERG report: section 6, (page 83)

Note: ERG considers the end of life criteria are met.
Note: In TA423 committee concluded the end of life criteria were met.

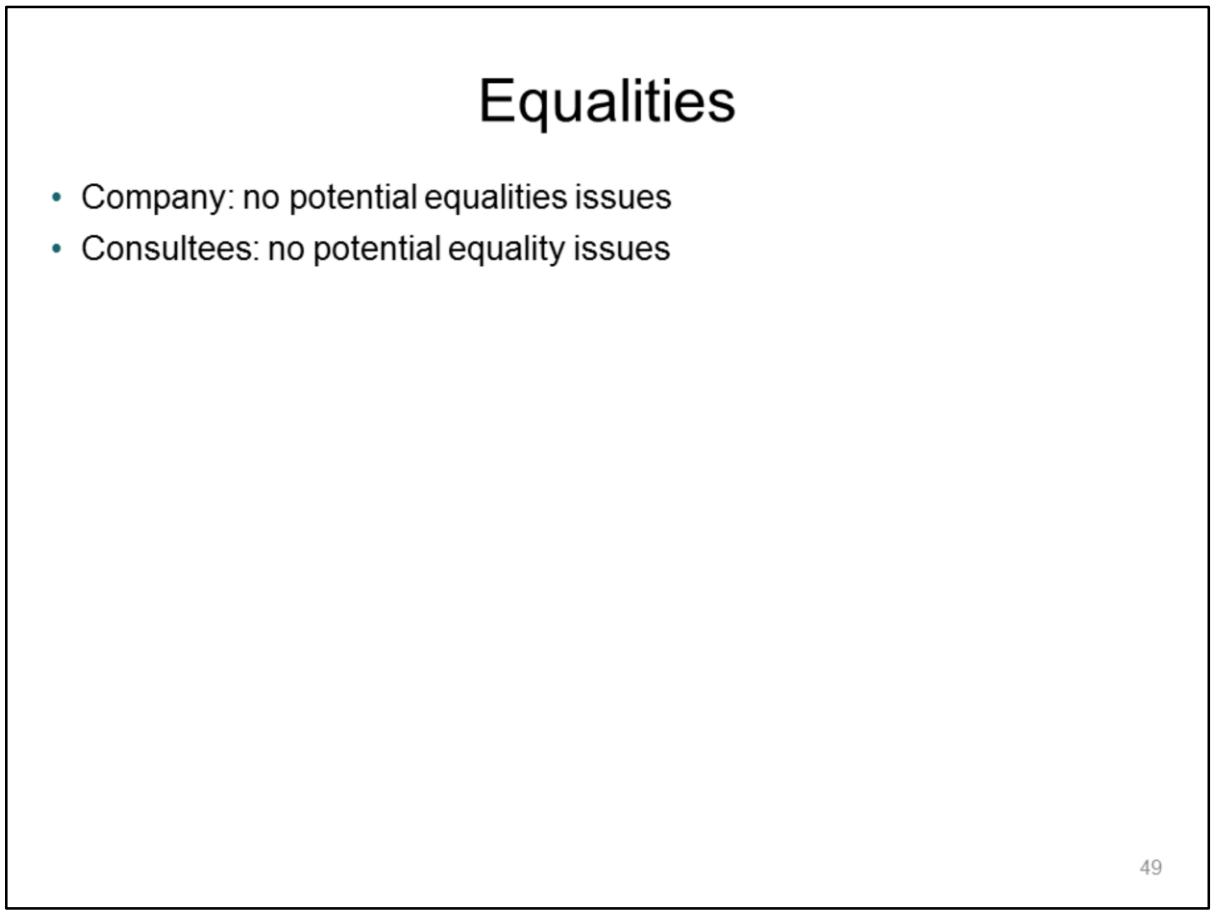
Relevant conclusions from TA423

- **Population:** Noted eribulin more widely used via CDF for HER2-negative disease because this has fewer treatment options.
- **Quality of life data:** Aware survey compliance decreases over time and data from 24 months only from very few people, but welcomed direct data from patients taking eribulin: of value but has inherent limitations.
- **Health utility values:** Crott and Briggs algorithm resulted in small decrease between stable and progressive disease that was not plausible. Lloyd et al. values considered more relevant; resulted in ~20% decline from stable to progressive disease; considered high by clinical experts. Concluded most plausible value likely to be in between.
- **Treatment costs:** Company used standard error instead of standard deviation, resulting in narrow range of body surface areas in the model. ERG's correction increased drug wastage and therefore costs, especially of eribulin. Concluded drug wastage somewhere in between company and ERG's estimates.
- **Subsequent treatments:** Cap for all lines of treatment implausible and likely to underestimate costs of subsequent treatments. Uncertainty about proportion of patients who might still be on treatment after 6 months and duration of subsequent treatments. Significant source of uncertainty in model that could not be resolved. Concluded somewhere in between company and ERG's estimates.47

Note: In TA423 Most plausible ICER between company's (£36k) and ERG's (£63k).



Source: Company submission: section 2.5 (pages 29-30)



Source: Company submission: section 3 (page 39)
Source: Breast Cancer Now submission: section 8 (page 9)

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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

File name	Version	Contains confidential information	Date
		No - redacted	**17 June 2016**

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.

Contents

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)

[redacted]

[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.

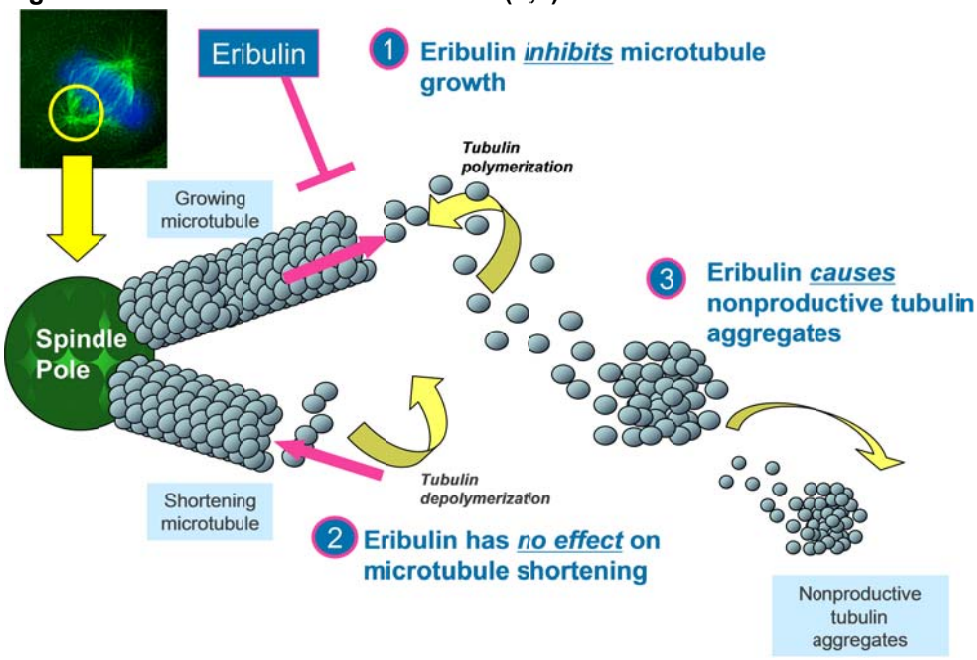
It is an innovative chemotherapy treatment which is a non-taxane inhibitor of microtubule dynamics, with a unique mechanism of action. Eribulin exerts its anticancer effects via a tubulin-based antimitotic mechanism leading to G2/M cell cycle arrest, disruption of mitotic spindles, and ultimately, apoptotic 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.

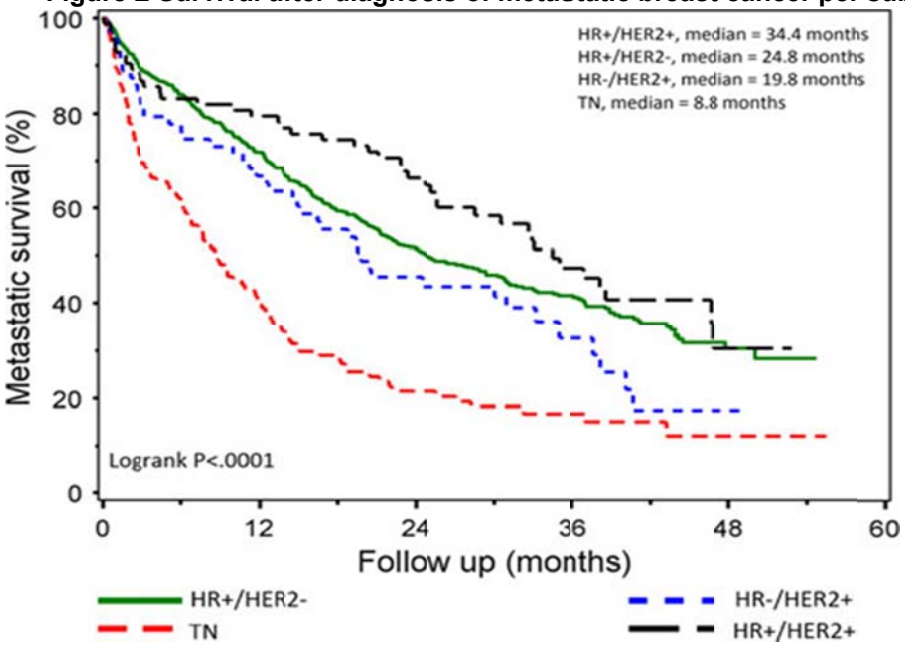
The extent or severity of the cancer can be determined by the Tumour, Nodes, Metastasis (TNM) staging system. The TNM staging system takes into account the size of the tumour, whether the lymph nodes are affected, and whether cancer has spread to other parts of the body (metastasised) (14,15).

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.**

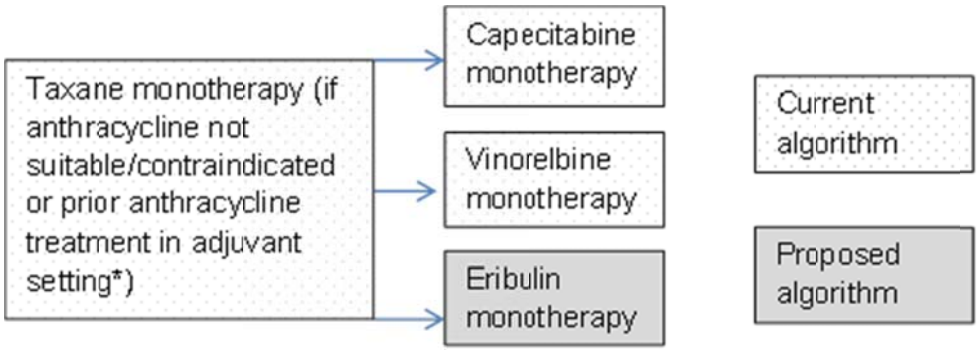
As described above, whereas historically, HER2+ tumour status has been associated with more aggressive disease and poorer patient outcomes; nowadays, those patient with a HER2+ status will receive targeted/biological agents. Therefore the prognosis for HER2-positive patients has reversed (22) and a recent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

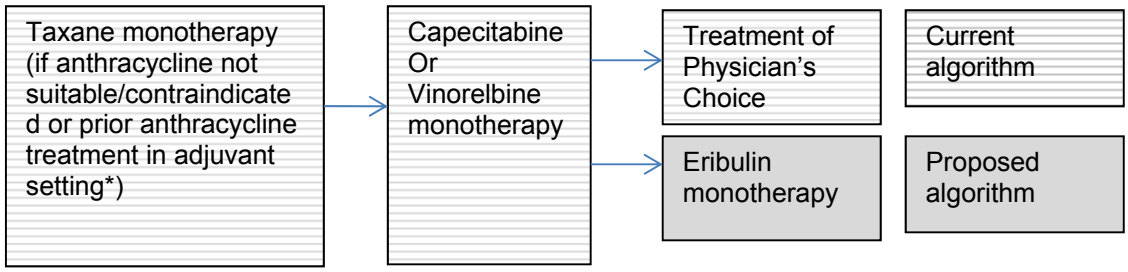
In study 305 (EMBRACE), the majority of patients received capecitabine as a second-line agent for advanced breast cancer. (7)

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)

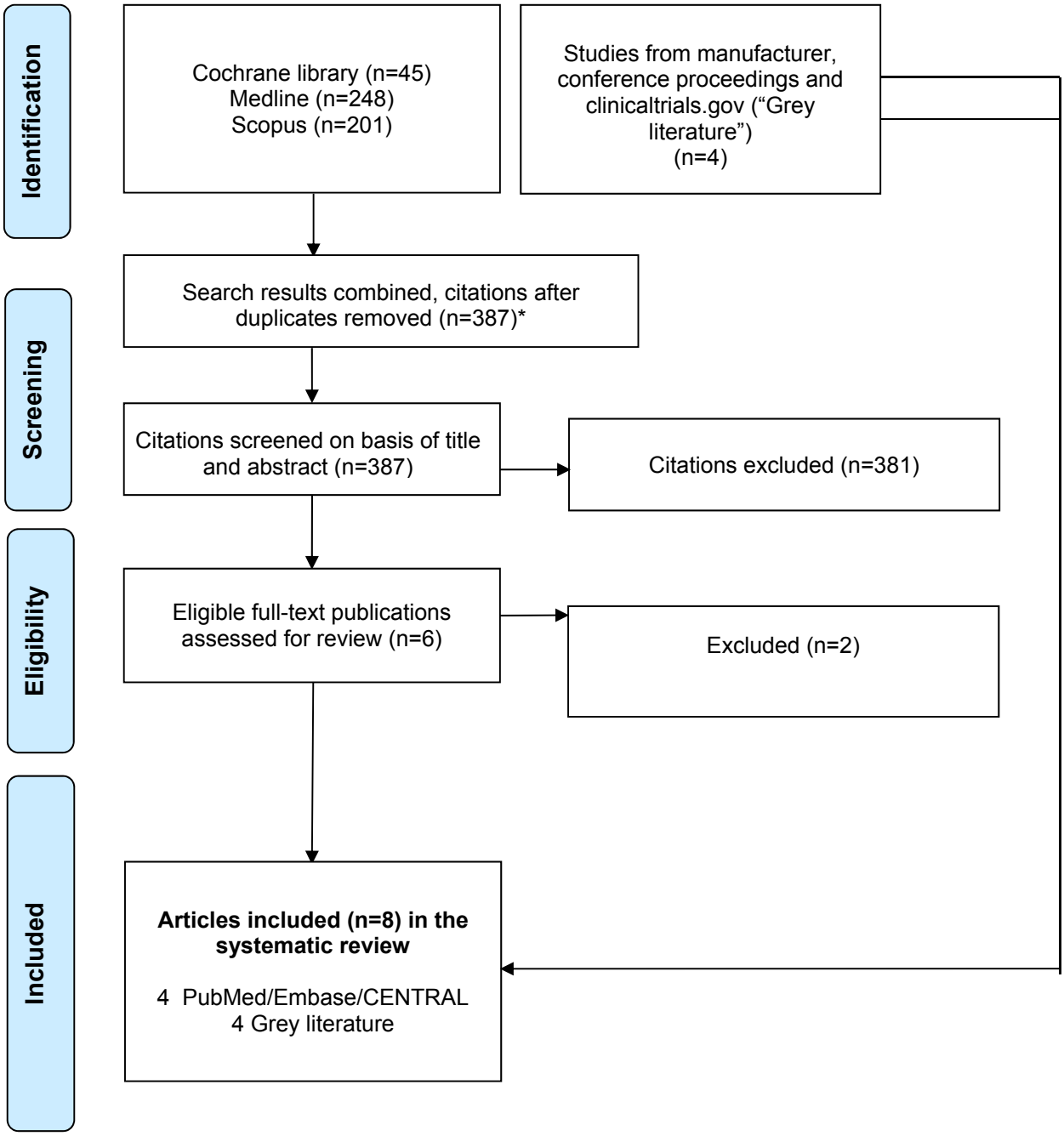
Two records, Twelves et al (48) and Twelves et al (49) were conference abstracts for the pooled analysis that has been subsequently published as a full manuscript by Twelves et al (46).

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)

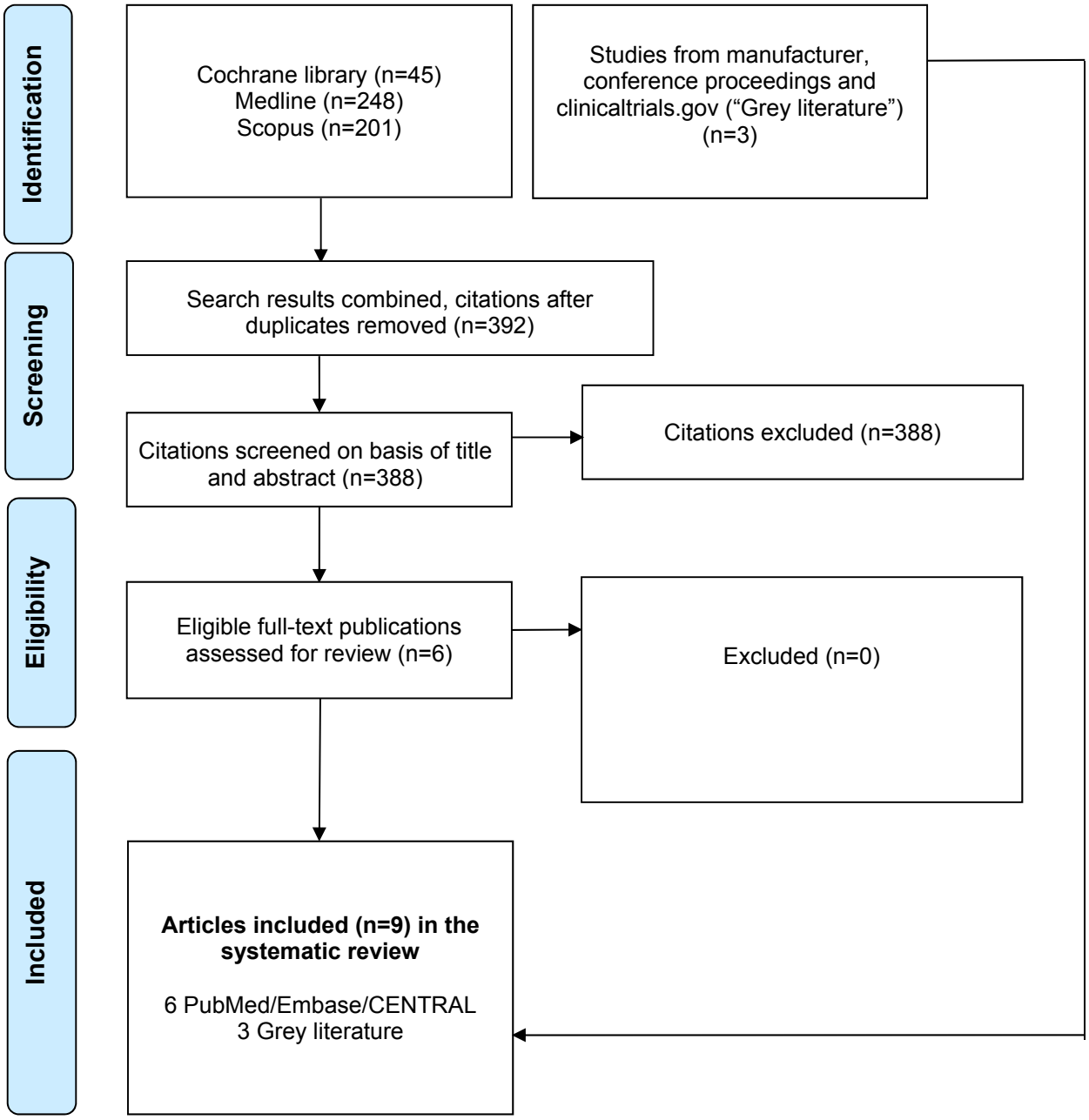
Three records were conference abstracts providing retrospective subgroup analyses of the EMBRACE study. These were all unplanned, exploratory, post-hoc analyses which did not provide additional information relevant to the subgroups described in the decision problem (Table 1) and are therefore not considered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

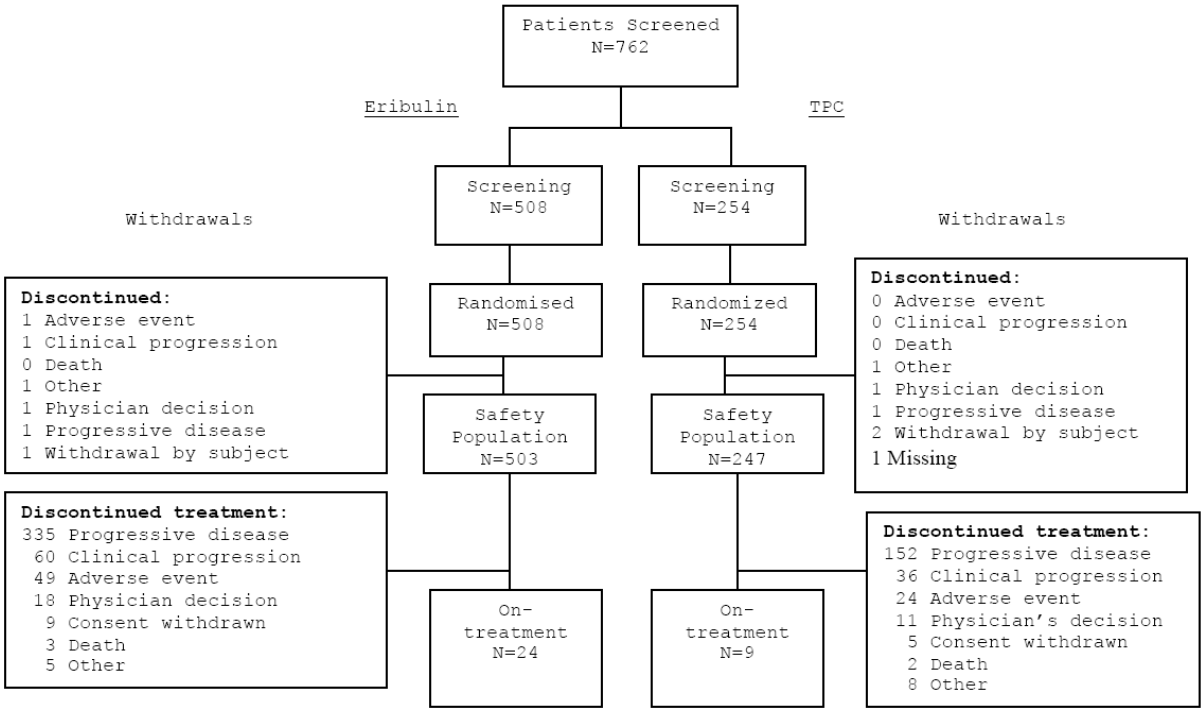
A total of 484 (95.3%) patients in the eribulin group and 244 (96.1%) patients in the TPC group had discontinued study treatment at the time of data cut-off for the primary analysis (when 55% of patients had died; See Section 4.7). The main reason for discontinuation in both treatment groups was progressive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

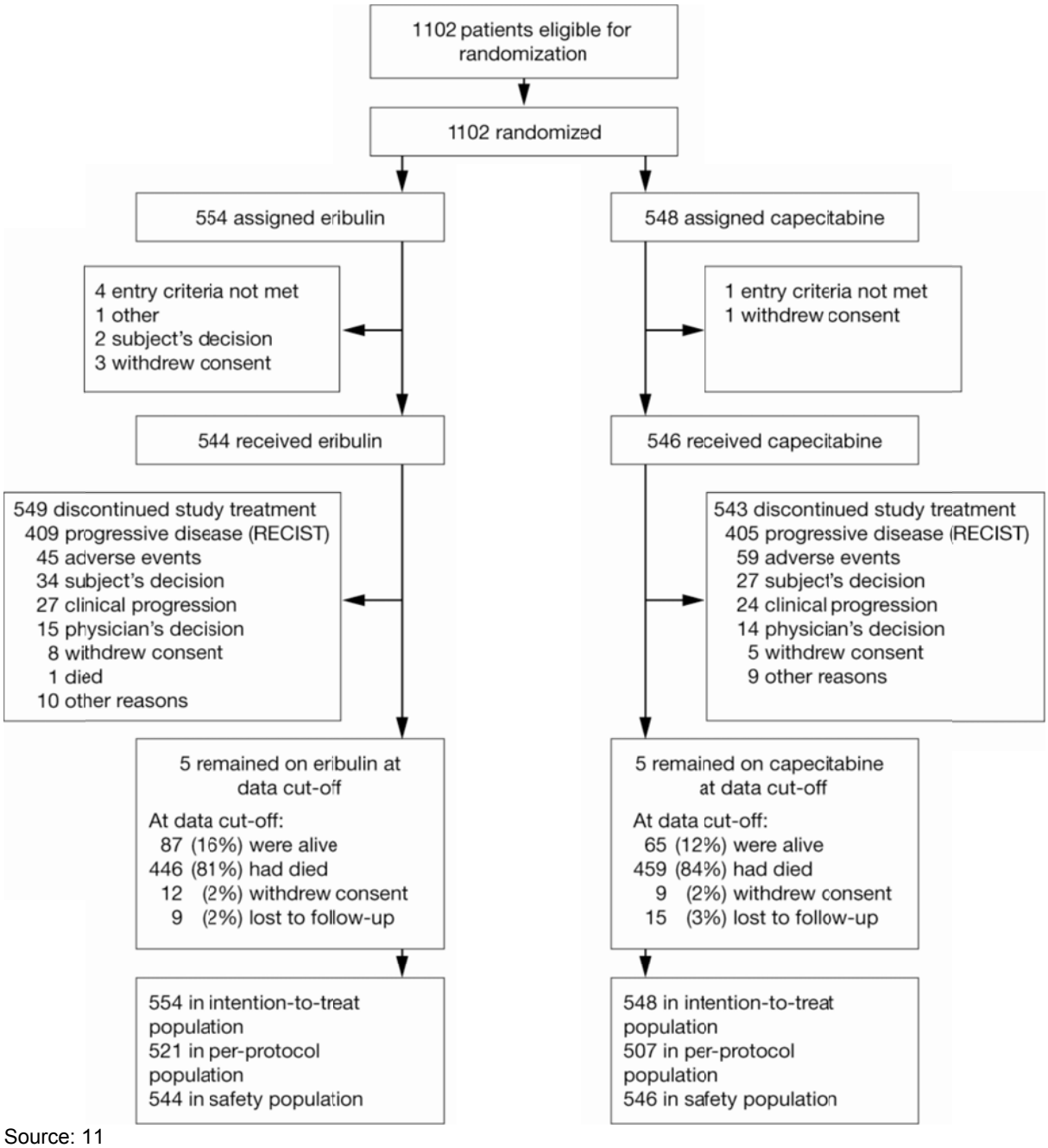
A total of 549 (99.1%) patients in the eribulin group and 543 (99.1%) patients in the capecitabine group had discontinued study treatment at the time of data cut-off; See Section 4.7). The main reason for discontinuation in both treatment groups was progressive disease (assessed by RECIST, Table 17).

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)

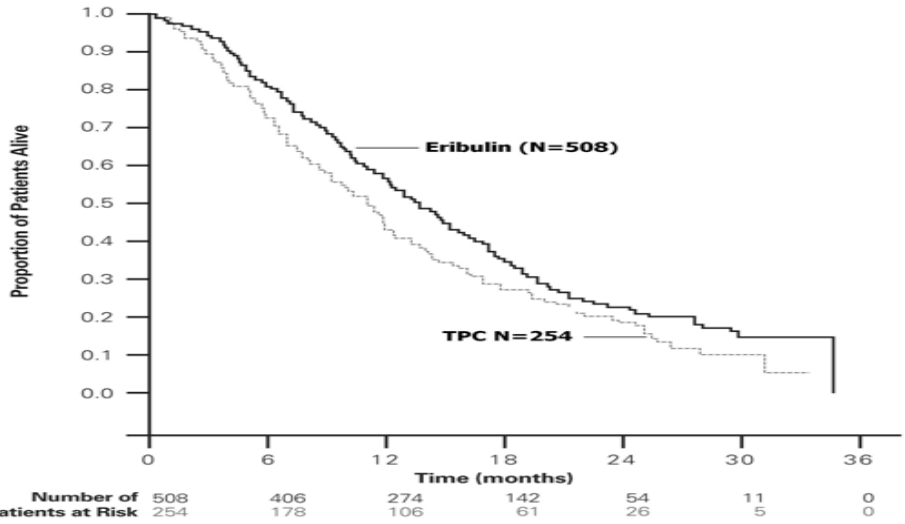
This result was confirmed with an updated OS analysis carried out when 77% of patients had died, with the median OS of the eribulin group (13.2 months/403 days) compared with the TPC group (10.5 months/321 days) improved by 2.7 months (82 days; HR 0.805, 95% CI: 0.667, 0.958, p=0.014) (Table 23 and Figure 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).

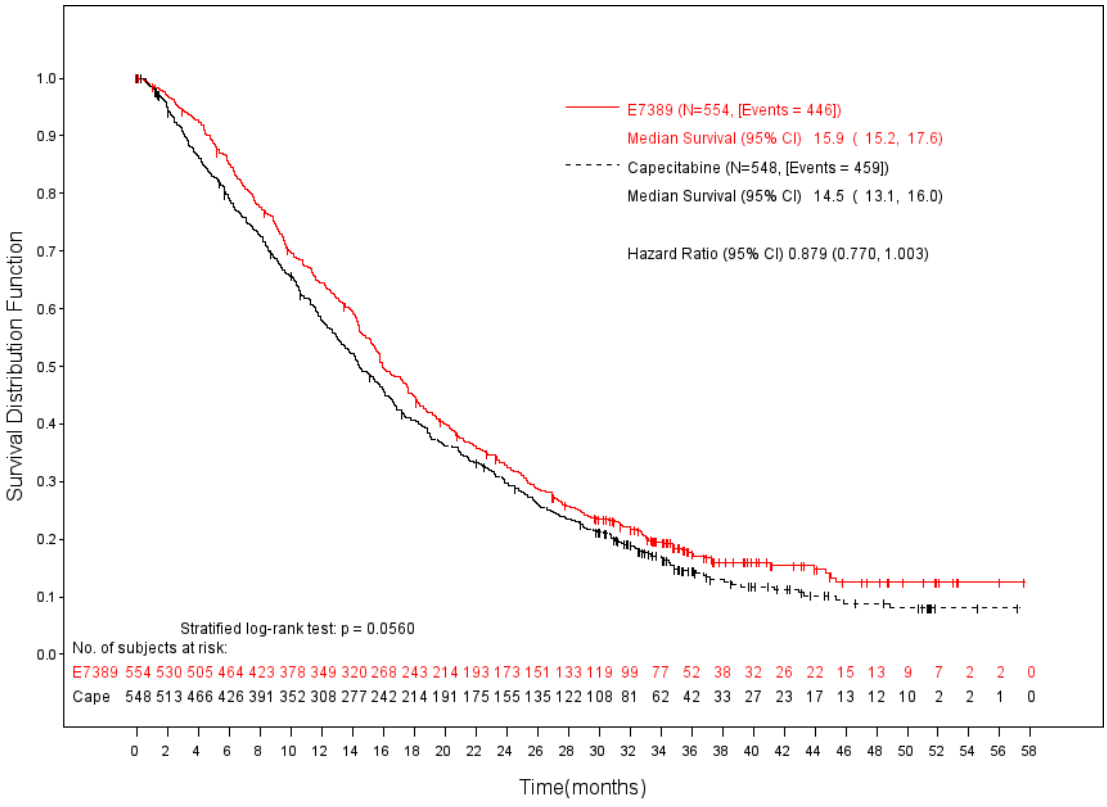
The benefit for OS emerged early and was maintained over the course of the study. Kaplan-Meier analysis of OS in the ITT population is shown in Figure 10, overleaf.

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.

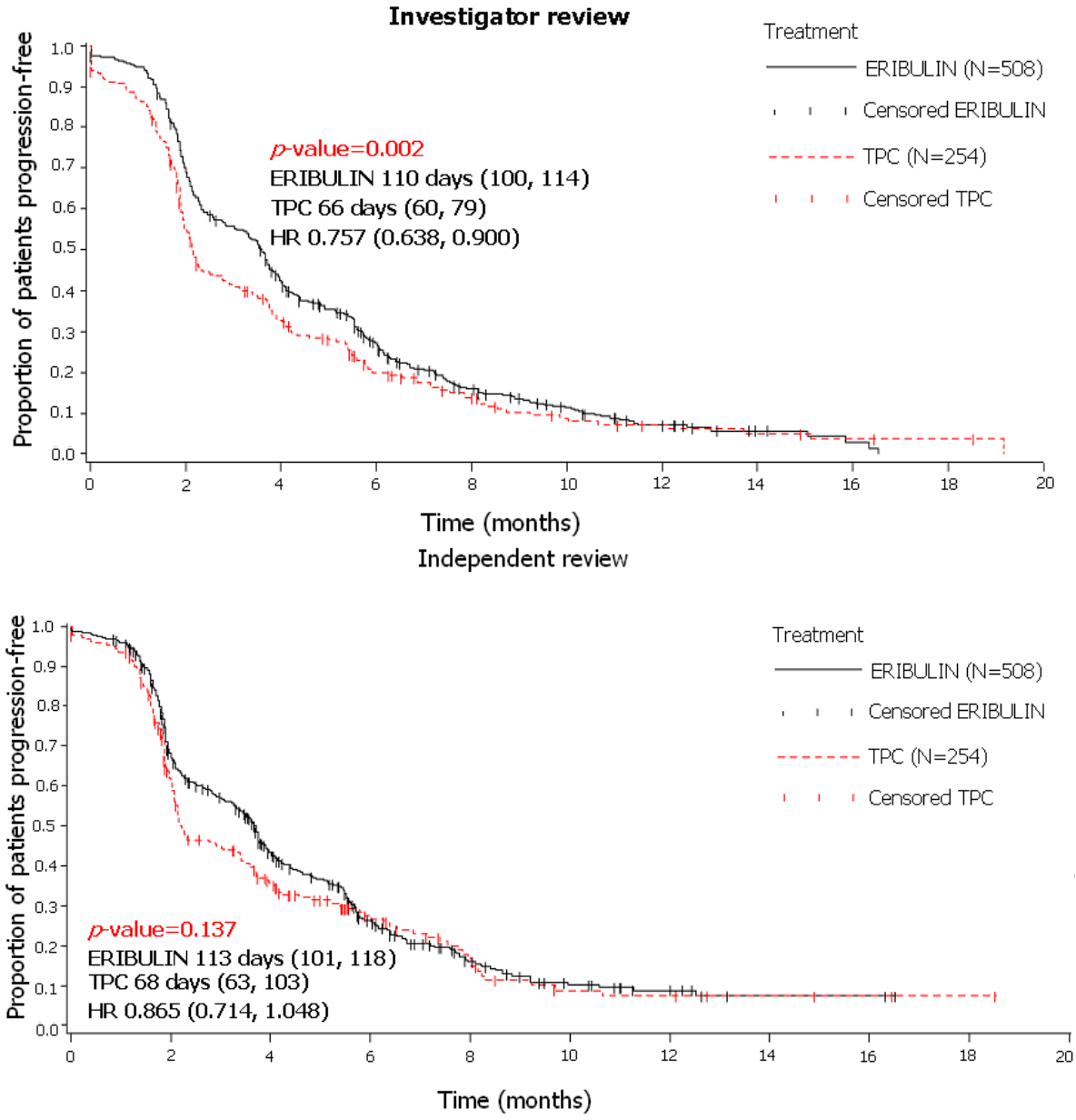
Table 25 Kaplan-Meier analysis of progression-free survival; Study 305 (EMBRACE) (ITT Population)

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.

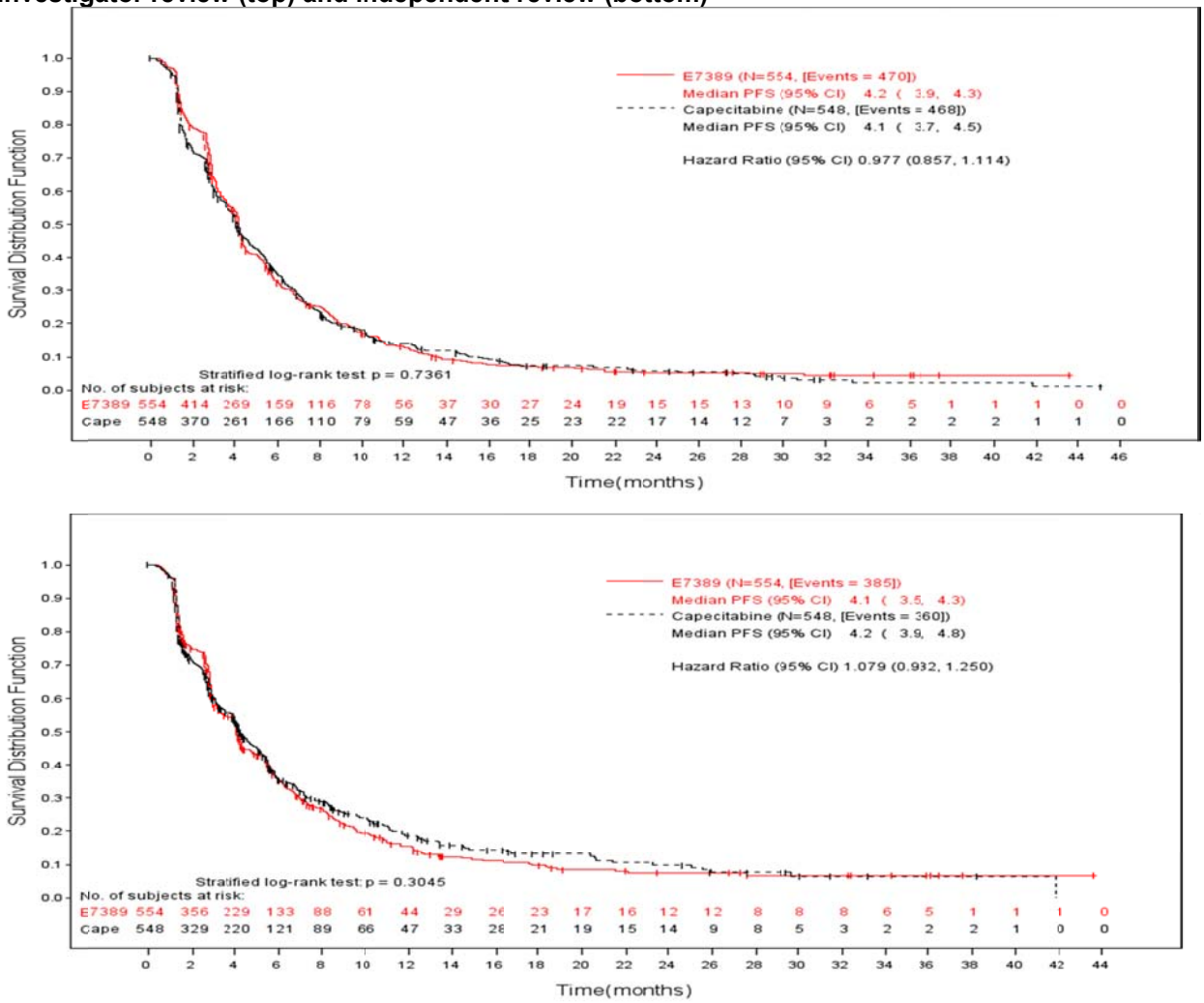
Table 26 Kaplan-Meier analysis of progression-free survival; Study 301 (ITT Population)

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]; $p<0.05$).

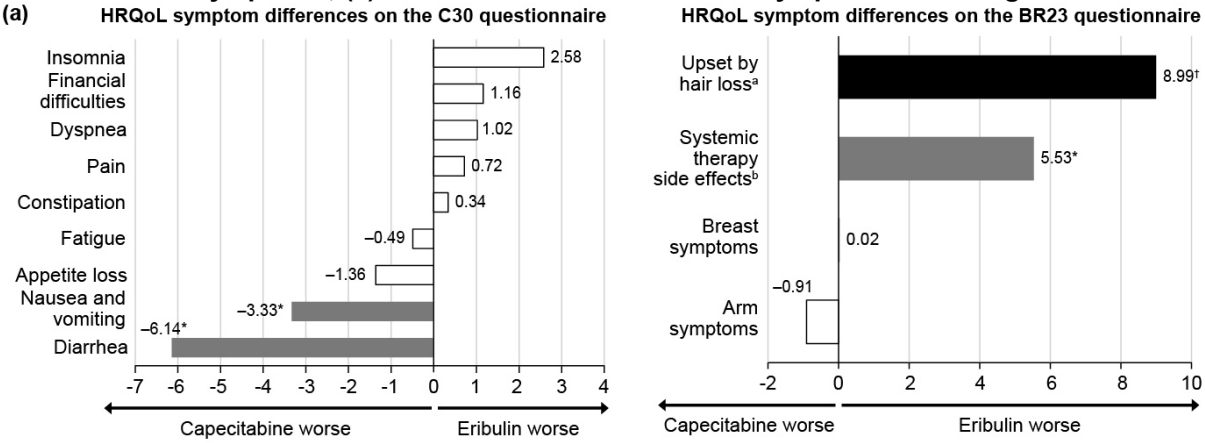
In comparison, patients receiving eribulin had worse mean scores for other systemic therapy side-effects including dry mouth, different tastes, irritated eyes, feeling ill, hot flushes, headaches, and hair loss ($p<0.001$), and upset by hair loss ($p<0.05$). A higher proportion of patients treated with 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

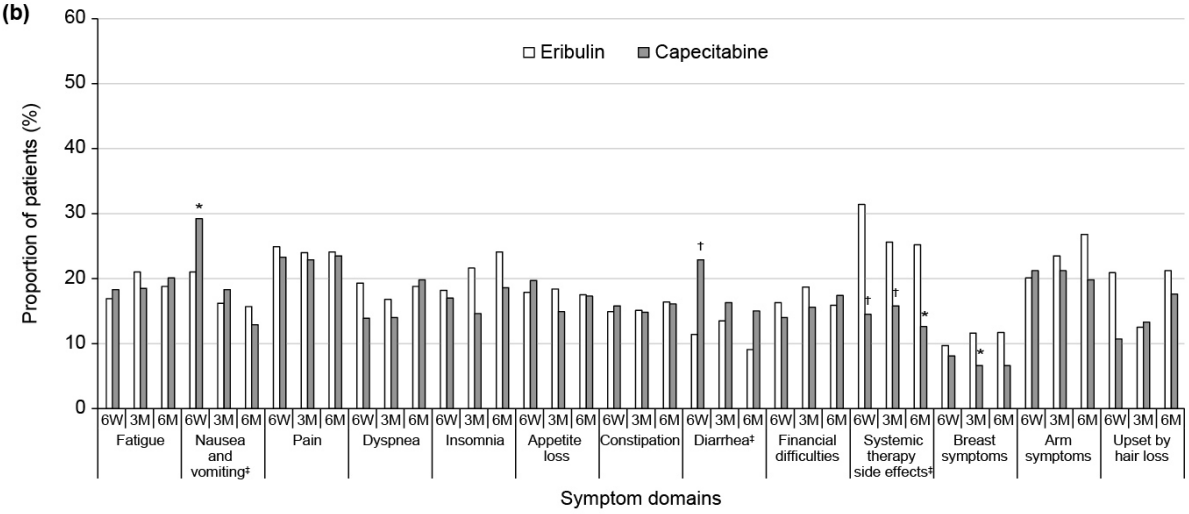
(a)



*P<0.001; †P<0.05

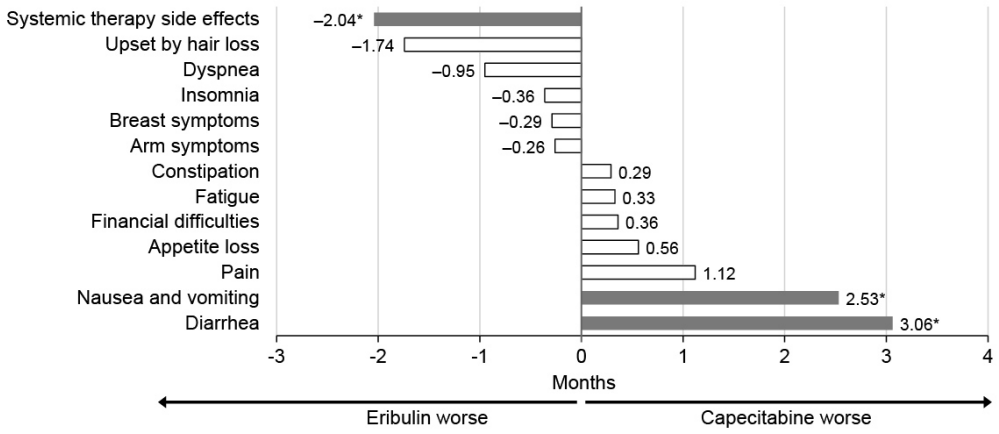
[a]Upset by hair loss is only answered by patients who experience hair loss. [b]Systemic therapy side effects include dry mouth, different tastes, irritated eyes, feel ill, hot flushes, headaches, hair loss. The linear mixed model estimated the change from baseline through month 24. Model adjusted with 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)

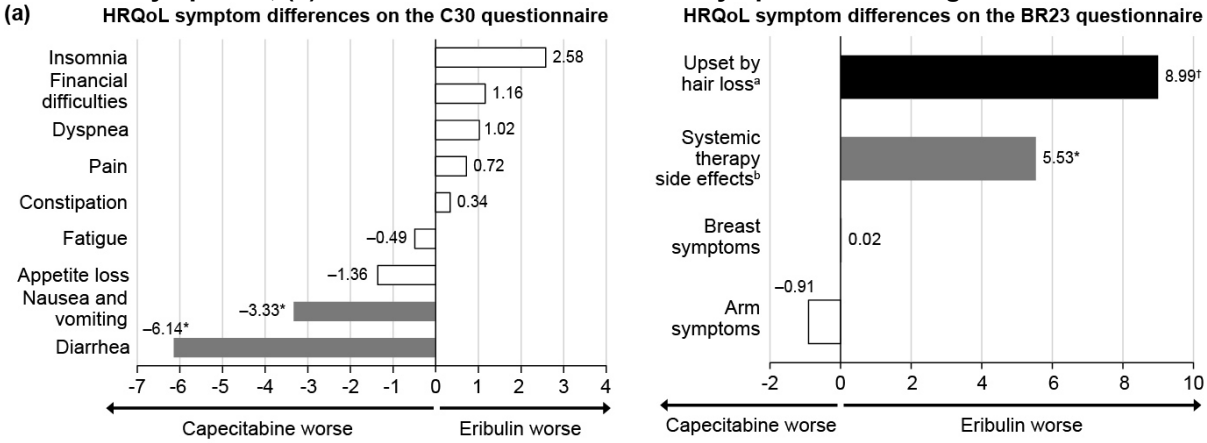
In the longitudinal analyses, baseline HRQoL scores were significantly associated with the change in HRQoL across all EORTC scales ($p<0.001$); that is, worse baseline scores were predictive of worse scores while on treatment. There were no differences between the 2 treatment arms in terms of impact 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]; $p<0.05$).

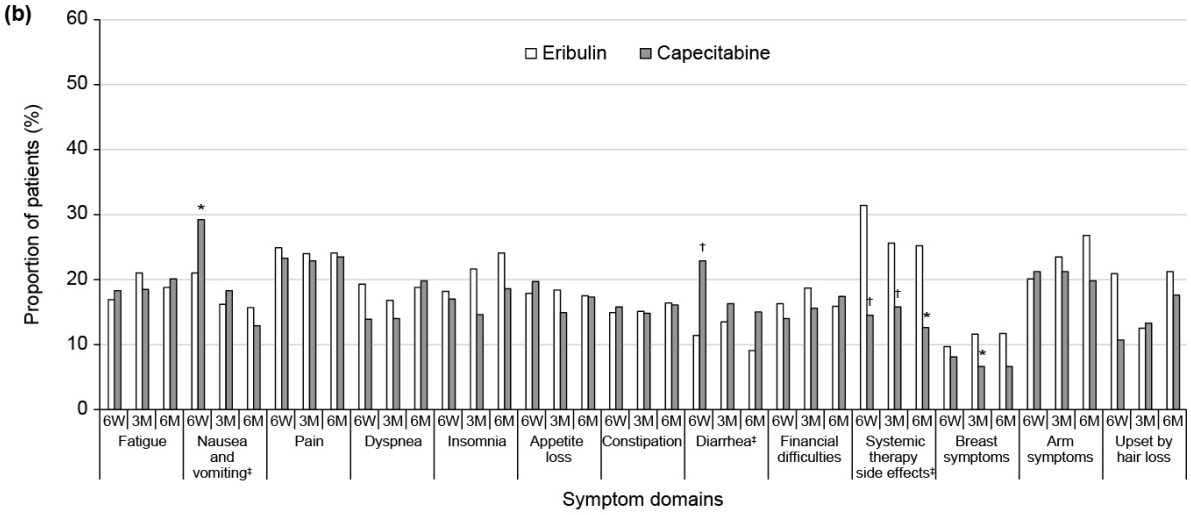
In the ITT population, median TSW was similar for the majority of the EORTC functional scales and the GHS/QoL scale, with only 1–2 months' difference between the treatment arms. Patients receiving eribulin had significantly longer TSW for body image (MID 10; 8.9 vs 6.0 months; $p<0.05$) and future perspective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

Results are shown in Figure 14 overleaf.

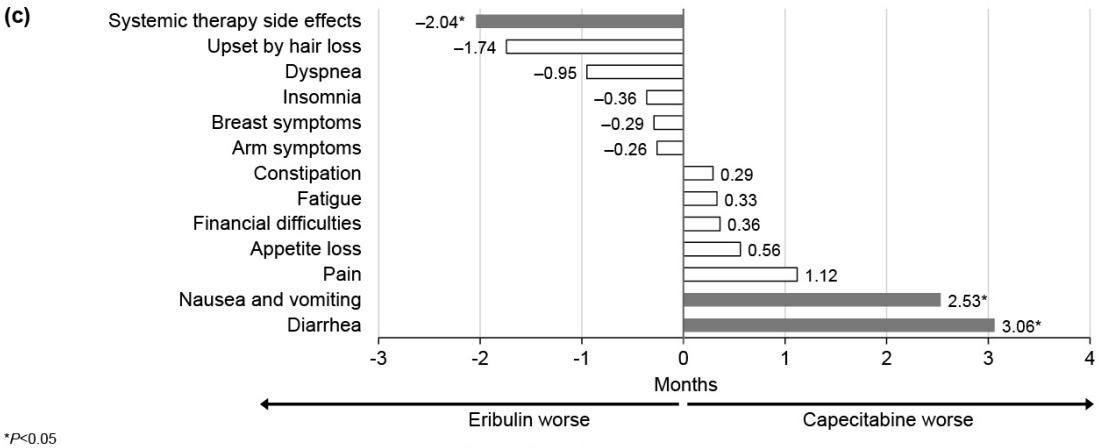
Figure 14 Effects of eribulin and capecitabine on function scales of the EORTC QLQ-C30 and QLQ-BR23 questionnaires (a) differences in mean scores; (b) proportion of patients with worsened symptoms; (c) differences in median time to symptom worsening



*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.

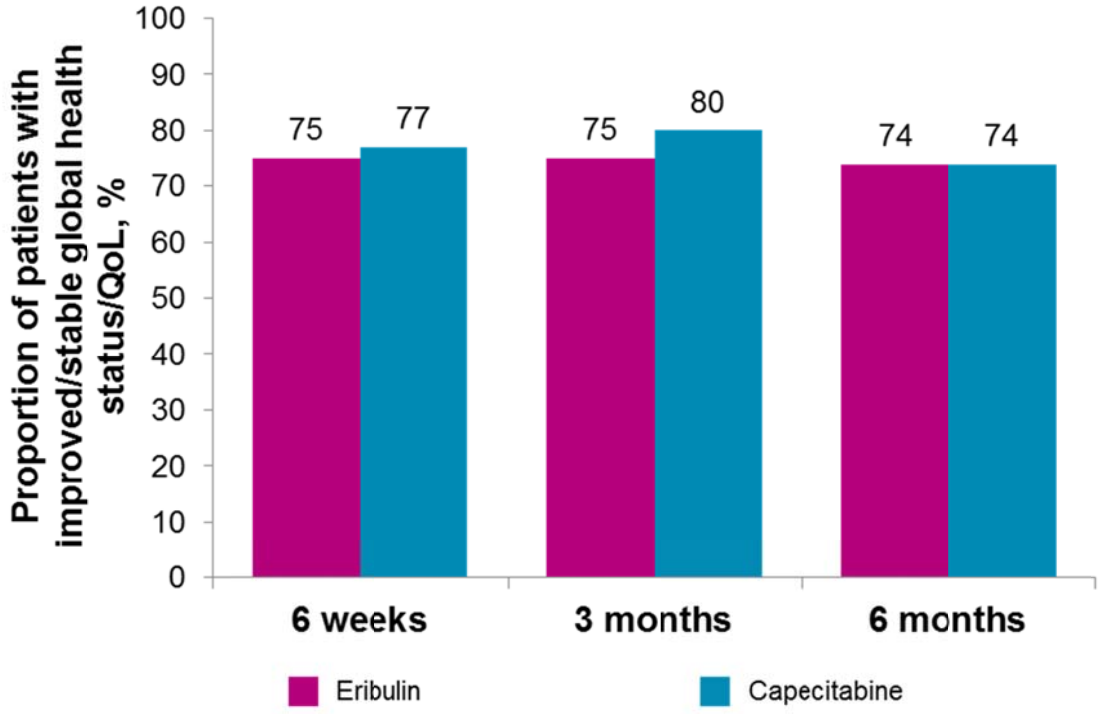


*P<0.05
The adjusted covariates include age group, race group, and categorical Eastern Cooperative Oncology Group score.
Source: 83

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.

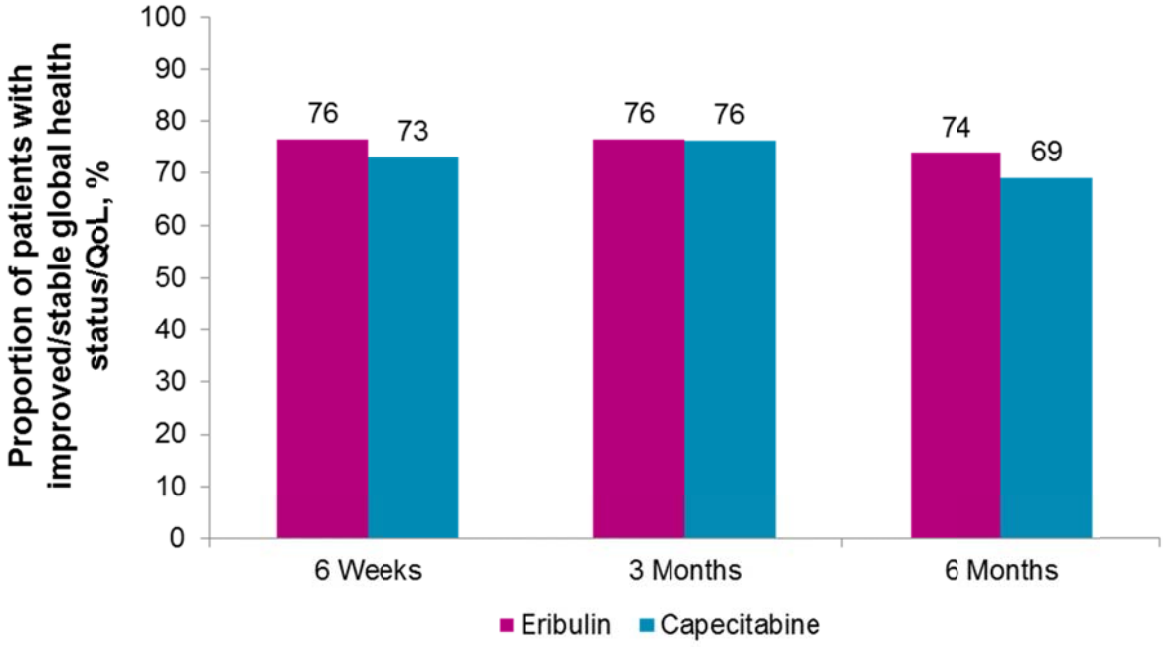
HRQoL in Subgroups 1 & 2

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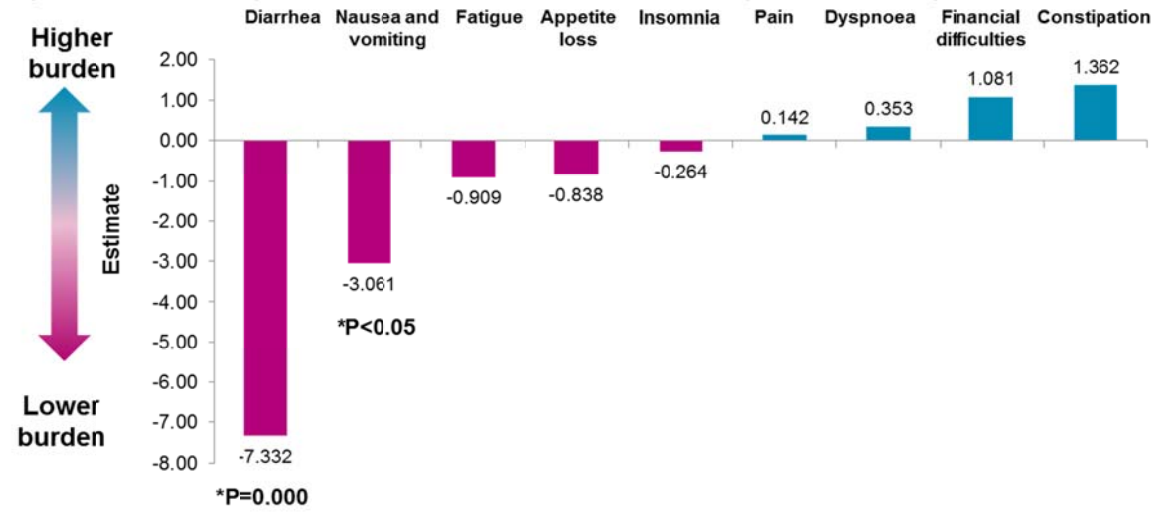
Patient burden of gastrointestinal adverse events was even more significantly lower for eribulin patients and is consistent with its known adverse event profile.

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

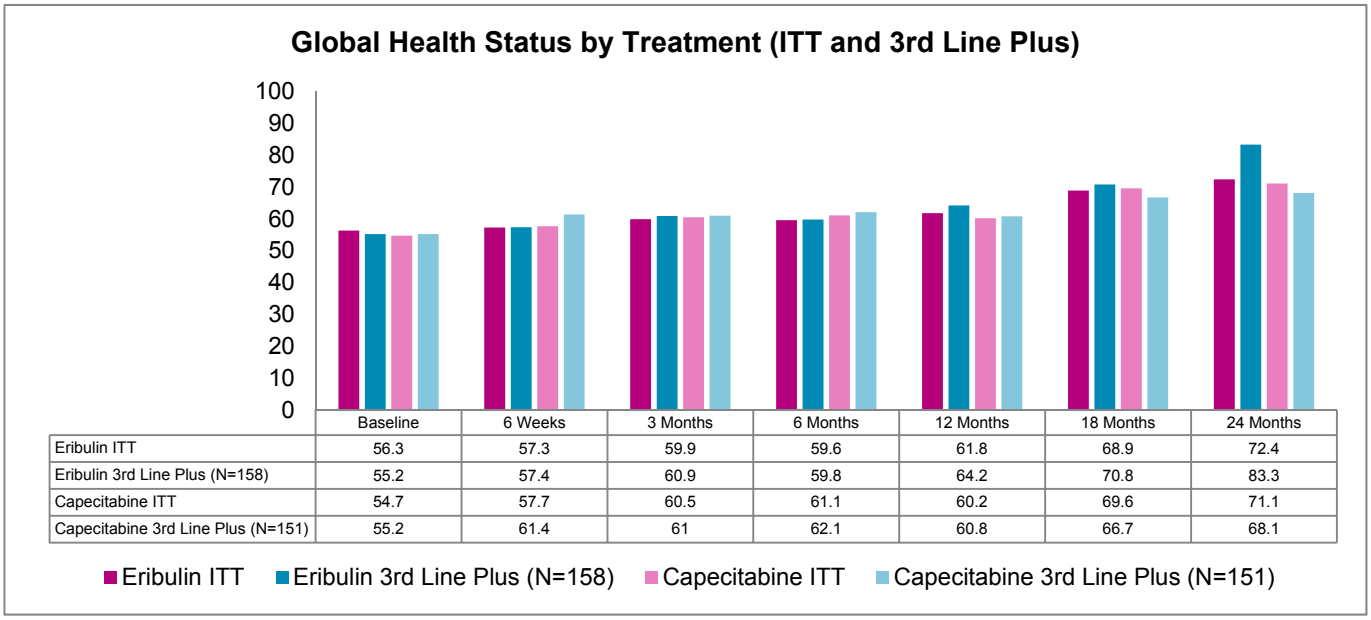


Subgroup 2

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)

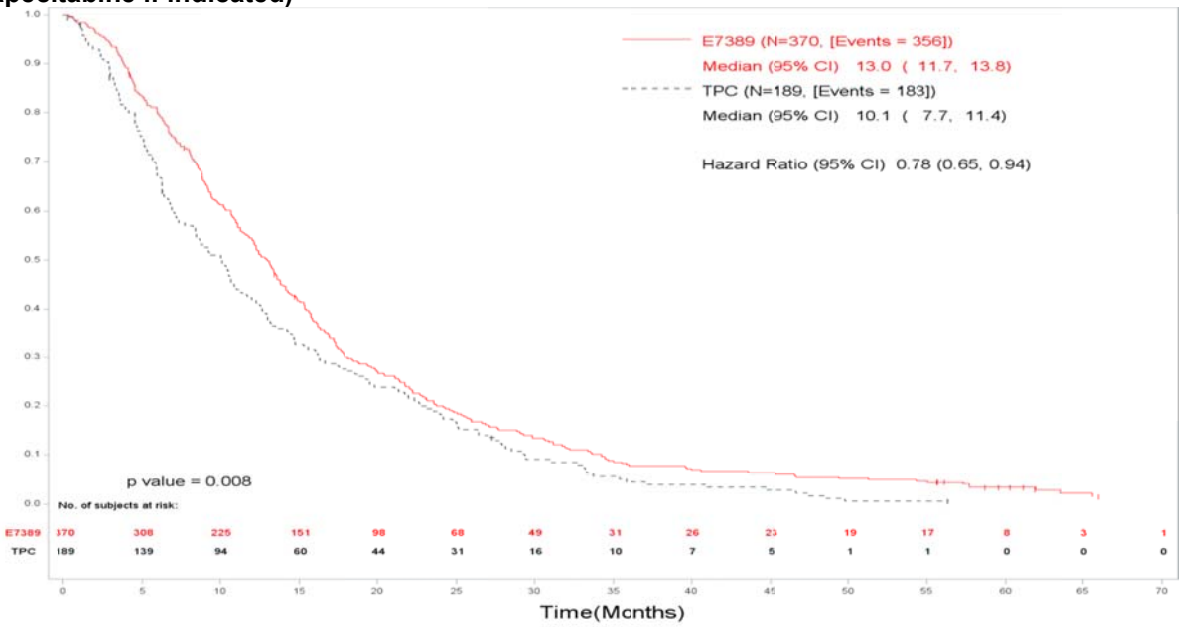
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, Oestrogen receptor; HER2, Human epidermal growth factor receptor 2; PR, progesterone receptor; TPC, Treatment of Physician's Choice

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.)

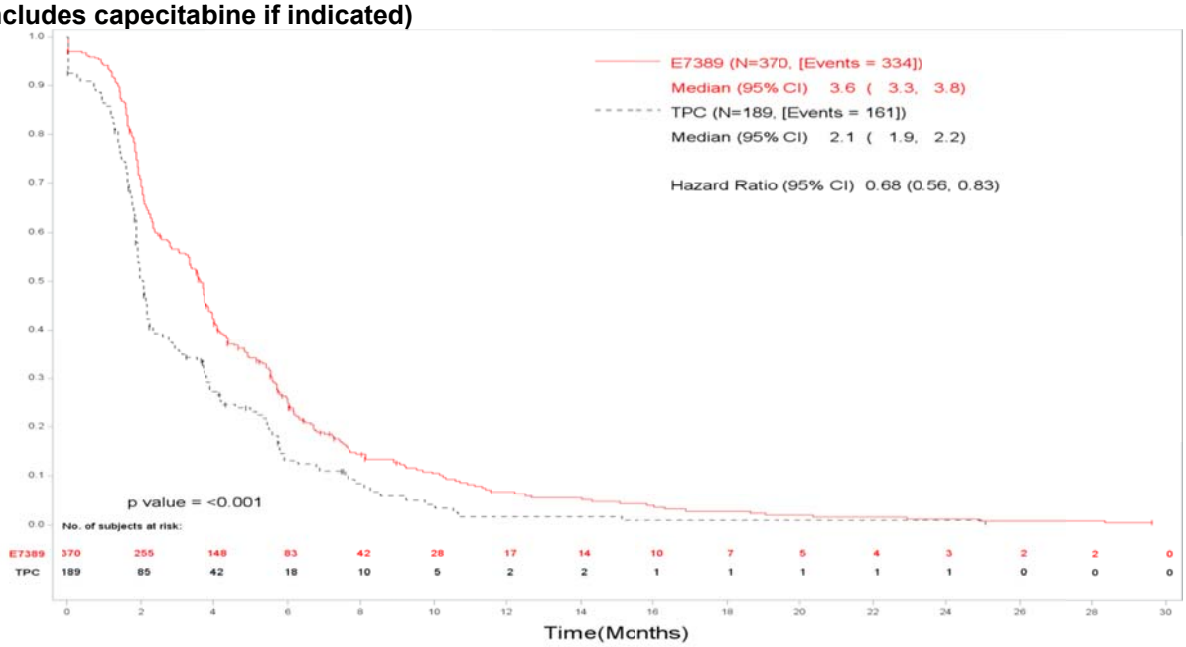
Figure 21 Kaplan Meier analysis of overall survival: Study 305 (Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine if indicated)



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;

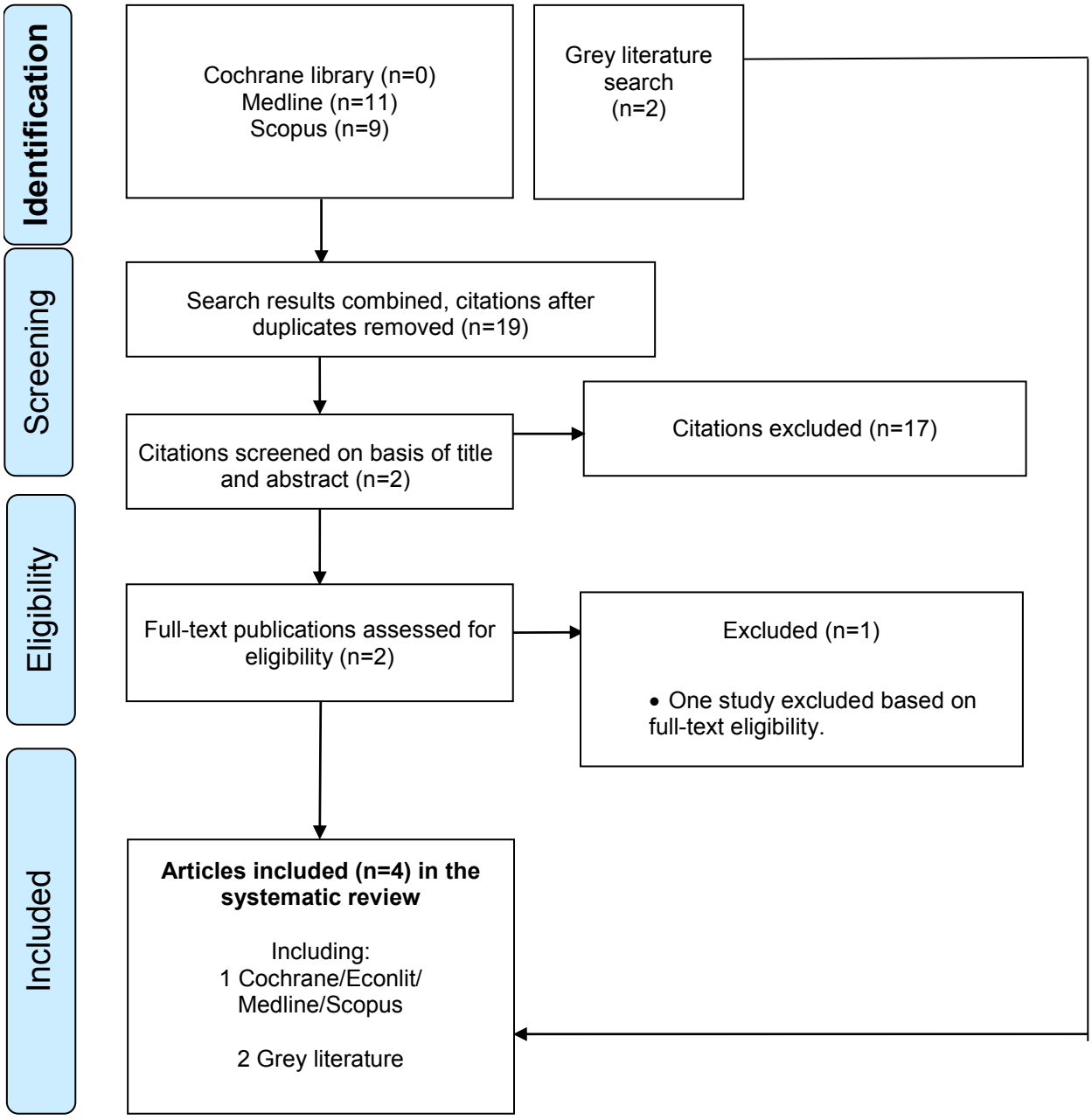
Flow Diagrams of included and excluded studies

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.

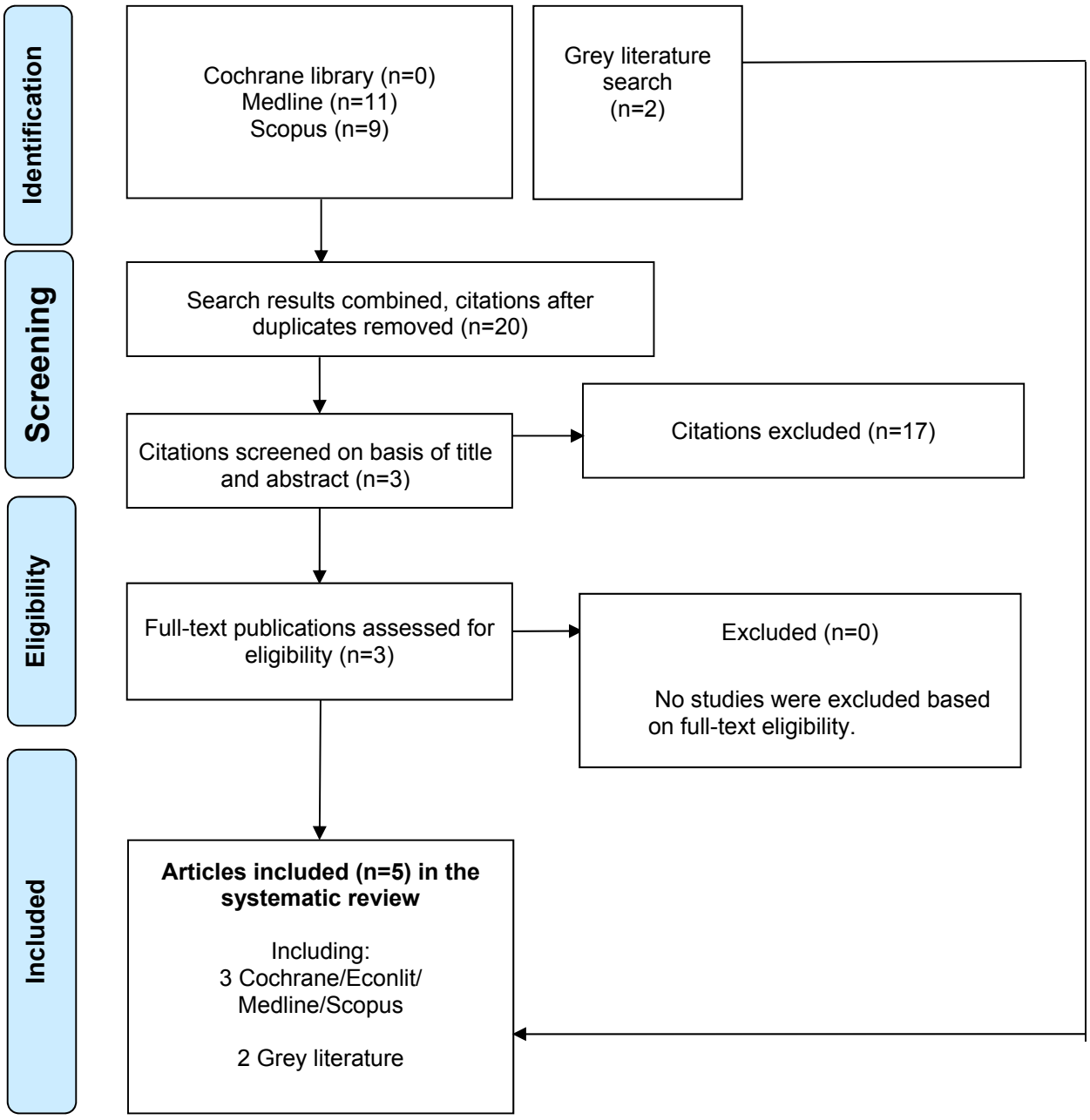


2. *Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated)*

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

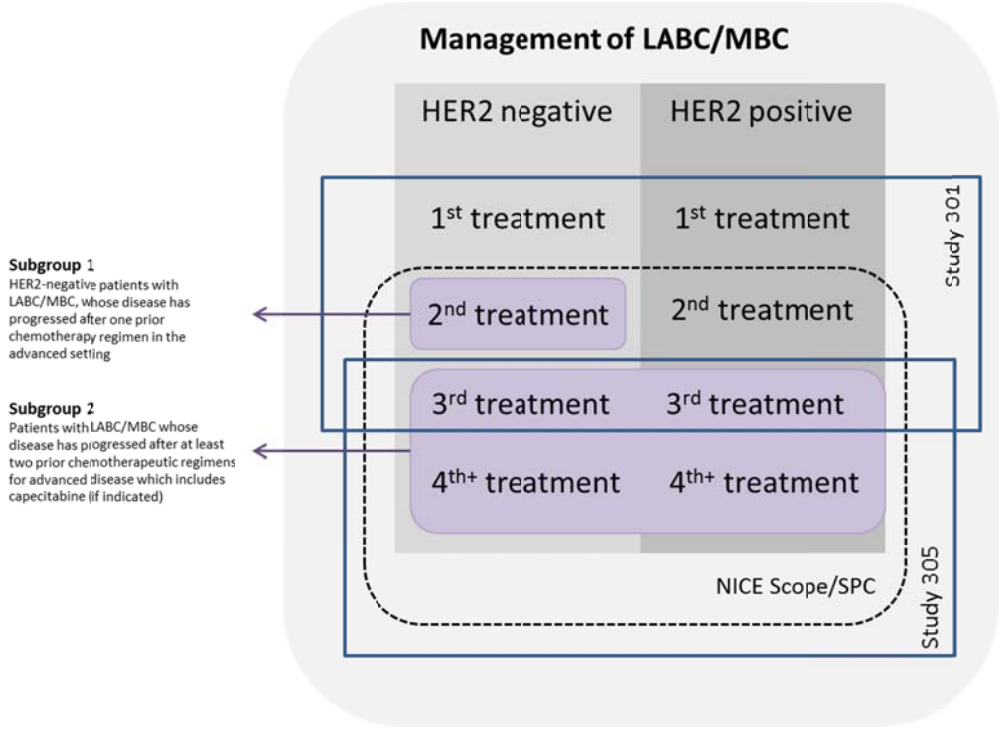


Table 40 Methodological issues of pooled patient data versus individual studies' patient level data

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

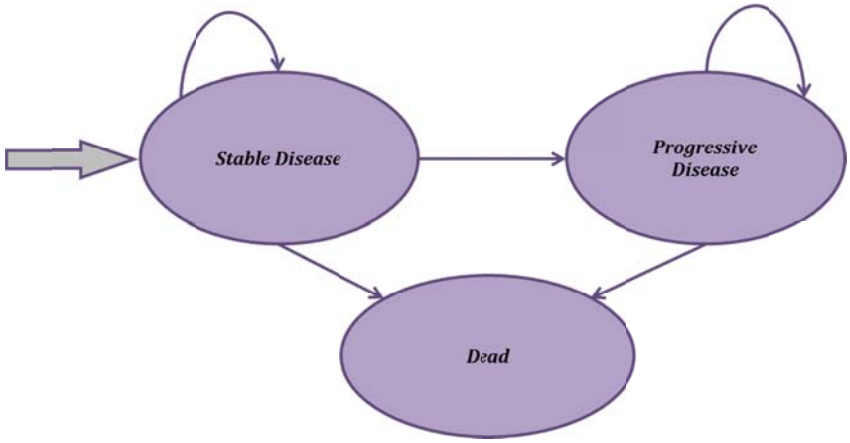
Structure Overview

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

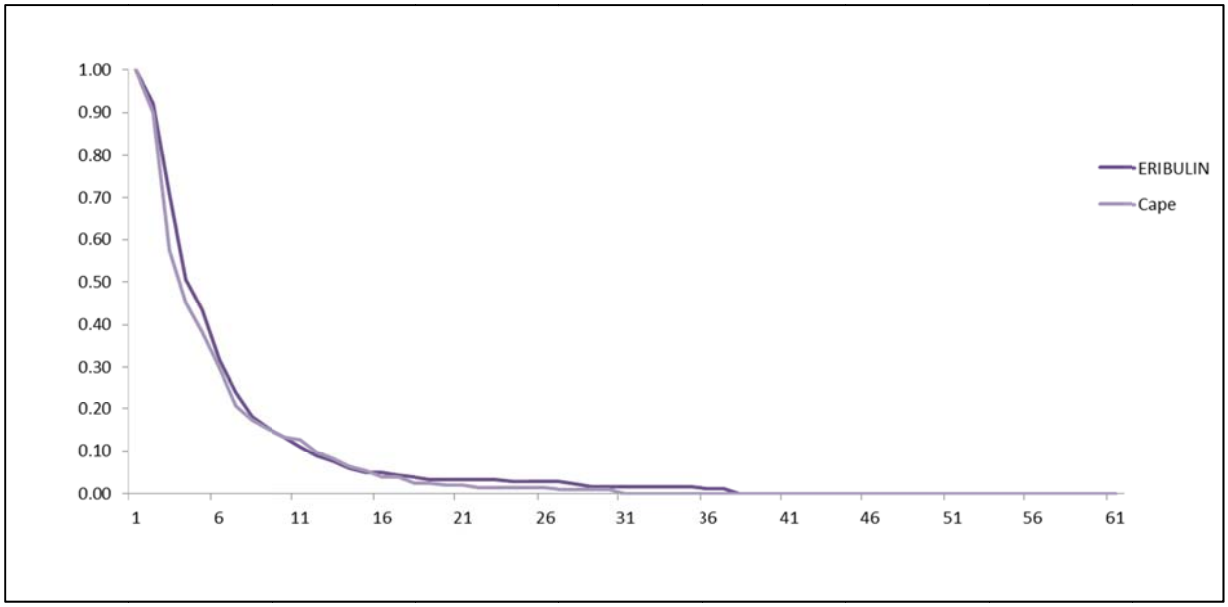


Figure 28 Subgroup 1 – OS KM curves of patients in different treatment groups

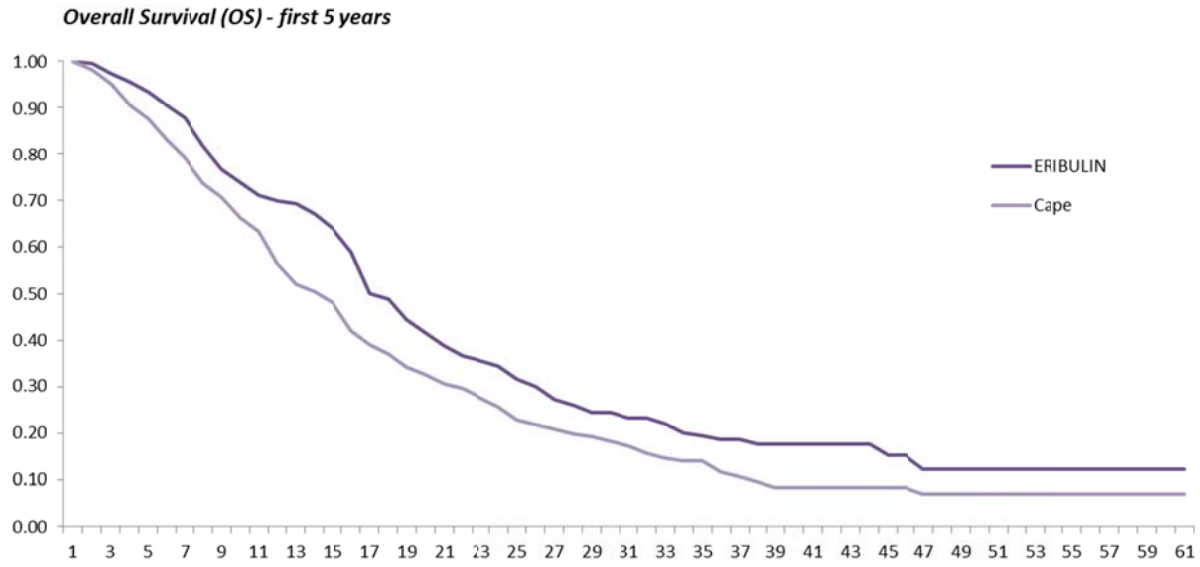
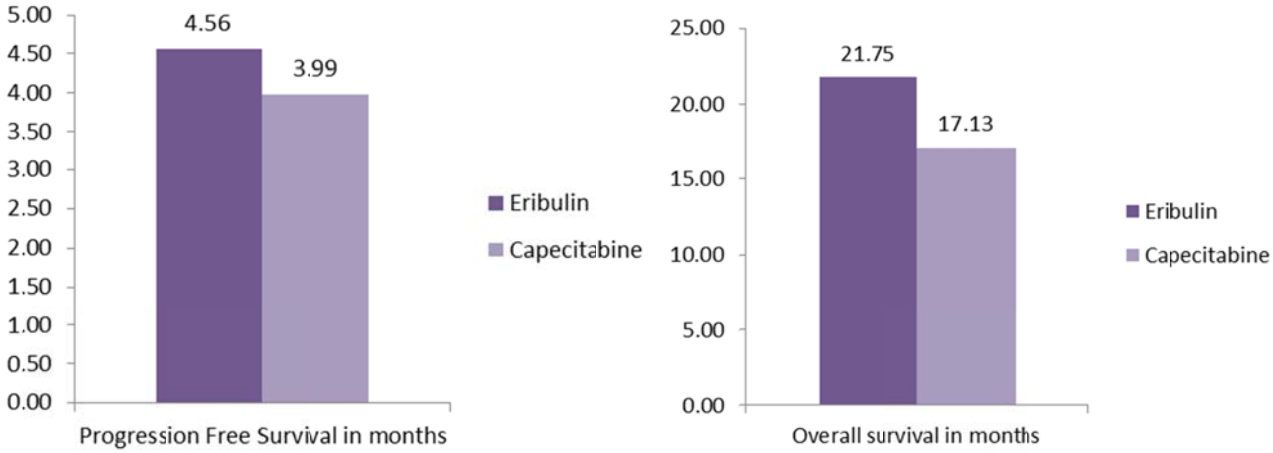


Figure 29 Subgroup 1 – PFS and OS of patients in different treatment groups



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:

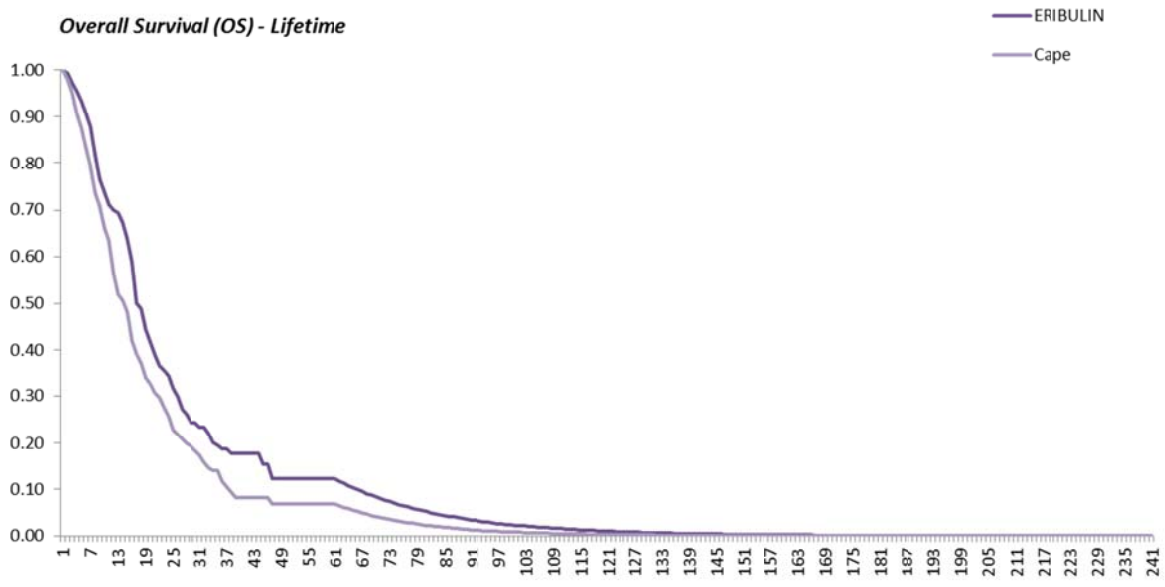
Despite the completeness of the study 301 OS data, 10 and 20 year time horizons were included in the model to approximate lifetime and meet the NICE Decision Problem requirements. To address that, data were extrapolated at the end of the Kaplan-Meier OS curve.

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

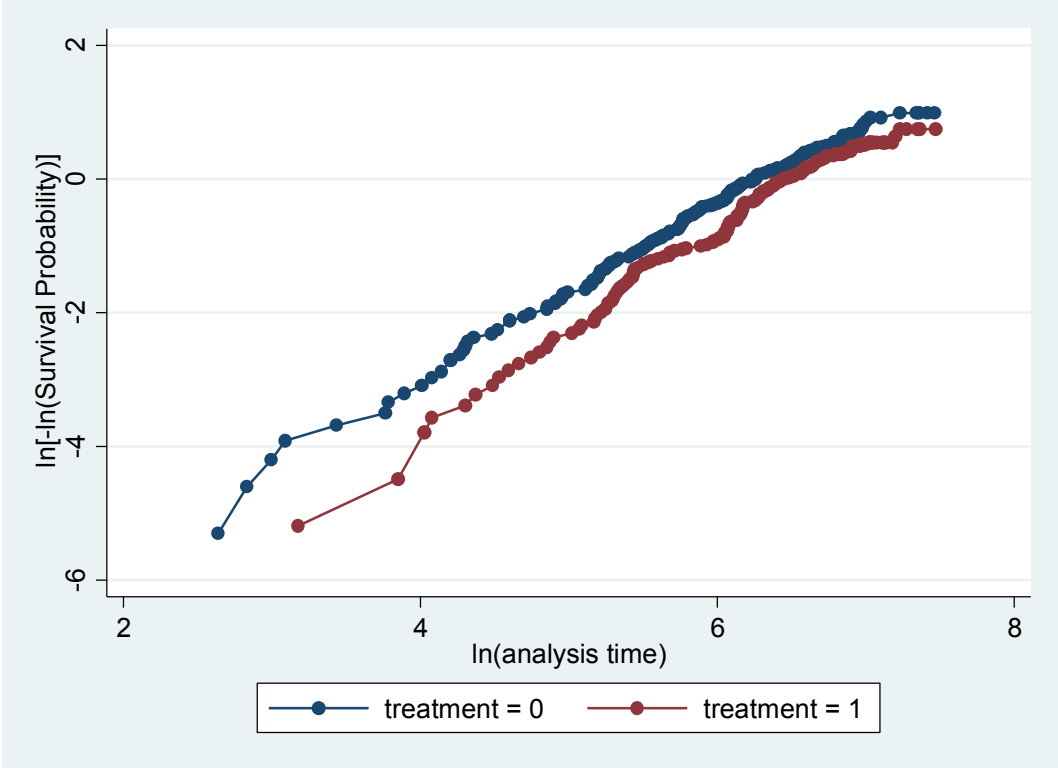


Table 46 PH Global Test results for subgroup 1

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

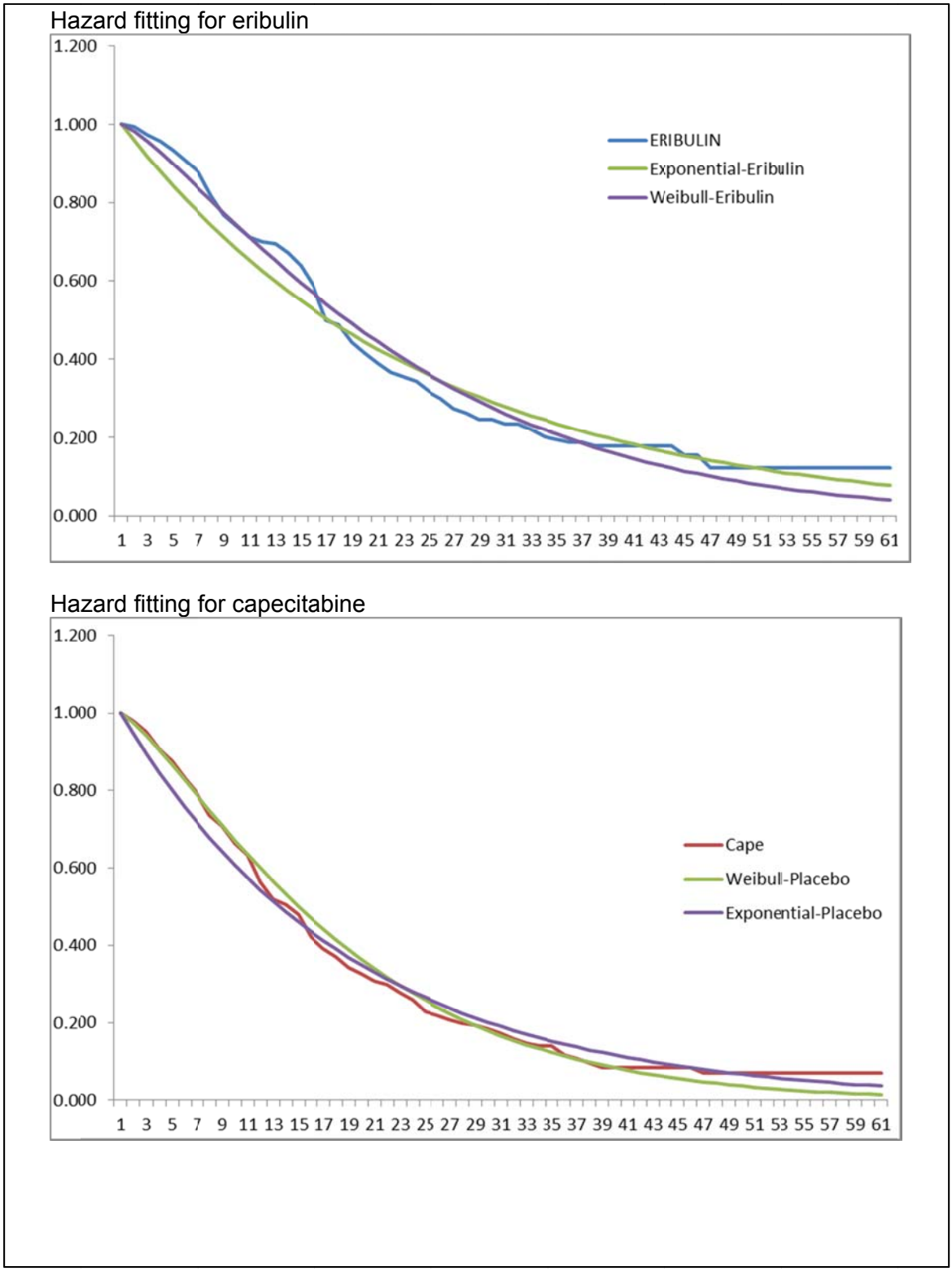


Table 47 Statistical criteria for subgroup 1

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

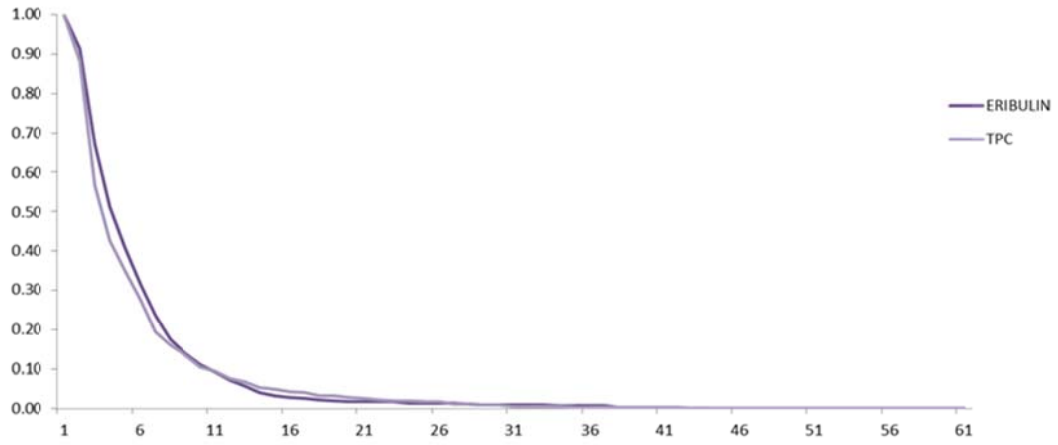


Figure 34 Subgroup 2 – OS KM curves of patients in different treatment groups

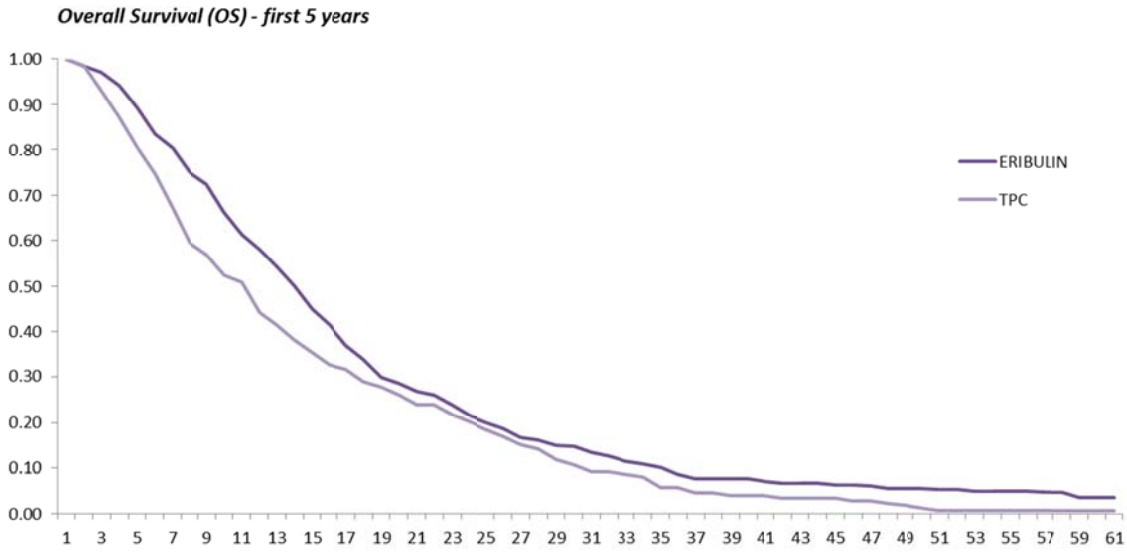
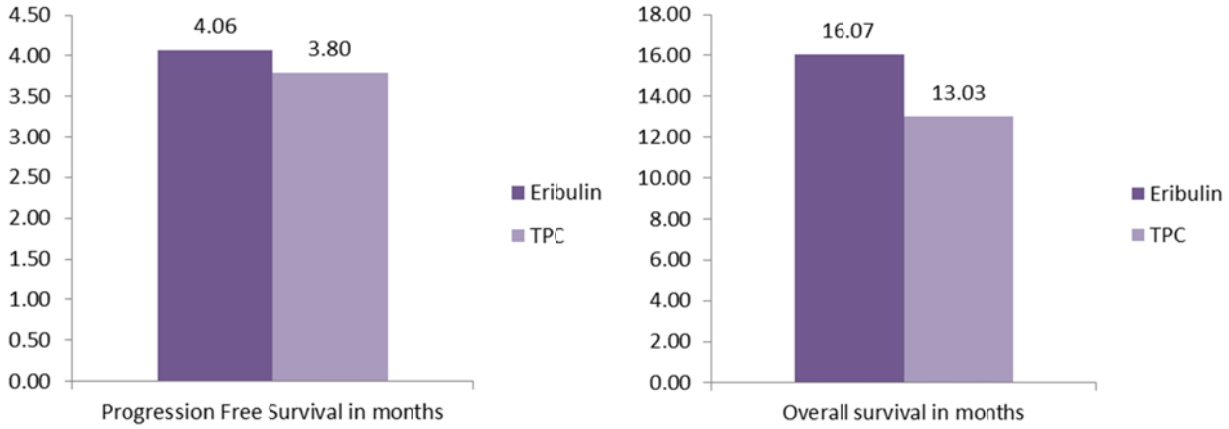


Figure 35 Subgroup 2 – PFS and OS of patients in different treatment groups



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.

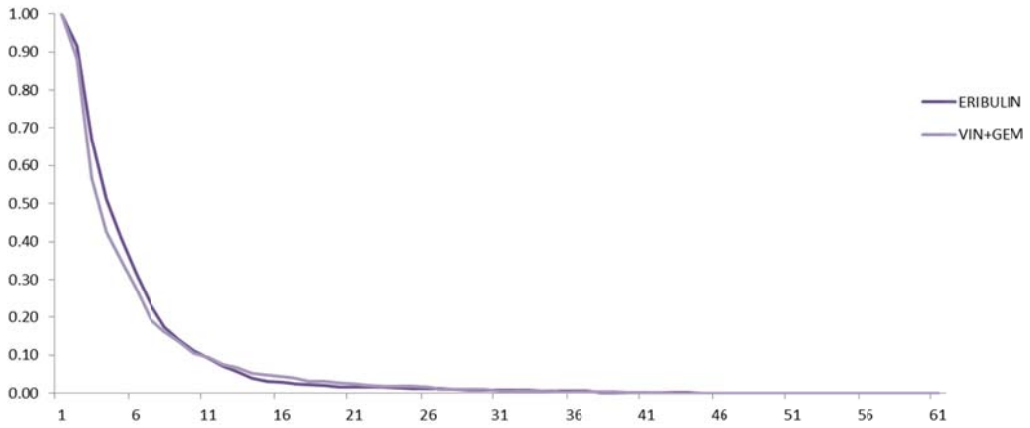
Vinorelbine component of the mix is assumed to be comprised of 50% oral formulation and 50% IV formulation.

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).

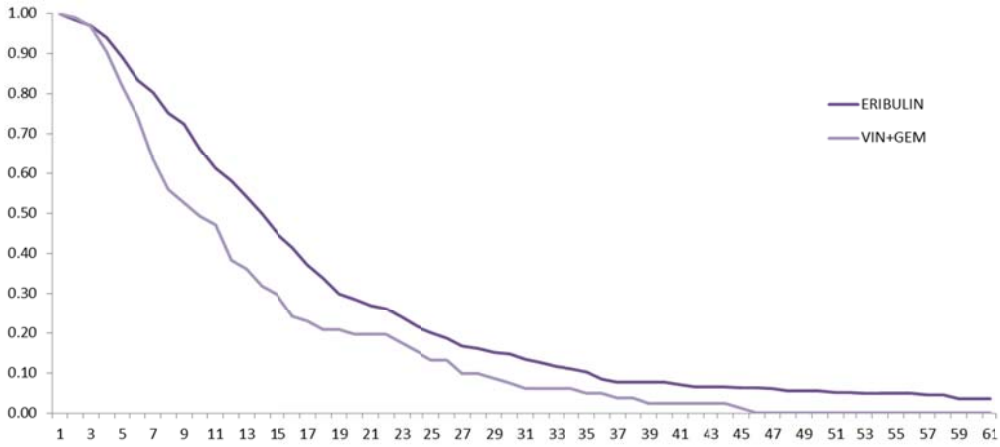
The figures overleaf summarise the efficacy results of this sensitivity scenario.

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.

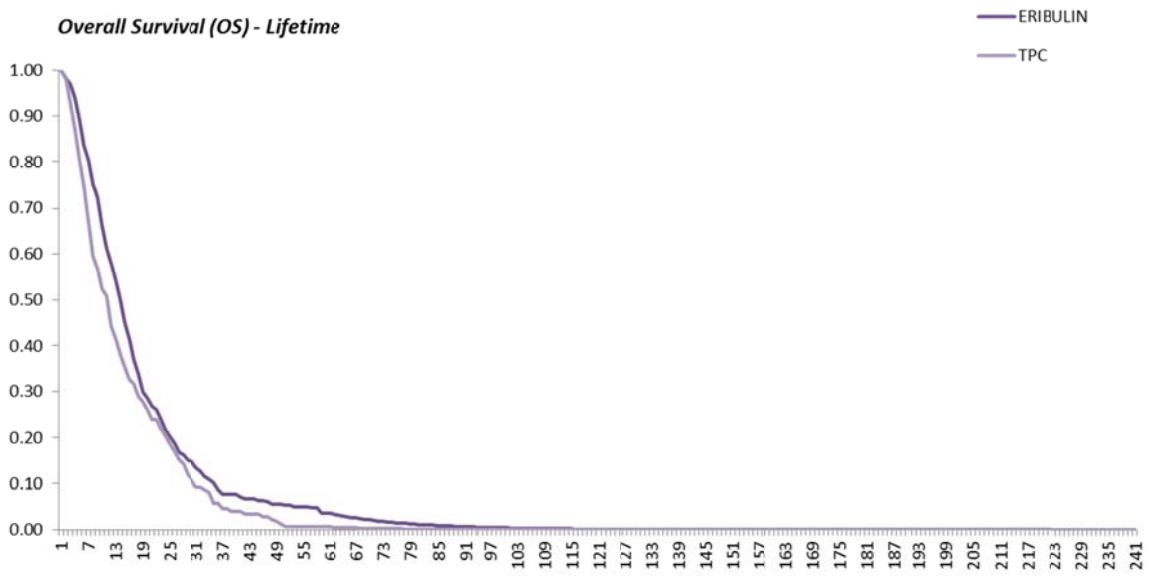
In detail, exponential and Weibull parametric functions including treatment covariate were used to extrapolate the OS curves of eribulin and TPC. The extrapolation was performed over 20 years. The parametric functions were then used to extrapolate the tail of the Kaplan-Meier curves used in the model.

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

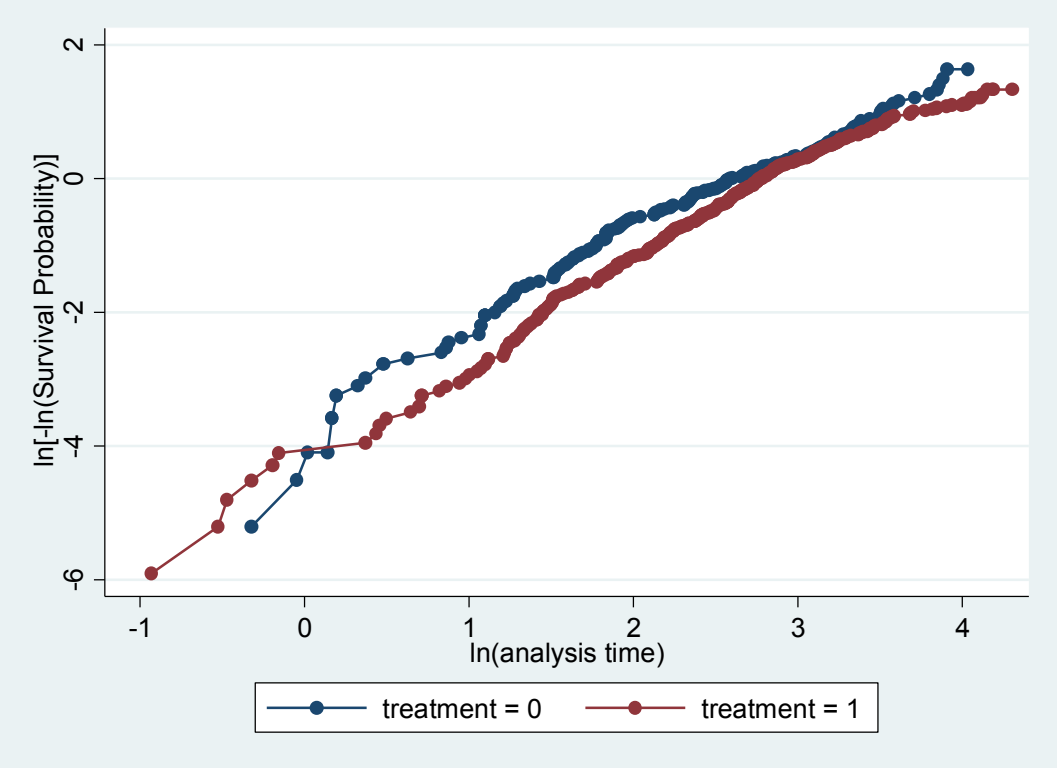


Table 48 PH Global Test results for subgroup 2

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

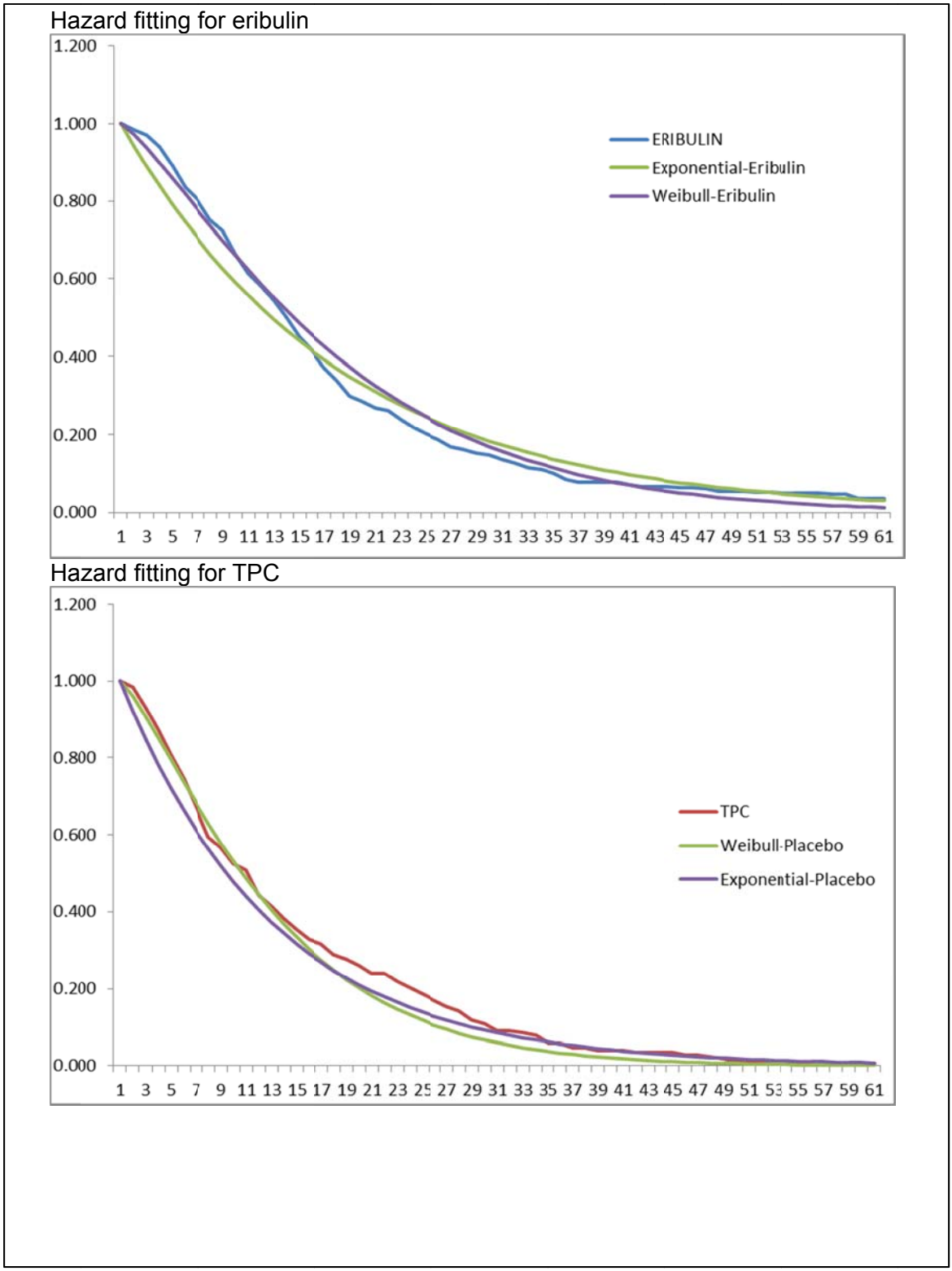


Table 49 Statistical criteria for subgroup 2

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

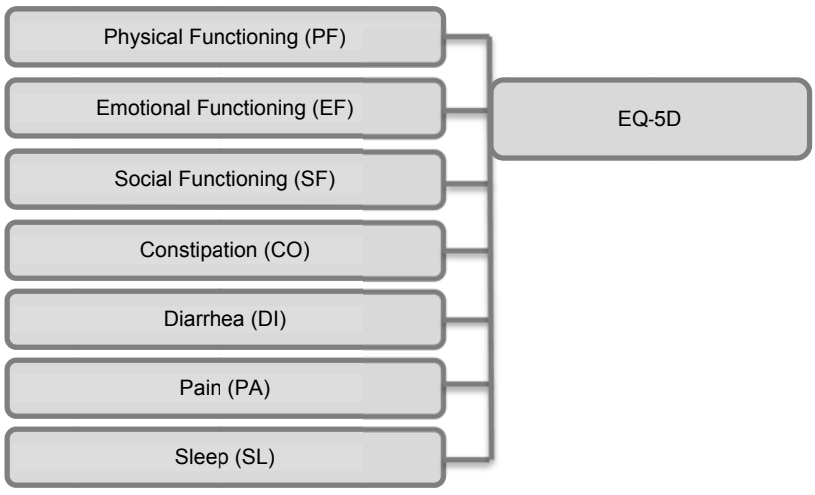
Health-related quality-of-life data from clinical trials

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

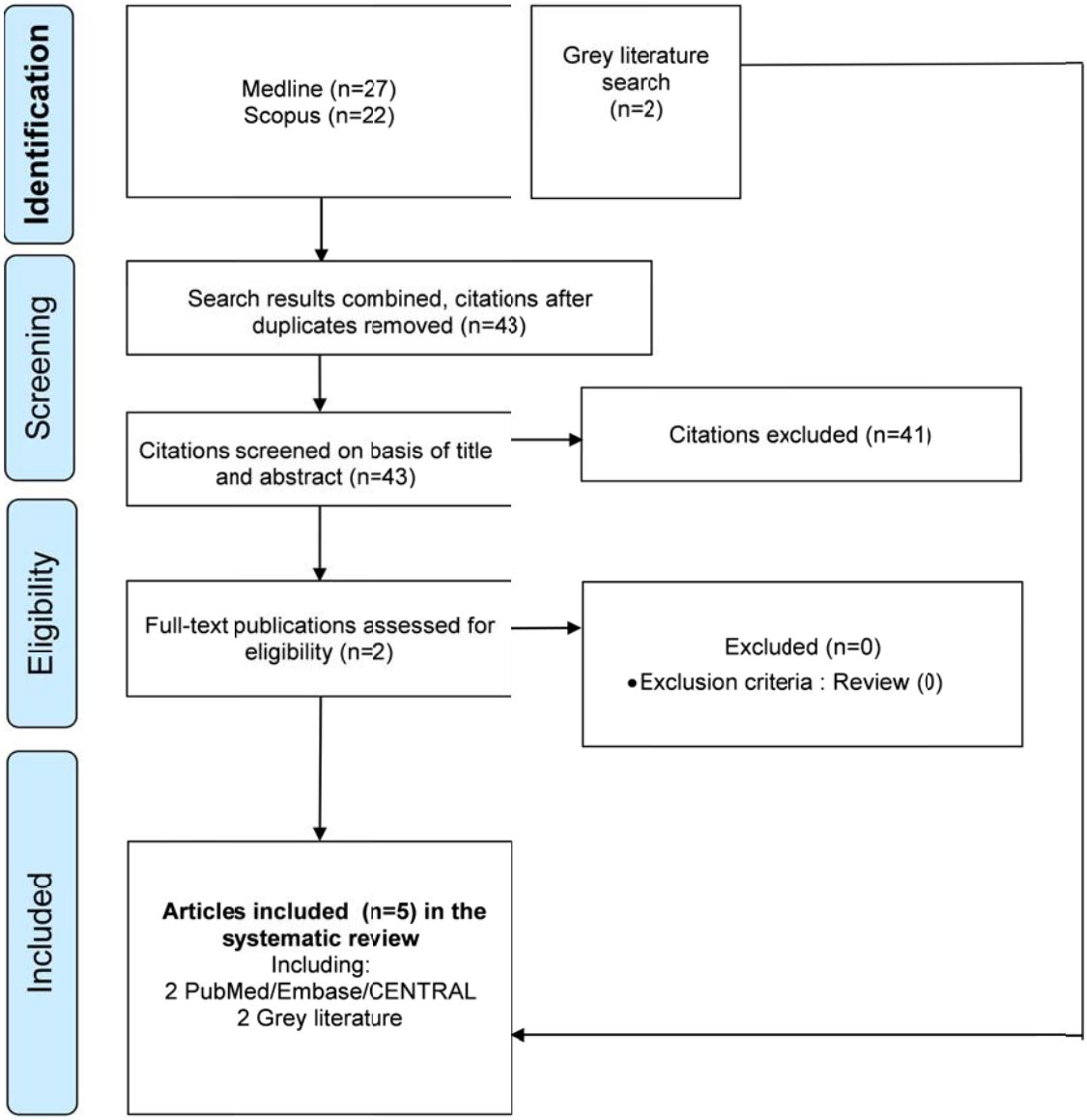
Flow Diagrams of included and excluded studies

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.

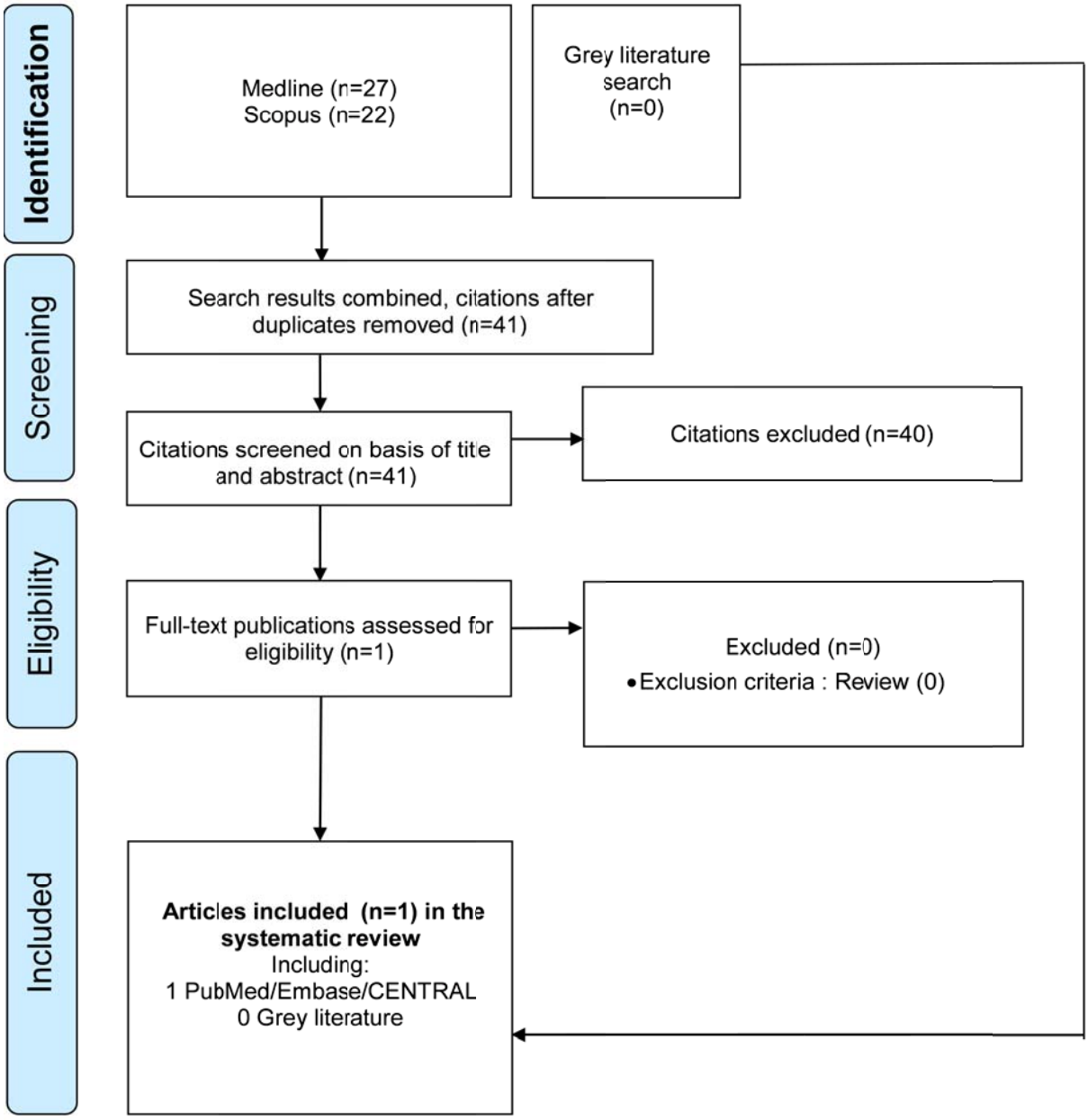


2. *Patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (if indicated)*

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

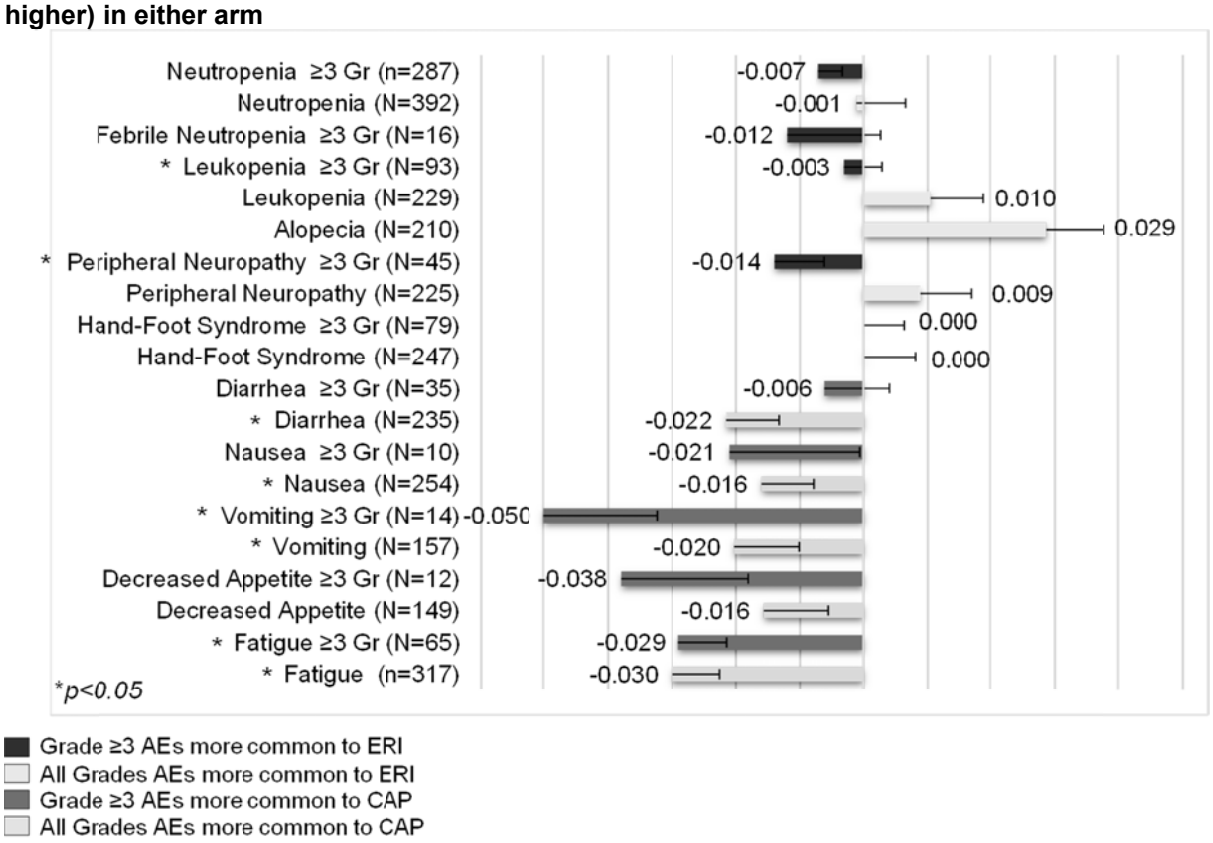
	Eribulin (n=503)		Capecitabine (n=247)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Neutropenia	54%	46%	16%	5%
Febrile Neutropenia	2%	2%	1%	1%
Leukopenia	31%	15%	10%	2%
Alopecia (hair loss)	35%	0%	18%	0%
Peripheral Neuropathy	13%	3%	7%	1%
Hand-foot syndrome	0%	0%	45%	14%
Diarrhea	14%	1%	29%	5%
Nausea	22%	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	[redacted]	[redacted]	3.02	2.71
OS	[redacted]	[redacted]	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.

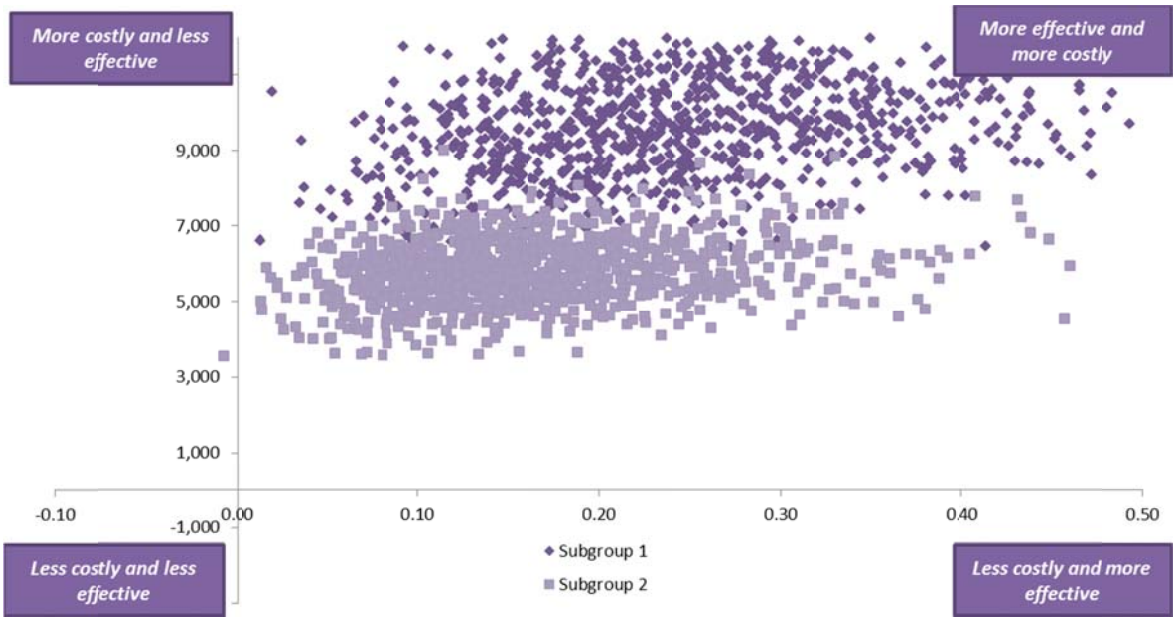
The ICERs in the Probabilistic Model were observed to be between £27,000 and £48,000 for subgroup 1 and between £20,000 and £60,000 for subgroup 2. These were obtained by varying all the utility and survival parameters such as Baseline Utility, Tumour Response Utility, Progression Utility, Pre-progression 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							

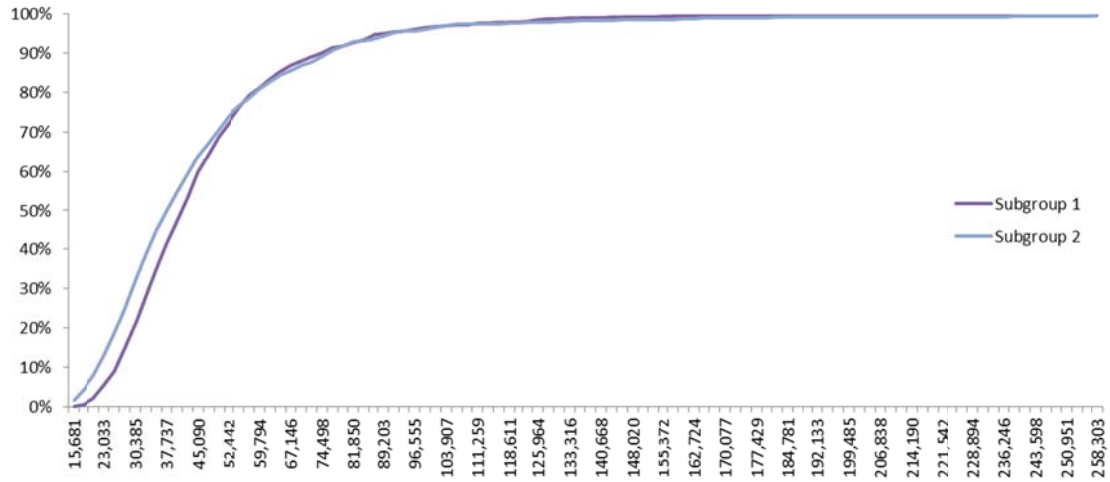
**Source: Briggs, A.H. and Goeree, R. and Blackhouse, G. and O'Brien, B.J. (2002) Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. Medical Decision Making 22(4):pp. 290-308 (90)*

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

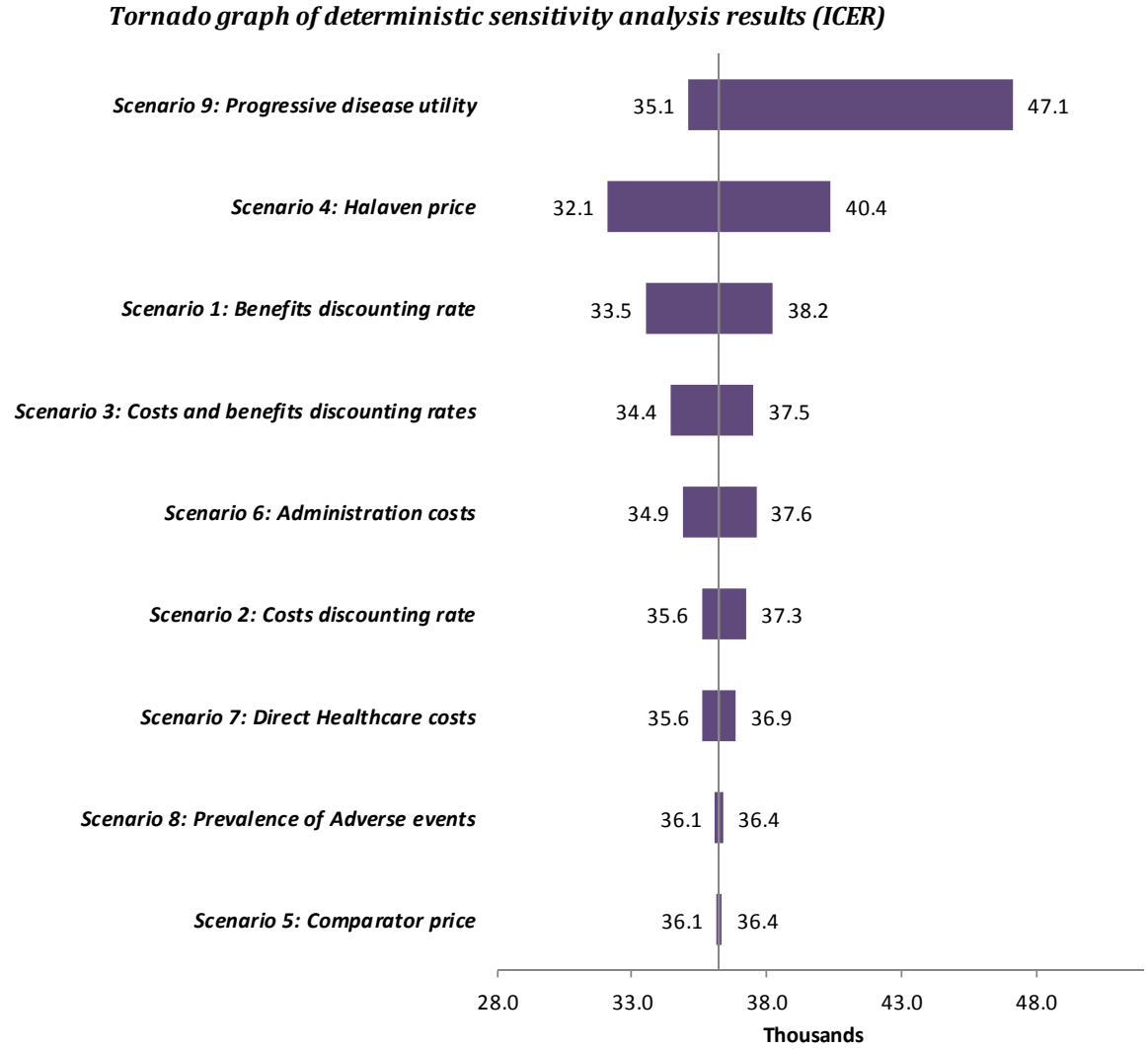
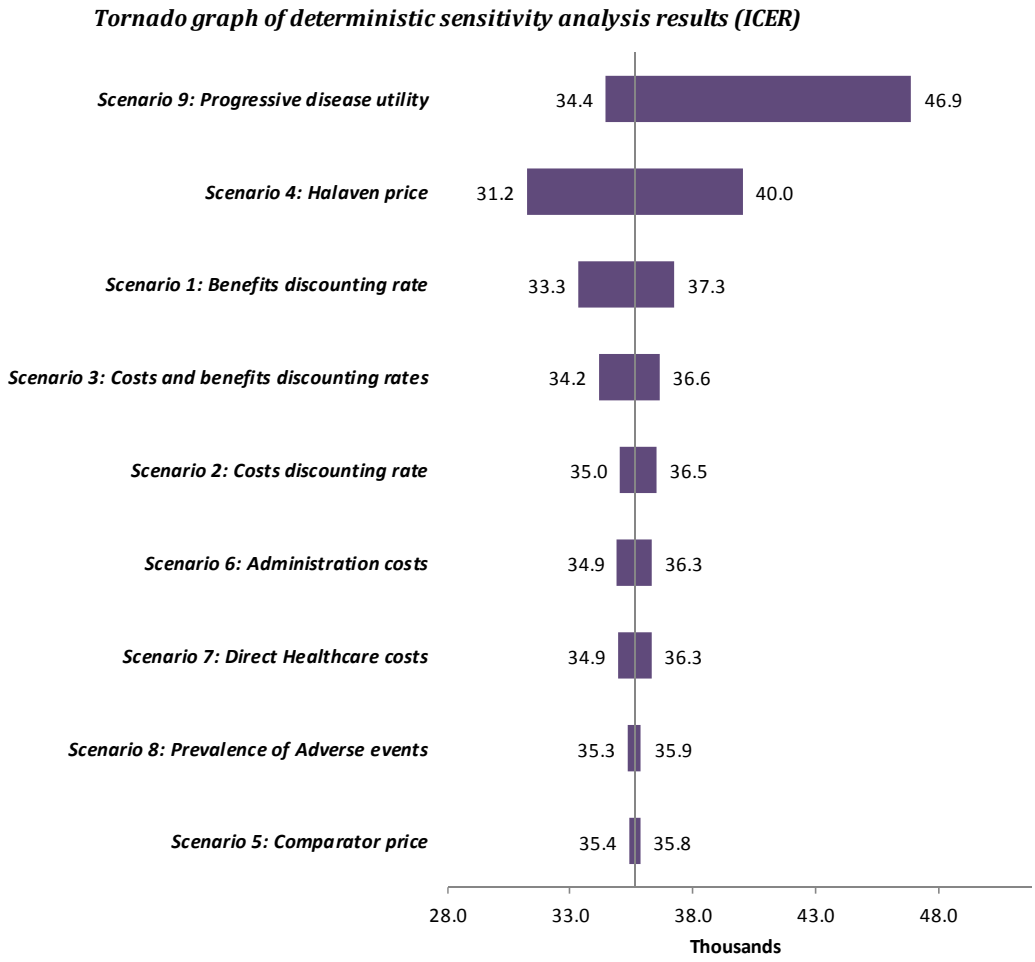


Figure 48 Tornado graph for subgroup 2



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%

7 References

1. Jordan MA, Kamath K, Manna T, et al. The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. Mol Cancer Ther 2005 Jul;4(7):1086-95
2. Benbow SJ, Cook BM, Reifert J, et al. Effects of Paclitaxel and Eribulin in Mouse Sciatic Nerve: A Microtubule-Based Rationale for the Differential Induction of Chemotherapy-Induced Peripheral Neuropathy. Neurotox Res 2016; 29:299–313
3. Wozniak KM, Nomoto K, Lapidus RG, et al. Comparison of Neuropathy-Inducing Effects of Eribulin Mesylate, Paclitaxel, and Ixabepilone in Mice. Cancer Research 2011;71(11):3952-3962
4. Kuznetsov G, TenDyke K, Yu M, et al. Antiproliferative effects of halichondrin B analog eribulin mesylate (E7389) against paclitaxel-resistant human cancer cells *in vitro*. AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics, 22-26 October 2007, San Francisco. Abstract C58
5. Funahashi Y, Okamoto K, Adachi Y, et al. Eribulin mesylate reduces tumor mircroenvironment abnormality by vascular remodelling in preclincal human breast cancer models. Cancer Sci 2014; 105(10):1334-1342
6. Cortes J, O'Shaughnessy JO, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011; 377: 914–923
7. Eisai Ltd data on file. The "EMBRACE" Trial: Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389. A Phase III Open-Label, Randomized, Parallel, Two-arm, Multi-center Study of E7389 Versus "Treatment of Physician's Choice" in Patients With Locally Recurrent, Metastatic Breast Cancer, Previously Treated With At Least Two and a Maximum of Five Prior Chemotherapy Regimens, Including an Anthracycline and a Taxane (E7389-G000-305). Clinical study report.
8. Eisai Ltd data on file. Overall Survival Update Analysis. Protocol Number: E7389-G000-305. The EMBRACE. Trial: Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389. A Phase 3 Open Label, Randomized Parallel Two-Arm Multi-Center Study of E7389 versus .Treatment of Physician's Choice. in Patients with Locally Recurrent or Metastatic Breast Cancer, Previously Treated with At Least Two and a Maximum of Five Prior Chemotherapy Regimens, Including an Anthracycline and a Taxane. 2010.
9. Eisai Ltd data on file. 95% OS data post-cape
10. 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
11. Eisai Ltd data on file. A Phase III Open Label, Randomized Two-Parallel-Arm Multicenter Study of E7389 Versus Capecitabine in Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes (E7389-G000-301). Clinical study report.
12. Eisai Ltd data on file. HER2-negative 2nd line
13. Cancer Research UK. UK breast cancer incidence statistics 2013; http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero, accessed 26th April 2016
14. Cancer Research UK (CancerHelp UK). TNM breast cancer staging; http://www.cancerhelp.org.uk/type/breast-cancer/treatment/tnm-breast-cancer-staging, accessed 26th April 2016.
15. Cancer Research UK (CancerHelp UK). Number of stages of breast cancer; http://www.cancerhelp.org.uk/type/breast-cancer/treatment/number-stages-of-breast-cancer, accessed 26th April 2016.
16. Berkowitz N, Gupta S, Silberman G. Estimates of the lifetime direct costs of treatment for metastatic breast cancer. Value Health 2000 Jan-Feb;3(1):23-30
17. National Institute for Health and Care Excellence. NICE clinical guideline 81: Advanced breast cancer: diagnosis and treatment - full guideline. 2009.
18. Wilson KA, Dowling AJ, Abdolell M, et al. Perception of quality of life by patients, partners and treating physicians. Qual Life Res 2000;9(9):1041-52
19. Klee M, Groenvold M, Machin D. Quality of life of Danish women: population-based norms of the EORTC QLQ-C30. Qual Life Res 1997 Jan;6(1):27-34

20. Aranda S, Schofield P, Weih L, et al. Mapping the quality of life and unmet needs of urban women with metastatic breast cancer. Eur J Cancer Care (Engl) 2005 Jul;14(3):211-22
21. Kissane DW, Grabsch B, Love A, et al. Psychiatric disorder in women with early stage and advanced breast cancer: a comparative analysis. Aust N Z J Psychiatry 2004 May;38(5):320-6
22. Roché H and Vahdat LT. Treatment of metastatic breast cancer: second line and beyond. Annals of Oncology 2011;22(5):1000-1010
23. Lobbezoo, DJ, van Kampen, RJW, Voogd, AC, et al. Prognosis of metastatic breast cancer subtypes: the hormone receptor/HER2-positive subtype is associated with the most favorable outcome. Breast Cancer Research and Treatment 2013;141(3):507–514
24. Schleinitz MD, DePalo D, Blume J, et al. Can differences in breast cancer utilities explain disparities in breast cancer care? Journal of General Internal Medicine 2006;21:1253–1260
25. Efficace F, Rees J, Fayers P, et al. Overcoming barriers to the implementation of patient-reported outcomes in cancer clinical trials: the PROMOTION Registry. Health and Quality of Life Outcomes 2014;12:86
26. European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4) 2013; http://www.ema.europa.eu/ema/accessed 15th February 2016
27. Sheik-Yousouf A, Gandhi S, Dukhovny S, et al. A comparison of physician and patient perceptions of clinically important endpoints in the treatment of Metastatic Breast Cancer (MBC). Eur J Cancer, Abstract Book EBCC7 - European Breast Cancer Conference 2010 March;8(3):77
28. Jassem J, Carroll C, Ward SE, et al. The clinical efficacy of cytotoxic agents in locally advanced or metastatic breast cancer patients pretreated with an anthracycline and a taxane: a systematic review. Eur J Cancer 2009 Nov;45(16):2749-58
29. National Institute for Health and Care Excellence. NICE clinical guideline 81: Advanced breast cancer (update): diagnosis and treatment. 2014.
30. Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). The Breast 2014; 23(5): 489-502
31. Partridge AH, Rumble RB, Carey LA, et al. Chemotherapy and Targeted Therapy for Women with Human Epidermal Growth Factor Receptor 2-Negative (or unknown) Advanced Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2014; 32(29): 3307-3329
32. Twelves C, Jove M and Cortes J. Recognizing the Place of Trials With Treatment of Physician's Choice As the Control Arm. J Clin Oncol 2015; 33(11): 1300
33. Krop IE, Kim SB, González-Martín A, et al: Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): A randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:689-699
34. Perez EA, Awada A, O'Shaughnessy J, et al. Etirinotecan pegol (NKTR-102) versus treatment of physician's choice in women with advanced breast cancer previously treated with an anthracycline, a taxane, and capecitabine (BEACON): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2015; 16: 1556-1568
35. Thanopoulou E, Omarini C, Yeo B, et al. Safety and efficacy of eribulin mesylate (EM) in patients with advanced breast cancer: The Royal Marsden experience. J Clin Oncol 2014; 32 (suppl): Abstract e12004 and Eribulin Audit slides presented at First Thoughts Meeting in London, January 2014
36. Walshaw RC, Shaukat S, Chan K, et al. Eribulin for advanced breast cancer. Clinical experience in the real world. J Clin Oncol 2014; 32 (suppl): Abstract e12003
37. Ramaswami R, O'Cathail SM, Brindley JH, et al. Activity of eribulin mesylate in heavily pretreated breast cancer granted access via the Cancer Drugs Fund. Future Oncol 2014; 10(3): 363-376
38. Cancer Research UK. UK breast cancer survival statistics; http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero, accessed 26th April 2016
39. Liverpool Reviews and Implementation Group (LRiG). Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2. 2010.
40. Moreno-Aspitia A, Perez EA. Treatment options for breast cancer resistant to anthracycline and taxane. Mayo Clin Proc 2009 Jun;84(6):533-45
41. Dufresne A, Pivot X, Tournigand C, et al. Impact of chemotherapy beyond the first line in patients with metastatic breast cancer. Breast Cancer Res Treat 2008 Jan;107(2):275-9
42. Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. J Exp Clin Cancer Res 2008;27:32

43. Kowal-Podmore S, Munakata J, Tencer T, et al. The economic burden of adverse events associated with salvage treatment in advanced and metastatic breast cancer. ISPOR 11th Annual European Congress 8-11 November, 2008, Athens, Greece. PCN62
44. Visovsky C, Collins M, Abbott L, et al. Putting evidence into practice: evidence-based interventions for chemotherapy-induced peripheral neuropathy. Clin J Oncol Nurs 2007 Dec;11(6):901-13
45. Navelbine (vinorelbine) 10 mg / ml concentrate for solution for infusion Summary of Product Characteristics. http://www.medicines.org.uk/emc/medicine/16029, accessed 26th April 2016
46. Twelves C, Cortes J, Vahdat L, et al. Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies. Breast Cancer Research and Treatment 2014;148(3): 553–61.
47. Twelves C, Cortes J, Vahdat L, et al. **Erratum** to: Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies. Breast Cancer Res Treat 2015;149(1):313.
48. Twelves C, Cortes J, Vahdat LT, et al. Efficacy of eribulin in patients (pts) with metastatic breast cancer (MBC): A pooled analysis by HER2 and ER status. Journal of Clinical Oncology 2014;32(Suppl 5). Abstr 631 and poster #95 http://meetinglibrary.asco.org/
49. Twelves C, Cortes J, Olivo M, He, et al. Efficacy of eribulin in a second-line or later settin in patients (pts) with metastatic breast cancer (MBC): a pooled analysis. Annals of Oncology 2014;25(suppl 4): iv129–iv130. ESMO abstract and poster 393P
50. Vahdat, LT, Garcia, AA, Vogel, C, et al. Eribulin mesylate versus ixabepilone in patients with metastatic breast cancer: a randomized Phase II study comparing the incidence of peripheral neuropathy. Breast Cancer Res Treat 2013;140(2): 341–51.
51. Twelves C, Loesch D, Blum JL, et al. A phase III study (EMBRACE) of eribulin mesylate versus treatment of physician's choice in patients with locally recurrent or metastatic breast cancer previously treated with an anthracycline and a taxane. Journal of Clinical Oncology 2010;28(18 Suppl): 958 Abstract CRA1004.
52. Vahdat LT, Twelves CJ, Seegobin S, et al. Survival Outcomes with Eribulin Mesylate vs. Treatment of the Physician's Choice (TPC) in Heavily Pretreated Subjects with Locally Recurrent or Metastatic Breast Cancer in North America, Western Europe, and Australia: Results of the Phase III EMBRACE Study. Thirty-Third Annual CTRC-AARC San Antonio Breast Cancer Symposium, 8-12 December 2010: Abstract P6-13-02.
53. Blum JL , Twelves CJ , Akerele C , et al. Impact of the Number of Prior Chemotherapy Regimens on Overall Survival (OS) among Subjects with Locally Recurrent or Metastatic Breast Cancer Treated with Eribulin Mesylate : Results from the Phase III EMBRACE Study. Thirty-Third Annual CTRC-AARC San Antonio Breast Cancer Symposium, 8-12 December 2010: Abstract P6-13-01.
54. Cardoso F, Twelves C, Vahdat LT, et al. Eribulin mesylate EMBRACE study - Survival analysis excluding patients re-challenged with therapies of the same class. European journal of cancer 2011;47: S331
55. Cortes J, Twelves C, Wanders J, et al. Clinical response to eribulin in patients with metastatic breast cancer is independent of time to first metastatic event. EMBRACE study group. The Breast 2011; 20: S48 (P0107)
56. Therasse P, Arbuck SG, Eisenhauer EA , et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000 Feb 2;92(3):205-16
57. Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996;14:2756-2768
58. EORTC Manual. (2001). http://www.eortc.be/qol/files/SCManualQLQ-C30.pdf. Accessed June 3, 2015
59. Little RJ, Rubin DB. Statistical analysis with missing data. 2nd edition. 2002. John Wiley & Sons, New York, NY
60. Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol 2011;29:89-96
61. Osoba D, Slamon DJ, Burchmore M, et al. Effects on quality of life of combined trastuzumab and chemotherapy in women with metastatic breast cancer. J Clin Oncol 2002;20:3106-3113
62. Eisai Ltd Data on File ERI-102

63. Harrison CN, Mesa RA, Kiladjian JJ, et al. Health-related quality of life and symptoms in patients with myelofibrosis treated with ruxolitinib versus best available therapy. Br J Haematol 2013;162:229-239
64. 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
65. Beusterien K, Grinspan J, Kuchuk I, et al. Use of Conjoint Analysis to Assess Breast Cancer Patient Preferences for Chemotherapy Side Effects. The Oncologist 2014; 19:127-134
66. Dell'Ova M, De Maio E, Guiu S, et al. Tumour biology, metastatic sites and taxanes sensitivity as determinants of eribulin mesylate efficacy in breast cancer: results from the ERIBEX retrospective, international multicenter study. BMC Cancer 2015; 15: 659
67. Ruiz-Borrego M, Garcia-Saenz JA, Hornedo FJ, et al. First year daily clinical experience with eribulin in Spain: EUFORIA-1 study (Eribulin Use FOR the treatment of advanced breast cancer: observational, retrospective analysis). Poster presented at ESMO 2013 Congress, 27 September – 1 October, Amsterdam. Abstract 1899
68. DiBonaventura M, Copher R, Basurto E, et al. Patient Preferences and Treatment Adherence Among Women Diagnosed with Metastatic Breast Cancer. Am Health Drug Benefits 2014; 7(7): 386-396
69. National Institute for Health and Clinical Excellence. NICE technology appraisal guidance 116: Gemcitabine for the treatment of metastatic breast cancer. 2007
70. 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
71. 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
72. 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.
73. 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
74. Lopes G, Glück S, Avancha K, et al. 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.
75. Jones TE, Tremblay G, Majethia U, et al. Cost Effectiveness Analysis of Eribulin Mesylate (Halaven®) as a Treatment for Metastatic Breast Cancer in Mexico. ISPOR 5th Latin American Conference, 6-8 September 2015, Santiago, Chile. PCN84
76. Sacco J, Botten J, Macbeth F, et al. The average body surface area of adult cancer patients in the UK: a multicenter retrospective study. PLos One 2010; 5(1):e8933.
77. Kantar Health. Treatment Architecture: Western Europe Breast Cancer. Kantar Health 2013
78. NICE DSU technical support document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf
79. Aaronson N, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993: 365-376.
80. Osoba D, Zee B, Pater JW, et al. Psychometric properties and responsiveness of the EORTC quality of Life Questionnaire (QLQ-C30) in patients with Breast, Ovarian and Lung Cancer. Quality of Life Research 1994: 353-364.
81. Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. Eur J Health Econ 2010: 427-434.
82. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997: 1095-1108

83. 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.
84. 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
85. eMit National database. https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Accessed 26th May 2016
86. MIMS. www.mims.co.uk. Accessed 26th May 2016
87. Electronic medicines compendium. http://www.medicines.org.uk/emc/. Accessed 26th May 2016
88. Department of Health. NHS Reference Costs. Available at: https://www.gov.uk/government/collections/nhs-reference-costs. Accessed 26th May 2016
89. Curtis, L and Burns A. Unit Costs of Health and Social Care. PSSRU 2015
90. Briggs AH, Goeree R, Blackhouse G, et al. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. Medical Decision Making 2002;22(4):290-308
91. Briggs AH. Model Parameter Estimation and Uncertainty Analysis A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group. Medical Decision Making 2012; 32:722–732.
92. Taylor M. What is sensitivity analysis? http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/What_is_sens_analy.pdf
93. National Institute for Health and Clinical Excellence. NICE technology appraisal guidance 371: Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane. 2015
94. Tremblay G, Haines P, and Briggs, A. A criterion-based approach for the systematic and transparent extrapolation of clinical trial survival data. Journal of Health Economics and Outcomes Research 2015;2(2):147-160.
95. Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. Br J Cancer 2006;18;95(6): 683–690.
96. NICE DSU technical support document 11. http://www.nicedsu.org.uk/TSD11%20Alternatives%20to%20EQ-5D_final.pdf
97. Cancer Mpact database, Kantar Health

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 [ID 1072]

Dear Cyndy,

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.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **Tuesday 5 September 2017**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals via this link:
https://appraisals.nice.org.uk/request/32518

If you have any further queries on the technical issues raised in this letter then please contact Anna Brett, Technical Lead (Anna.Brett@nice.org.uk). Any procedural questions should be addressed to Thomas Feist, Project Manager (TACommA@nice.org.uk) in the first instance.

Yours sincerely

Janet Robertson

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Associate Director – Appraisals
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Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **Priority Question**: Please clarify that the data for Study 301 reported in the submission are from the most recent data-cut.

A2. **Priority Question**: The updated scope from NICE (August 2016) identifies the relevant population to be as follows:

Adults with locally advanced or metastatic breast cancer that has progressed after one prior chemotherapeutic regimen for advanced disease (anthracycline and a taxane, unless these treatments were not suitable).

In relation to this population, the company submitted evidence for patients with HER2-negative disease who had received only one prior chemotherapeutic regimen for advanced disease (Subgroup 1).

Please clarify:

a. The rationale for focussing only on patients with HER2-negative disease.

b. For OS and PFS, whether statistically significant findings were found between arms in Study 301 for all patients who had received one prior chemotherapeutic regimen for advanced disease, regardless of their HER2 status.

A3. Please clarify whether any adverse event data has been collected specifically for Subgroup 1 in Study 301 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.

A4. For Study 301, please provide a participant flow diagram for patients included in Subgroup 1 (in a format similar to Figure 8 of the company submission).

A5. For Study 301, please provide a table with study drug exposure for Subgroup 1 (in a format similar to Table 18 of the company submission).

A6. For Study 301, in order to fully compare the baseline characteristics of Subgroup 1 with the ITT trial population, please provide the missing baseline characteristics in Table 1 of this clarification letter. Please also confirm whether the data marked as academic in confidence in Table 1 of this clarification letter should still be marked as academic in confidence.

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Table 1 Baseline characteristics in Study 301 – ITT population and Subgroup 1

Characteristic	ITT population			Subgroup1		
	Eribulin (n = 554)	Capecitabine (n = 548)	Total (n = 1102)	Eribulin (n = 186)	Capecitabine (n = 206)	Total (n = 392)
Median Age, years (range)	54.0 (24–80)	53.0 (26–80)	54.0 (24–80)			
Age distribution, n (%)						
≤ 40 yrs	59 (10.6)	73 (13.3)	132 (12.0)	16 (8.6)	36 (17.5)	52 (13.3)
40 to < 65 yrs	399 (72.0)	413 (75.4)	812 (73.7)	135 (72.6)	150 (72.8)	285 (72.7)
≥ 65 yrs	96 (17.4)	62 (11.3)	158 (14.3)	35 (18.8)	20 (9.7)	55 (14.0)
Race, n (%)						
White	496 (89.5)	495 (90.3)	991 (89.9)	163 (87.6)	191 (92.7)	354 (90.3)
Black or African American	15 (2.7)	16 (2.9)	31 (2.8)	6 (3.2)	1 (0.5)	7 (1.8)
Asian/Pacific Islander	18 (3.2)	18 (3.3)	36 (3.3)	7 (3.8)	8 (3.9)	15 (3.8)
Other	25 (4.5)	19 (3.5)	44 (4.0)	10 (5.4)	6 (2.9)	16 (4.1)
Geographic region, n (%)						
North America, Western Europe, Asia	137 (24.7)	132 (24.1)	269 (24.4)	46 (24.7)	56 (26.9)	100 (25.5)
Eastern Europe	307 (55.4)	305 (55.7)	612 (55.5)	99 (53.2)	112 (54.4)	211 (53.8)
Latin America, South Africa	110 (19.9)	111 (20.3)	221 (20.1)	41 (22.0)	38 (18.4)	79 (20.2)
Median time since original diagnosis (range), years	3.0 (0.2, 28.3)	2.6 (0.2, 21.6)	2.8 (0.2, 28.3)			
ER Status, n (%)						
+	259 (46.8)	278 (50.7)	537 (48.7)	104 (55.9)	116 (56.3)	220 (56.1)
–	233 (42.1)	216 (39.4)	449 (40.7)	82 (44.1)	87 (42.2)	169 (43.1)
Not done	62 (11.2)	54 (9.9)	116 (10.5)	0	3 (1.5)	4 (1.0)
HER2 status, n (%)						
+	86 (15.5)	83 (15.1)	169 (15.3)	0	0	0
–	375 (67.7)	380 (69.3)	755 (68.5)	186 (100.0)	206 (100.0)	392 (100.0)
Not done	93 (16.8)	85 (15.5)	178 (16.2)	0	0	0
Triple negative (ER/PR/HER2-negative), n (%)	150 (27.1)	134 (24.5)	284 (25.8)	73 (39.2)	72 (35.0)	145 (37.0)

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Characteristic	ITT population			Subgroup1		
	Eribulin (n = 554)	Capecitabine (n = 548)	Total (n = 1102)	Eribulin (n = 186)	Capecitabine (n = 206)	Total (n = 392)
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 Total, 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)			
Site of disease, n (%)*						
Visceral				[redacted]	[redacted]	
Non-visceral only				[redacted]	[redacted]	
Disease progression within 60 days of last dose of taxane				[redacted]	[redacted]	

* Visceral/non-visceral determined by independent assessment

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A7. Please provide in Table 2 of this clarification letter, the number and proportion of patients in Study 301 (complete ITT population and Subgroup 1) who received subsequent treatment (including any crossover from one arm to another) on disease progression with details about the subsequent treatment received.

Table 2 Subsequent treatment received on disease progression in Study 301

Treatment on disease progression	**ITT population**		**Subgroup 1**	
	Eribulin (n = 554)	**Capecitabine (n = 548)**	**Eribulin (n = 186)**	**Capecitabine (n = 206)**
Any, n (%)	390 (70.4)	340 (62.0)		
Eribulin, n (%)		2 (0.4)		
Capecitabine, n (%)	275 (49.6)			
Treatment A, n (%)				
Treatment B, n (%)				
Treatment C, n (%)				
Treatment D, n (%)				
Etc				

A8. For health-related quality of life (HRQoL) data from Study 301, please provide the following information:

a. The numbers of patients represented in each bar of Figure 15 of the company submission.

b. The number of patients (in each arm) for which HRQoL data were available for Subgroup 1.

c. The numbers of patients represented in each bar of Figure 16 of the company submission.

d. The numbers of patients represented in each bar of Figure 17 of the company submission.

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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 Subgroup 1 patients of Study 301 (i.e. HER-2 negative patients with LABC/MBC, whose disease progressed after one prior chemotherapy), including all patients lost to follow-up or withdrawing from trial.

Trial data set: Study 301 latest data cut.

Censoring: Censor lost to follow-up and withdrawn patients at the date recorded. Patients still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off; i.e. not when last known to be alive (OS/PPS), and not at the date of last tumour assessment (PFS).

The rationale for this request is as follows: All Kaplan-Meier analyses are specified to use the 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 patients are exposed to risk but is much less likely to understate events, especially deaths. The result is that the inter-event period hazard rates 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 hazards. 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.

*Format: Please present analysis outputs using the format of the sample table (*Table 3 of this clarification letter*) shown below.*

a. Time to death from any cause (OS): Kaplan-Meier analysis stratified by treatment arm (eribulin vs capecitabine)

b. Time to disease progression or death (PFS): Kaplan-Meier analysis based on investigator assessment, stratified by treatment arm (eribulin vs capecitabine)

c. Time from disease progression by investigator assessment to death from any cause (PPS): Kaplan-Meier analysis stratified by treatment arm (eribulin vs capecitabine). NB exclude from the analysis any patients who died without disease progression

d. Time to the last dose of randomized treatment: Kaplan-Meier analysis stratified by treatment arm (eribulin vs capecitabine).

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Table 3 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

B2. **Priority question:** Please provide the results of the Extent of Exposure analysis as shown in Table 30 of the clinical study report for Study 301, restricted to the Subgroup 1 patients (i.e. 186 patients who received eribulin, and 206 patients who received capecitabine).

B3. **Priority Question**: Please provide results of health state utilities (EQ-5D values mapped from EORTC QLQ-C30) restricted to patients in Subgroup1 formatted as in Table 4 of this clarification letter.

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Table 4 Results of health state utilities (EQ-5D values mapped from EORTC QLQ-C30) restricted to patients in Subgroup1

Health state	Time	Eribulin			Capecitabine		
		Mean	SD	N	Mean	SD	N
Stable	6 weeks						
	3 months						
	6 months						
	12 months						
	18 months						
	24 months						
Response to treatment	6 weeks						
	3 months						
	6 months						
	12 months						
	18 months						
	24 months						
Progressive disease	6 weeks						
	3 months						
	6 months						
	12 months						
	18 months						
	24 months						

SD = standard deviation

Section C: Textual clarifications and additional points

C1. **Priority Question**: Please provide the trial protocol for Study 301.

C2. **Priority Question**: Please provide the Statistical Analysis Plan for Study 301.

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Single Technology Appraisal (STA)

Eribulin for treating locally advanced or metastatic breast cancer after chemotherapy [ID 1072]

Dear Cyndy,

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.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **Tuesday 5 September 2017**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be uploaded to NICE Docs/Appraisals via this link:
https://appraisals.nice.org.uk/request/32518

If you have any further queries on the technical issues raised in this letter then please contact [redacted], Technical Lead [redacted] Any procedural questions should be addressed to [redacted], Project Manager (TACommA@nice.org.uk) in the first instance.

Yours sincerely

Janet Robertson
Associate Director – Appraisals

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Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **Priority Question**: Please clarify that the data for Study 301 reported in the submission are from the most recent data-cut.

Eisai can confirm that the data for Study 301 reported in the submission are from the most recent, final data-cut.

A2. **Priority Question**: The updated scope from NICE (August 2016) identifies the relevant population to be as follows:

Adults with locally advanced or metastatic breast cancer that has progressed after one prior chemotherapeutic regimen for advanced disease (anthracycline and a taxane, unless these treatments were not suitable).

In relation to this population, the company submitted evidence for patients with HER2-negative disease who had received only one prior chemotherapeutic regimen for advanced disease (Subgroup 1).

Please clarify:

a. The rationale for focussing only on patients with HER2-negative disease.

b. For OS and PFS, whether statistically significant findings were found between arms in Study 301 for all patients who had received one prior chemotherapeutic regimen for advanced disease, regardless of their HER2 status.

The main rationale for focussing only on patients with HER2-negative disease is due to current clinical practice and the unmet clinical need in this difficult to treat patient population.

As highlighted in the Eisai evidence submission, approximately 85% of patients with LABC/MBC are diagnosed with HER2-negative disease.

Whereas historically, HER2+ tumour status has been associated with more aggressive disease and poorer patient outcomes; nowadays, those patients with a HER2+ status will receive targeted/biological agents. Therefore the prognosis for HER2-positive patients has reversed (1) 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) (2). There is therefore still a medical unmet need within this specific patient subgroup and chemotherapy treatments such as eribulin continue to play a key role.

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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) 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.

For those patients in study 301 who had received one prior chemotherapeutic regimen for advanced disease, regardless of HER2-negative disease, the OS results for eribulin were statistically significant versus capecitabine (HR: 0.83; 95% CI, 0.69 to 1.00, p=0.050). As per the investigator-assessed PFS results for patients in Subgroup 1, no difference in median PFS was observed between the eribulin and capecitabine treatment groups for those patients in study 301 who had received one prior chemotherapeutic regimen for advanced disease, regardless of HER2-negative disease (HR: 1.029; 95% CI 0.84 to 1.260).

A3. Please clarify whether any adverse event data has been collected specifically for Subgroup 1 in Study 301 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 1 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 301 (Table 34 in the CS) versus the incidence of the same adverse events in Subgroup 1.

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Table 1 Most commonly reported adverse events by treatment group: Study 301 (ITT population and Subgroup 1)

	ITT Population		Subgroup 1	
System organ class AEs	**Eribulin N=544 n (%)**	**Capecitabine N=546 n (%)**	**Eribulin N=184 n (%)**	**Capecitabine N=205 n (%)**
Blood and Lymphatic				
Neutropenia	295 (54.2%)	87 (15.9%)	98 (53.3%)	30 (14.6%)
Anaemia	104 (19.1%)	96 (17.6%)	39 (21.2%)	40 (19.5%)
Leucopoenia	171 (31.4%)	57 (10.4%)	57 (31.0%)	19 (9.3%)
Gastrointestinal				
Nausea	121 (22.2%)	133 (24.4%)	38 (20.7%)	43 (21.0%)
Constipation	<10%	<10%	13 (7.1%)	15 (7.3%)
Diarrhoea	78 (14.3%)	157 (28.8%)	26 (14.1%)	51 (24.9%)
Vomiting	65 (11.9%)	92 (16.8%)	25 (13.6%)	39 (19.0%)
General disorders and administration site				
Asthenia/fatigue	174 (32%)	163 (30%)	58 (31.5%)	52 (25.4)
Pyrexia	70 (12.9%)	31 (5.7%)	26 (14.1%)	10 (4.9%)
Mucosal inflammation	<10%	<10%	10 (5.4%)	16 (7.8%)
Investigations				
Weight decreased	<10%	<10%	9 (4.9%)	10 (4.9%)
Metabolism and nutrition				
Anorexia	68 (12.5%)	81 (14.8%)		
Musculoskeletal and connective tissue				
Arthralgia/ myalgia	<10%	<10%	8 (4.3%)	1 (0.5%)
Back pain	56 (10.3%)	43 (7.9%)	20 (10.9%)	16 (7.8%)
Bone pain	<10%	<10%	18 (9.8%)	18 (8.8%)
Pain in extremity	<10%	<10%	18 (9.8%)	9 (4.4%)
Nervous system				
Headache	69 (12.7%)	57 (10.4%)	24 (13.0%)	23 (11.2%)
Peripheral sensory neuropathy	73 (13.4%)	38 (7.0%)	30 (16.3%)	10 (4.9%)
Respiratory, thoracic and mediastinal				
Dyspnoea	56 (10.3%)	59 (10.8%)	23 (12.5%)	26 (12.7%)

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	ITT Population		Subgroup 1	
System organ class AEs	**Eribulin N=544 n (%)**	**Capecitabine N=546 n (%)**	**Eribulin N=184 n (%)**	**Capecitabine N=205 n (%)**
Cough	<10%	<10%	15 (8.2%)	21 (10.2%)
Skin and subcutaneous tissue				
Alopecia Palmar-plantar erythrodysaesthesia syndrome	188 (34.6%) 1 (0.2%)	22 (4.0%) 246 (45.1%)	64 (34.8%) 1 (0.5%)	6 (2.9%) 99 (48.3%)

Abbreviations: AE, Adverse event; ITT, Intention to treat

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A4. For Study 301, please provide a participant flow diagram for patients included in Subgroup 1 (in a format similar to Figure 8 of the company submission).

The table overleaf presents the information on participant flow for patients included in Subgroup 1, as requested.

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	Treatment Group	
	Eribulin	Capecitabine
Randomised	186	206
Discontinued: ENTRY CRITERIA NOT MET	1	1
Discontinued: WITHDRAWAL OF CONSENT	1	
Safety Population	184	205
Discontinued treatment: ADVERSE EVENT	15	19
Discontinued treatment: CLINICAL PROGRESSION	7	13
Discontinued treatment: PHYSICIAN DECISION	1	3
Discontinued treatment: PROGRESSIVE DISEASE	145	155
Discontinued treatment: WITHDRAWAL OF CONSENT	3	
Discontinued treatment: OTHER	1	3
Discontinued treatment: DEATH	1	
Discontinued treatment: PATIENT'S DECISION BUT ALLOW FOR SURVIVAL FOLLOWUP	9	10
On Treatment	2	2
Survival Status At Data Cut off 12Mar2012, n (%)		
Alive	32(17.2)	22(10.7)
Dead	148(79.6)	180(87.4)
Withdrew Consent	5(2.7)	0
Lost to Follow-Up	1(0.5)	4(1.9)

Subgroup 1: Patients with HER2-negative disease who had received only one prior chemotherapeutic regimen for advanced disease.

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A5. For Study 301, please provide a table with study drug exposure for Subgroup 1 (in a format similar to Table 18 of the company submission).

Please find below Table 18 from the company submission which has been updated to include study drug exposure for Subgroup 1, as requested.

Table 2 Exposure to eribulin: Study 301 (Safety population)

	ITT Population		Subgroup 1	
	Eribulin (N=544)	**Capecitabine (N=546)**	**Eribulin (N=184)**	**Capecitabine (N=205)**
Duration of exposure, median days (min, max)[a]	125 (21–1372)	119 (21-1442)	126 (21-1183)	119 (21-994)
Number of cycles received, n (%)				
1–2	118 (21.7%)	151 (27.7%)	37 (20.1%)	58 (28.3%)
3–4	120 (22.1%)	107 (19.6%)	37 (20.1%)	39 (19.0%)
5–6	107 (19.7%)	73 (13.4%)	38 (20.7%)	28 (13.7%)
> 6	199 (36.6%)	215 (39.4%)	72 (39.1%)	80 (39.0%)
Range	1–65 cycles	1-61 cycles	1-53 cycles	1-42 cycles
Dose intensity, median mg/m^2/week (min, max)[b]	0.86 (0.4, 1.0)	10524.40 (1694.3, 12455.7)	0.88 (0.4, 1.0)	10661.88 (5047.9, 12160.7)
Relative dose intensity, % (min, max)[c]	92% (40, 100)	90% (10, 100)	94% (40, 100)	91% (40, 100)
Patients with dose interruption, n (%)	7 (1.3%)	NA	1 (0.5%)	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).

A6. For Study 301, in order to fully compare the baseline characteristics of Subgroup 1 with the ITT trial population, please provide the missing baseline characteristics in Table 3 of this clarification letter. Please also confirm whether the data marked as academic in confidence in Table 3 of this clarification letter should still be marked as academic in confidence.

Please find overleaf Table 3 which has been updated with the missing baseline characteristics, as requested. The academic in confidence marking has been removed as the data does not need to be marked as academic in confidence.

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Table 3 Baseline characteristics in Study 301 – ITT population and Subgroup 1

Characteristic	ITT population			Subgroup1		
	Eribulin (n = 554)	Capecitabine (n = 548)	Total (n = 1102)	Eribulin (n = 186)	Capecitabine (n = 206)	Total (n = 392)
Median Age, years (range)	54.0 (24–80)	53.0 (26–80)	54.0 (24–80)	55 (31-74)	52 (30-80)	53 (30-80)
Age distribution, n (%)						
≤ 40 yrs	59 (10.6)	73 (13.3)	132 (12.0)	16 (8.6)	36 (17.5)	52 (13.3)
40 to < 65 yrs	399 (72.0)	413 (75.4)	812 (73.7)	135 (72.6)	150 (72.8)	285 (72.7)
≥ 65 yrs	96 (17.4)	62 (11.3)	158 (14.3)	35 (18.8)	20 (9.7)	55 (14.0)
Race, n (%)						
White	496 (89.5)	495 (90.3)	991 (89.9)	163 (87.6)	191 (92.7)	354 (90.3)
Black or African American	15 (2.7)	16 (2.9)	31 (2.8)	6 (3.2)	1 (0.5)	7 (1.8)
Asian/Pacific Islander	18 (3.2)	18 (3.3)	36 (3.3)	7 (3.8)	8 (3.9)	15 (3.8)
Other	25 (4.5)	19 (3.5)	44 (4.0)	10 (5.4)	6 (2.9)	16 (4.1)
Geographic region, n (%)						
North America, Western Europe, Asia	137 (24.7)	132 (24.1)	269 (24.4)	46 (24.7)	56 (26.9)	100 (25.5)
Eastern Europe	307 (55.4)	305 (55.7)	612 (55.5)	99 (53.2)	112 (54.4)	211 (53.8)
Latin America, South Africa	110 (19.9)	111 (20.3)	221 (20.1)	41 (22.0)	38 (18.4)	79 (20.2)
Median time since original diagnosis (range), years	3.0 (0.2, 28.3)	2.6 (0.2, 21.6)	2.8 (0.2, 28.3)	3.4 (0.2, 18.7)	2.7 (0.2, 21.6)	3.0 (0.2, 21.6)
ER Status, n (%)						
+	259 (46.8)	278 (50.7)	537 (48.7)	104 (55.9)	116 (56.3)	220 (56.1)
–	233 (42.1)	216 (39.4)	449 (40.7)	82 (44.1)	87 (42.2)	169 (43.1)
Not done	62 (11.2)	54 (9.9)	116 (10.5)	0	3 (1.5)	4 (1.0)
HER2 status, n (%)						
+	86 (15.5)	83 (15.1)	169 (15.3)	0	0	0
–	375 (67.7)	380 (69.3)	755 (68.5)	186 (100.0)	206 (100.0)	392 (100.0)
Not done	93 (16.8)	85 (15.5)	178 (16.2)	0	0	0
Triple negative (ER/PR/HER2-negative), n (%)	150 (27.1)	134 (24.5)	284 (25.8)	73 (39.2)	72 (35.0)	145 (37.0)

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Characteristic	ITT population			Subgroup1		
	Eribulin (n = 554)	Capecitabine (n = 548)	Total (n = 1102)	Eribulin (n = 186)	Capecitabine (n = 206)	Total (n = 392)
No. of organs involved, n (%)						
1	113 (20.4)	92 (16.8)	205 (18.6)	37 (19.9)	27 (13.1)	64 (16.3)
2	174 (31.4)	177 (32.3)	351 (31.9)	59 (31.7)	62 (30.1)	121 (30.9)
3	153 (27.6)	149 (27.2)	302 (27.4)	50 (26.9)	60 (29.1)	110 (28.1)
4	80 (14.4)	80 (14.6)	160 (14.5)	26 (14.0)	32 (15.5)	58 (14.8)
5	25 (4.5)	31 (5.7)	56 (5.1)	9 (4.8)	14 (6.8)	23 (5.9)
≥ 6	9 (1.6)	18 (3.3)	27 (2.5)	5 (2.7)	11 (5.3)	16 (4.1)
Missing	0	1 (0.2)	1 (0.1)	0	0	0
Tumour sites in > 10% patients Total, n (%)						
Bone	299 (54.0)	308 (56.2)	607 (55.1)	108 (58.1)	120 (58.3)	228 (58.2)
Liver	247 (44.6)	271 (49.5)	518 (47.0)	83 (44.6)	105 (51.0)	188 (48.0)
Lymph nodes	268 (48.4)	274 (50.0)	542 (49.2)	87 (46.8)	107 (51.9)	194 (49.5)
Lung	279 (50.4)	280 (51.1)	559 (50.7)	97 (52.2)	107 (51.9)	204 (52.0)
Pleura	57 (10.3)	57 (10.4)	114 (10.3)	20 (10.8)	28 (13.6)	48 (12.2)
Breast	113 (20.4)	104 (19.0)	217 (19.7)	35 (18.8)	38 (18.4)	73 (18.6)
Skin	56 (10.1)	65 (11.9)	121 (11.0)	19 (10.2)	27 (13.1)	46 (11.7)
ECOG performance status, n (%)						
0	250 (45.1)	230 (42.0)	480 (43.6)	90 (48.4)	86 (41.7)	176 (44.9)
1	293 (52.9)	301 (54.9)	594 (53.9)	93 (50.0)	116 (56.3)	209 (53.3)
2	11 (2.0)	16 (2.9)	27 (2.5)	3 (1.6)	4 (1.9)	7 (1.8)
3	0	1 (0.2)	1 (0.1)	0	0	0
Site of disease, n (%)*						
Visceral	467 (84.3)	483 (88.1)	950 (86.2)	154 (82.8)	187 (90.8)	341 (87)
Non-visceral only	81 (14.6)	61 (11.1)	142 (12.9)	30 (16.1)	18 (8.7)	48 (12.2)
Disease progression within 60 days of last dose of taxane	250 (45.1)	260 (47.4)	510 (46.3)	81 (43.5)	118 (57.3)	199 (50.8)

* Visceral/non-visceral determined by independent assessment

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A7. Please provide in Table 4 of this clarification letter, the number and proportion of patients in Study 301 (complete ITT population and Subgroup 1) who received subsequent treatment (including any crossover from one arm to another) on disease progression with details about the subsequent treatment received.

Please find below Table 4 which now includes the number and proportion of patients in Study 301 (complete ITT population and Subgroup 1) who received subsequent treatment on disease progression with details about the subsequent treatment received, as requested.

Table 4 Subsequent treatment received on disease progression in Study 301

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

A8. For health-related quality of life (HRQoL) data from Study 301, please provide the following information:

a. The numbers of patients represented in each bar of Figure 15 of the company submission.

Please find overleaf an updated Figure 15 from the company submission which includes the number of patients, as requested.

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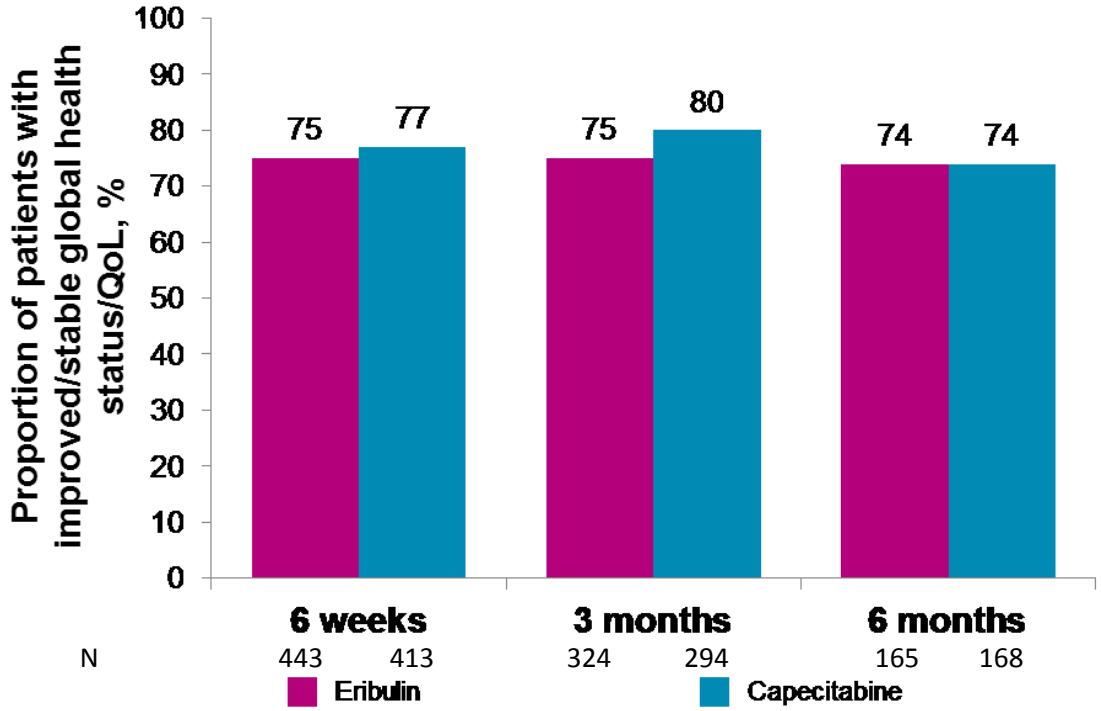

b. The number of patients (in each arm) for which HRQoL data were available for Subgroup 1.

As per the company submission, HRQoL is available from the HER2-negative subgroup of study 301. For clarity, this is not specific to only those patients who have received one prior chemotherapeutic regimen in the advanced setting.

The table below provides information on the number of patients (in each arm) for which HRQoL data were available for the HER2-negative subgroup of study 301.

Visit	Eribulin (N=375)	Capecitabine (N=380)
Baseline	358 (95.5%)	360 (94.7%)
6 Weeks	289 (88.9%)	282 (85.5%)
3 Months	213 (87.3%)	191 (84.9%)
6 Months	106 (85.5%)	104 (88.9%)
12 Months	37 (88.1%)	44 (91.7%)
18 Months	15 (75.0%)	21 (91.3%)
24 Months	8 (80.0%)	14 (87.5%)

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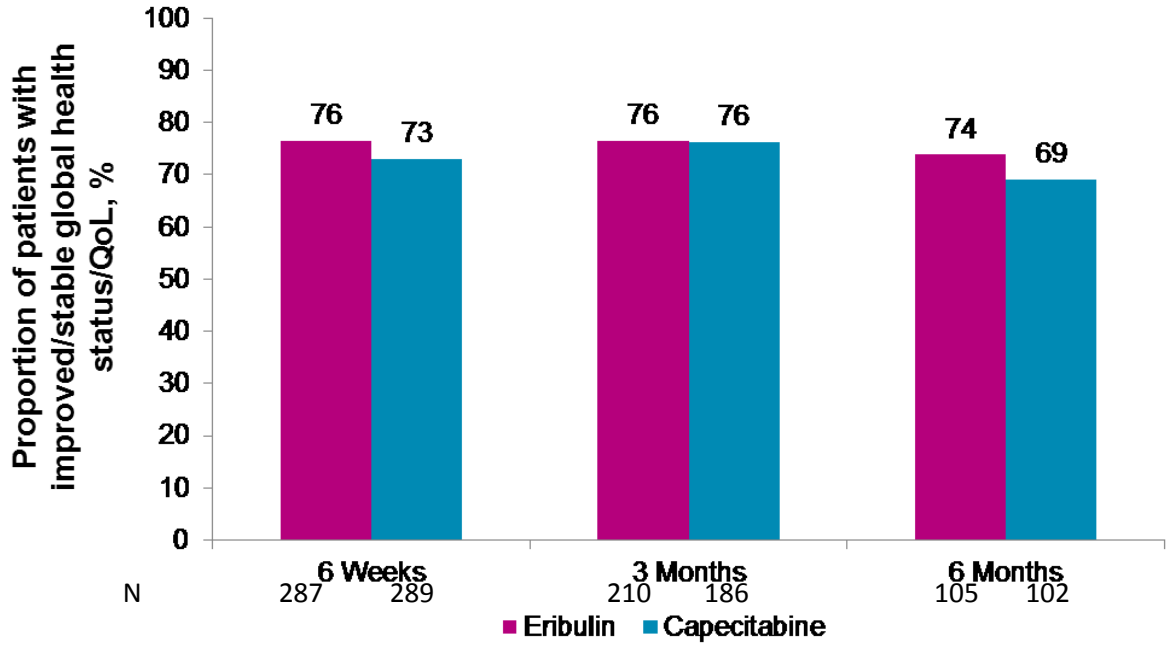
c. The numbers of patients represented in each bar of Figure 16 of the company submission.

Please find below an updated Figure 16 from the company submission which includes the number of patients, as requested.



d. The numbers of patients represented in each bar of Figure 17 of the company submission.

The calculations presented in Figure 17 are based on the HER2-negative subgroup of study 301. The relevant patient numbers are as per the table provided in response to question A8 b.

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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 Subgroup 1 patients of Study 301 (i.e. HER-2 negative patients with LABC/MBC, whose disease progressed after one prior chemotherapy), including all patients lost to follow-up or withdrawing from trial.

Trial data set: Study 301 latest data cut.

Censoring: Censor lost to follow-up and withdrawn patients at the date recorded. Patients still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off; i.e. not when last known to be alive (OS/PPS), and not at the date of last tumour assessment (PFS).

The rationale for this request is as follows: All Kaplan-Meier analyses are specified to use the 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 patients are exposed to risk but is much less likely to understate events, especially deaths. The result is that the inter-event period hazard rates 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 hazards. 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.

*Format: Please present analysis outputs using the format of the sample table (*Table 5 of this clarification letter*) shown below.*

a. Time to death from any cause (OS): Kaplan-Meier analysis stratified by treatment arm (eribulin vs capecitabine)

b. Time to disease progression or death (PFS): Kaplan-Meier analysis based on investigator assessment, stratified by treatment arm (eribulin vs capecitabine)

c. Time from disease progression by investigator assessment to death from any cause (PPS): Kaplan-Meier analysis stratified by treatment arm (eribulin vs capecitabine). NB exclude from the analysis any patients who died without disease progression

d. Time to the last dose of randomized treatment: Kaplan-Meier analysis stratified by treatment arm (eribulin vs capecitabine).

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Table 5 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

The relevant Kaplan-Meier analyses (listed in a to d above) have been provided as four separate attachments via NICE docs.

B2. **Priority question:** Please provide the results of the Extent of Exposure analysis as shown in Table 30 of the clinical study report for Study 301, restricted to the Subgroup 1 patients (i.e. 186 patients who received eribulin, and 206 patients who received capecitabine).

Please refer to the response to question A5.

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B3. **Priority Question**: Please provide results of health state utilities (EQ-5D values mapped from EORTC QLQ-C30) restricted to patients in Subgroup1 formatted as in **Error! Reference source not found.** of this clarification letter.

As per the company submission, some HRQoL data is available from the HER2-negative subgroup of study 301. For clarity, this is not specific to only those patients who have received one prior chemotherapeutic regimen in the advanced setting ie Subgroup 1.

Eisai does not have the relevant HRQoL data to complete Table 6 of the clarification letter.

It is worth noting that as per the company submission, the HRQoL results that are available for the HER2-negative subgroup of study 301 are consistent with those of the ITT population.

Section C: Textual clarifications and additional points

C1. **Priority Question**: Please provide the trial protocol for Study 301.

Please see the trial protocol for Study 301 which has been uploaded separately via NICE docs.

C2. **Priority Question**: Please provide the Statistical Analysis Plan for Study 301.

Please see the SAP for Study 301 which has been uploaded separately via NICE docs.

References

1. Roché H and Vahdat LT. Treatment of metastatic breast cancer: second line and beyond. Annals of Oncology 2011;22(5):1000-1010
2. Lobbezoo, DJ, van Kampen, RJW, Voogd, AC, et al. Prognosis of metastatic breast cancer subtypes: the hormone receptor/HER2-positive subtype is associated with the most favorable outcome. Breast Cancer Research and Treatment 2013;141(3):507–514

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: Senior Policy Officer

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.

NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Marina Parton**

2. Name of organisation	**Royal Marsden Hospital NHS Trust**
3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐**X** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Eribulin is used to palliate metastatic breast cancer, by preventing disease progression, improving or preventing symptoms and potentially prolonging life.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Clinical benefit from therapy can be measured by stabilising metastatic breast cancer (no growth in tumour), reduction in tumour size and improvement in of symptoms from disease (reduction in pain, cachexia, improved mobility or function).
9. In your view, is there an unmet need for patients and	Currently eribulin is only available in the third line setting. Due to increasing use of other drugs in the adjuvant or neo-adjuvant setting (anthracyclines, taxanes and more recently capecitabine for high risk triple negative breast cancer after standard neo-adjuvant chemotherapy), there may be fewer effective options for people in the second line setting. Eribulin is the only drug to demonstrate overall survival benefit in the

healthcare professionals in this condition?	metastatic setting for all types of breast cancer. Many patients would benefit from the earlier use of this therapy in their care.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Metastatic breast cancer is managed largely by systemic therapies (endocrine therapy, chemotherapy, targeted and biological agents). A number of therapies are available depending on the type of breast cancer. For many people with breast cancer (triple negative breast cancer, some hormone positive HER2 negative breast cancer) the mainstay of their therapy is chemotherapy based. Some chemotherapies are recognised to be more effective than others, and depending on the effectiveness and side effects, will be prioritised and offered to people during their treatments. Effective chemotherapy with few side effects enables better control of metastatic disease to prolong life with better quality of life for people.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Guidelines are available at national and international levels- for example 3rd ESO – ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3) 2016 F. Cardoso, A. Costa, E. Senkus et al. Annals of Oncology Ann Oncol 2016, JCO: Chemotherapy and Targeted Therapy for Women with HER2-ve (or unknown) Advanced Breast Cancer; ASCO Clinical Practice Guidelines. 2014 *Journal of Clinical Oncology* 32, no. 29 (October 2014) 3307-3329 NICE Advanced Breast Cancer diagnosis and treatment CG81- last updated August 2017 https://www.nice.org.uk/guidance/cg81 London Cancer Alliance Breast Cancer Clinical Guidelines (last updated march 2016) http://www.londoncanceralliance.nhs.uk/information-for-healthcare-professionals/forms-and-guidelines/lca-forms,-protocols-and-guidance

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The breast cancer guidelines are fairly consistent with each other The appropriateness and sequencing of treatment is taught extensively in the Breast modules for all oncologists during their training in the UK. Breast oncology has a number of specialist local and national forums (for example, UK Breast Cancer Forum, Association of Breast Cancer Physicians) to enable discussion and self education. Many oncologists treat breast cancer similarly nationally. My experience is all based in the UK.
• What impact would the technology have on the current pathway of care?	The use of Eribulin earlier in the sequencing of therapy would allow better access to an effective treatment, if clinically appropriate for people. Eribulin is well tolerated and has shown to be effective in metastatic disease by prolonging life. It is recognised that earlier use of effective treatments has greater benefits for people.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Eribulin is already widely used in the third line setting for metastatic disease.
• How does healthcare resource use differ between the technology and current care?	Resources would not need to change substantially. The sequencing of chemotherapy may change for some patients as eribulin is given earlier in the patient pathways but these people are likely to be receiving chemotherapy any way
• In what clinical setting should the technology be used? (For example,	Specialist breast oncology clinics and chemotherapy units

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No substantial additional investment as services already exist to provide this
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Earlier access to effective therapy is likely to result in better outcomes for people with metastatic disease. It is widely recognised that offering therapies later in the pathway is less likely to benefit patients as they have a greater burden of disease and so may have more symptoms from their disease and previous treatments.
• Do you expect the technology to increase length of life more than current care?	Sub group analysis of the EMBRACE (305 study) data (Cortes J et al. *Lancet* 2011;377**:**914-923) demonstrated a significant improvement in overall survival in patients who had fewer prior lines of therapy (Blum et al, SABCS abstract 2010). The 301 study (Kaufman PA, et al. *J Clin Oncol.* 2015;33:594-601)demonstrated 2nd line eribulin prolonged the lives of those with triple negative breast cancer (14.4 months v 9.4 months) (Kaufman PA, Cortes J, et al. ASCO. 2013) compared to capecitabine. HER2 negative patients also had an increase in overall survival.
• Do you expect the technology to increase health-related quality of life more than current care?	The side effects are similar overall with current alternative standard of care therapies (305 and 301 study) There is no evidence from the literature or from experience that quality of life is any worse from side effects. The lack of significant hair loss particularly is appreciated by people receiving therapy. The better overall response in visceral disease in some tumour subtypes and the improved survival achieved with eribulin improves quality of life

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Data from EMBRACE and particularly the 301 study show that people with triple negative breast cancer have longer overall survival when treated with eribulin rather then other treatments given in such settings. Older patients benefit equally in terms of response and clinical benefit but as expected my experience more reported side effects. Hormone therapy and biological agents should be used where appropriate initially in treatment- this TA would not change that
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	I would not expect treatment delivery services to change as NHS resources and services are already using this drug routinely in this setting. Delivery is relatively simple with venous access and little or no requirement for pre-medication. The drug takes minutes to give at day 1 and day 8 (21day cycle) and there is no requirement for scalp cooling. There are no routine anti-emetics required subsequently. Grade V toxicities are uncommon. The main impact would be the availability of this drug earlier in the treatment pathway for oncologists.

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Standard assessments for monitoring of metastatic disease will be used. No particular requirements for eribulin.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes. This drug does not have some of the common side effects associated with chemotherapy at this point of the treatment pathway. People often report fewer side effects, do not feel nauseous and often do not lose their hair during treatment. This improves quality of life for many patients.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Using chemotherapy effectively at the best points of the patient pathways allows clinicians to sequence drugs that are most likely to help patients to feel better and potentially live longer with metastatic disease. This drug appears to be effective after other standard therapies, and the increased survival overall suggest that it allows patients to remain fit and still be sensitive to subsequent treatments. We have an increasing number of people who live with metastatic disease for many years. Careful sequencing to minimise side effects and main function/quality of life is very important as often people continue to work, be parents or carers.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Agree- use of drugs appropriately according to the evidence helps the NHS to utilise available treatments to improve patient care. The mainstay of most people with metastatic breast cancer is chemotherapy at some point.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, particularly with patients with triple negative breast cancers. There is evidence that this type of breast cancer responds particularly well to this treatment. This type of breast cancer can be the most aggressive and difficult to treat subtype of breast cancer effecting younger women. These patients can only be treated with chemotherapy outside clinical trials.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are comparable to other chemotherapy agents in this setting, a shown by prospective randomised trials comparing eribulin to other common agents (EMBRACE 305 study, Cortes J et al. *Lancet* 2011;377**:**914-923) and in the second line setting compared to capecitabine, currently commonly use in first or second line (301 study, Kaufman PA, et al. *J Clin Oncol.* 2015;33:594-601)
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, I believe so. The EMBRACE 305 study Cortes J et al. *Lancet* 2011;377**:**914-923) and the second line setting comparison to capecitabine, 301 study (Kaufman PA, et al. *J Clin Oncol.* 2015;33:594-601) both reflect practice in the UK in the choice of comparator arms and measures of outcomes. The subgroup analyses of Western Europe and North America demonstrate the better overall survival measures – and this may reflect the higher standard of health services available to these populations and improved outcomes overall. Again, this most closely resembles our own population.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are progression free survival , clinical benefit and overall survival. Quality of life measures and measures of toxicity from therapy (particularly Grade 3 and 4 side effects) . All of these were measured in both of the main clinical trials EMBRACE 305 and 301.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	As expected for real life use of drugs outside a clinical trial when less fit patients may be receiving therapy the dose intensity and progression free and overall survival outcomes have not been as good but published audit data generally has been acceptable and reflective of the clinical trials

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA457]?	I understand that the 301 study (Kaufman PA, et al. *J Clin Oncol.* 2015;33:594-601) and subgroup analyses of EMBRACE 305 study (Cortes J et al. *Lancet* 2011;377**:**914-923) of the use of eribulin in the second line setting was not considered at the early TA. This data and the use of eribulin is relevant to clinical practice in the UK and should be considered.
22. How do data on real-world experience compare with the trial data?	Real-world experience is broadly reflective of the clinical trials, from my own experience at the Royal Marsden Hospital of an audit of over 200 patients (currently being developed for publication), combined analysis of audit data of use in Eribulin third line setting with the Marsden, Guys Hospital and the Christie NHS Trusts and published European retrospectives (Martella et al, Future Oncology 2015;11 (15 suppl):31-6), Poletti et al, Future Oncology 2014 Feb;10(2);233-9)
Equality	
23a. Are there any potential equality issues that should be	No- the same expected efficacy in all people who are suitable for intravenous chemotherapy including older people

taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24.Current treatment pathway – clinical need What are the expected benefits to be gained from using eribulin? Where is this indication for eribulin likely to fit into the treatment pathway and for which patients? 24a. 2nd line treatment after an anthracycline or a taxane What is current practice at this stage in the treatment pathway? Do most patients	Second line eribulin is likely to be most suitable for women with triple negative breast cancer and hormone positive, HER2 negative breast cancer refractory or not suitable for endocrine therapy. Anthracycline and taxanes are likely to have been already received in the adjuvant setting although some patients may have a re-challenge of a taxane (for example, paclitaxel when docetaxel has been given before or there has been a long disease free interval) . Many people receive capecitabine first line and thus eribulin provides a greater choice in the second line setting with an acceptable toxicity profile with data to support better responses in triple negative cancers. For people receiving second line therapy after taxanes eribulin provides an alternative to capecitabine which has an acceptable toxicity profile and better overall survival in triple negative breast cancers. It is effective in visceral (liver and lung) disease as well as bone and nodal disease and thus provides an effective mono-therapy choice. Visceral disease is more common in triple negative breast cancer.

have capecitabine or vinorelbine? 24b. Gemcitabine Where is gemcitabine most commonly given in the treatment pathway (for example, 2nd line, 3rd line and/or 4th line)?	Yes, most patients receive capecitabine and vinorelbine second line. Triple negative breast cancer patients are more likely to be offered single agent carboplatin or combination gemcitabine carboplatin. Single agent gemcitabine is not widely used as a single agent except in late line or unfit people It is usually used in combination with carboplatin currenty. Combination chemotherapy is not routinely recommended in metastatic breast cancer (see ESMO and ASCO international and NICE UK guidelines listed above) unless the person is symptomatic or the disease bulky and likely to cause life threatening symptoms. Gemcitabine-carboplatin is often used in triple negative breast cancer , and may be used in any line although the data for carboplatin in non- germline mutation carriers suggests that is not superior to taxane in response and progression free survival . combination therapies have more side effects
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Eribulin is already widely routinely used in the 3rd line setting in the NHS with real –life data suggesting outcomes similar to the clinical trials demonstrating utility in the clinical setting.
- Current practice of the use of adjuvant anthracyclines and taxanes results in fewer preferred drug options in the first and second line setting. Eribulin could then be considered much earlier in the pathway, and there is supporting evidence of effectiveness and prolonging life
- There is prospective randomised data to suggest that people with chemotherapy dependent disease such a triple negative, and HER2 negative breast cancer have better responses and survival outcomes with eribulin
- Second line eribulin is well tolerated and an acceptable alternative to current commonly used second line drugs such a capecitabine and vinorelbine.
- Eribulin use would not adversely affect oncology resources as delivery is short (a few minutes) with no scalp cooling (short chemotherapy unit chair time) with relatively low risk of complications

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Breast Cancer Now and consequently I will not be submitting a personal statement.

Name: .Sally Greenbrook.....

Signed: .....

Date: ....20 October 2017.....

STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/148/12

Completed 5 October 2017

CONTAINS IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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

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Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Eribulin for treating locally advanced or metastatic breast cancer after chemotherapy [ID1072]: A Single Technology Appraisal. LR*i*G, University of Liverpool, 2017.

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

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence have been submitted to NICE by Eisai in support of the use of eribulin (Halaven®).

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

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

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

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

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

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

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

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

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

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

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

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

1.3 Summary of clinical effectiveness evidence submitted by the company

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1.5 Summary of submitted cost effectiveness evidence

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

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

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

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

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

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

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

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

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

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

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

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

1.8 ERG commentary on end of life criteria

The ERG considers:

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

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

1.9.1 Strengths

Clinical effectiveness evidence

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

Cost effectiveness evidence

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

1.9.2 Weaknesses and areas of uncertainty

Clinical effectiveness evidence

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

Cost effectiveness evidence

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

1.10 Summary of exploratory and sensitivity analyses undertaken by the ERG

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

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

2 CONTEXT

2.1 Introduction

2.1.1 Original NICE guidance TA250 (2012)

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

2.1.2 Updated EMA licence for eribulin (2014)

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

2.1.3 New NICE guidance TA423 (ID964, 2016)

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

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

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

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

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

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

2.1.4 Current single technology appraisal (2017)

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

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

2.2 Critique of company's description of underlying health problem

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

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

Incidence, survival and HER2 status

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

LABC/MBC and health-related quality of life

- Symptoms can be severe including cancer-related fatigue and uncontrolled local disease, along with further complications relating to the organ(s) to which the cancer has spread.[11]
- Overall, quality of life is poor in patients with MBC.[12]

Source: CS, Sections 1.3 and 3

2.3 Critique of company's overview of current service provision

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

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

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

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

Treatment aim

- As recognised in recent NICE guidelines,[11] one of the key priorities for treating this advanced stage of breast cancer is to prolong survival, while controlling the symptoms experienced and improving the patient's quality of life. However, none of the available NICE-approved treatment options have demonstrated a survival benefit over any other.[10,11]

Current treatment options

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

Human epidermal growth factor receptor (HER) status

- Pre-treated HER2-negative patients (e.g. patients who are not eligible for targeted agents and who have already received initial treatment with anthracyclines and taxanes), however, are a particularly challenging subgroup to manage effectively since by this stage patients will have progressed despite treatment, and further treatment options will have limited effectiveness.

Eribulin

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

Source: CS, Sections 1.3, 2.4 and 3

2.4 Number of patients potentially eligible for eribulin

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

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

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

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

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

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

HER2= human epidermal growth factor receptor 2

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

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

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

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

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

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

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

3.1 Population

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

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

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

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

LABC/MBC=locally advanced or metastatic breast cancer

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

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

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

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

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

3.2 Intervention

Eribulin is a first-in-class anti-neoplastic agent belonging to the halichondrin class of drugs. Anti-cancer effects are exerted via a tubulin-based antimitotic mechanism leading to G2/M cell cycle arrest, disruption of mitotic spindles and, ultimately, apoptotic cell death following prolonged mitotic blockage.[23,24] Eribulin monotherapy is administered intravenously over 2 to 5 minutes on days 1 and 8 of every 21-day cycle. The company notes that pre-medication (antihistamine or steroids) to prevent hypersensitivity reactions is not routinely required prior to injection with eribulin, which sets treatment with eribulin apart from many intravenous (IV) chemotherapy agents. The company also states that, for patients treated with eribulin, the location of care, level of staff usage, cost of administration, frequency and type of monitoring and tests are all of a similar magnitude to other IV chemotherapy agents currently used in clinical practice.

3.3 Comparators

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

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

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

3.4 Outcomes

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

3.5 Economic analysis

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

3.6 Other considerations

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

4 CLINICAL EFFECTIVENESS

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

4.1 Critique of the review methods

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

4.1.1 Literature search methods

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

Searches for evidence indexed in electronic databases

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

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

Searches for evidence presented at conferences

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

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

4.1.2 Eligibility criteria

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

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

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

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

4.1.3 Data extraction

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

4.1.4 Quality assessment methods

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

4.2 Identified studies in the systematic review

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

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

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

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

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

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

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

4.3 Risk of bias assessment for Study 301

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

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

Table 5 Assessment of risk of bias for Study 301

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

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

4.4 Summary of trial characteristics and methodology for Study 301

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

Table 6 Summary of Study 301 characteristics

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

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

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

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

Outcomes analysed in Study 301

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

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

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

ERG critique of statistical approach

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

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

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

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

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

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

4.5 Characteristics of patients enrolled in Study 301

4.5.1 Patient disposition

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

4.5.2 Exposure to treatment

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

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

4.5.3 Baseline characteristics

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

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

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

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

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

4.6 Results from Study 301

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

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

(Table 8).

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

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

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

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

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

[redacted]

4.6.2 Safety data

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

Adverse events reported by all patients in Study 301

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

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

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

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

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

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

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

4.6.3 Health-related quality of life data

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

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

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

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

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

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

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

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

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

4.7 Additional work on clinical effectiveness undertaken by ERG

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

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

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

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

Table 9 Additional efficacy subgroup analyses of Study 301

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

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

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

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

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

[c] The remaining patients were censored

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

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

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

4.8 Conclusions of the clinical effectiveness section

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

[redacted]

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

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

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

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

5 COST EFFECTIVENESS

5.1 Introduction

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

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

5.2.1 Objective of the company's systematic review

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

5.2.2 Eligibility criteria used in study selection

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

5.2.3 Included and excluded studies

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

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

5.2.4 Findings from the cost effectiveness review

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

5.2.5 ERG critique of the company's cost effectiveness review

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

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

5.3.1 ERG summary of the company's submitted economic evaluation

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

5.3.2 NICE reference case checklist

Table 10 NICE reference case checklist completed by ERG

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

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

5.3.3 Model structure

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

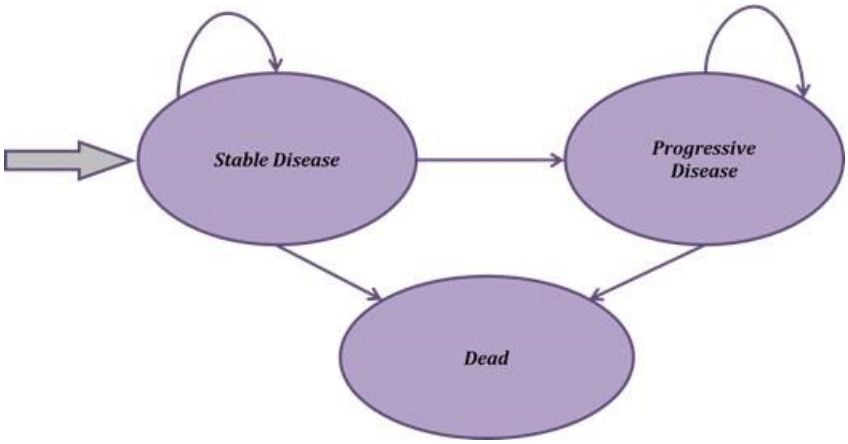


Figure 1 Company model structure

Source: CS, Figure 26

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

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

5.3.4 Population

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

5.3.5 Interventions and comparators

Primary treatments

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

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

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

Secondary treatments

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

Table 11 Subsequent treatment received on disease progression in company model

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

Source: CS, adapted from Table 43

Table 12 Subsequent treatment received on disease progression in Study 301

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

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

Treatment duration

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

Dose intensity

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

Wastage

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

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

5.3.6 Perspective, time horizon and discounting

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

5.3.7 Treatment effectiveness and extrapolation

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

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

5.3.8 Health-related quality of life

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

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

Table 13 Health state utility values

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

AEs=adverse events
Source: CS, Table 56

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

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

Table 14 Adverse event disutility values

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

Source: CS, Table 55

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

5.3.9 Adverse events

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

Table 15 Adverse event costs

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

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

5.3.10 Resources and costs

Drug costs

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

Table 16 Drug acquisition costs per pack/vial

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

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

Administration costs

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

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

Table 17 Cost of administration

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

Source: CS, adapted from Table 63

Direct medical costs

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

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

Table 18 Direct medical costs

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

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

5.3.11 Cost effectiveness results

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

Table 19 Base case cost effectiveness results

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

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

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

Table 20 Summary of predicted resource use by category of cost

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

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

5.3.12 Sensitivity analyses

Deterministic sensitivity analyses

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

Table 21 Results of deterministic sensitivity analysis

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

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

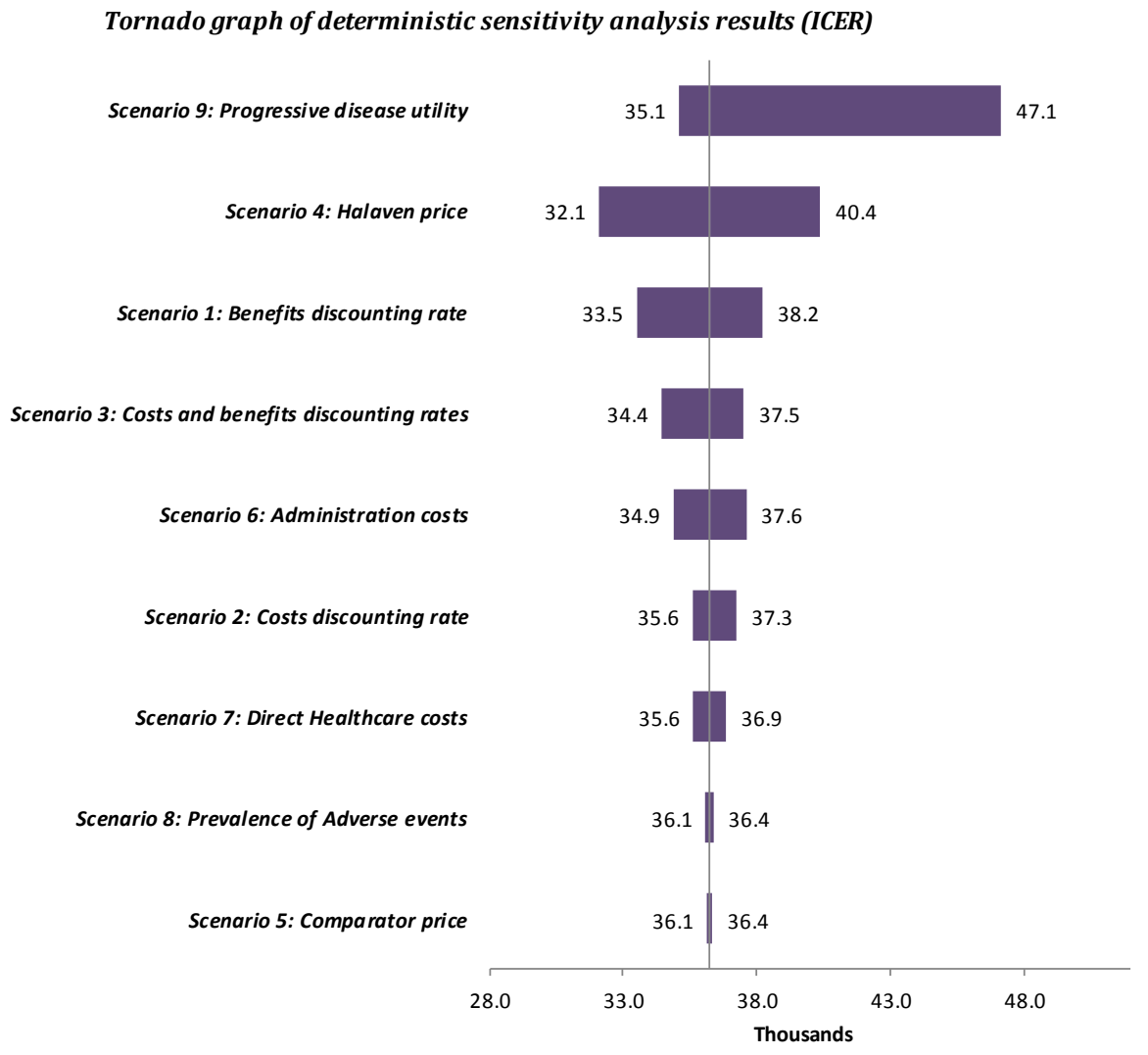


Figure 2 Deterministic sensitivity analysis results displayed in a tornado diagram

Source: CS, Figure 47

Probabilistic sensitivity analyses

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

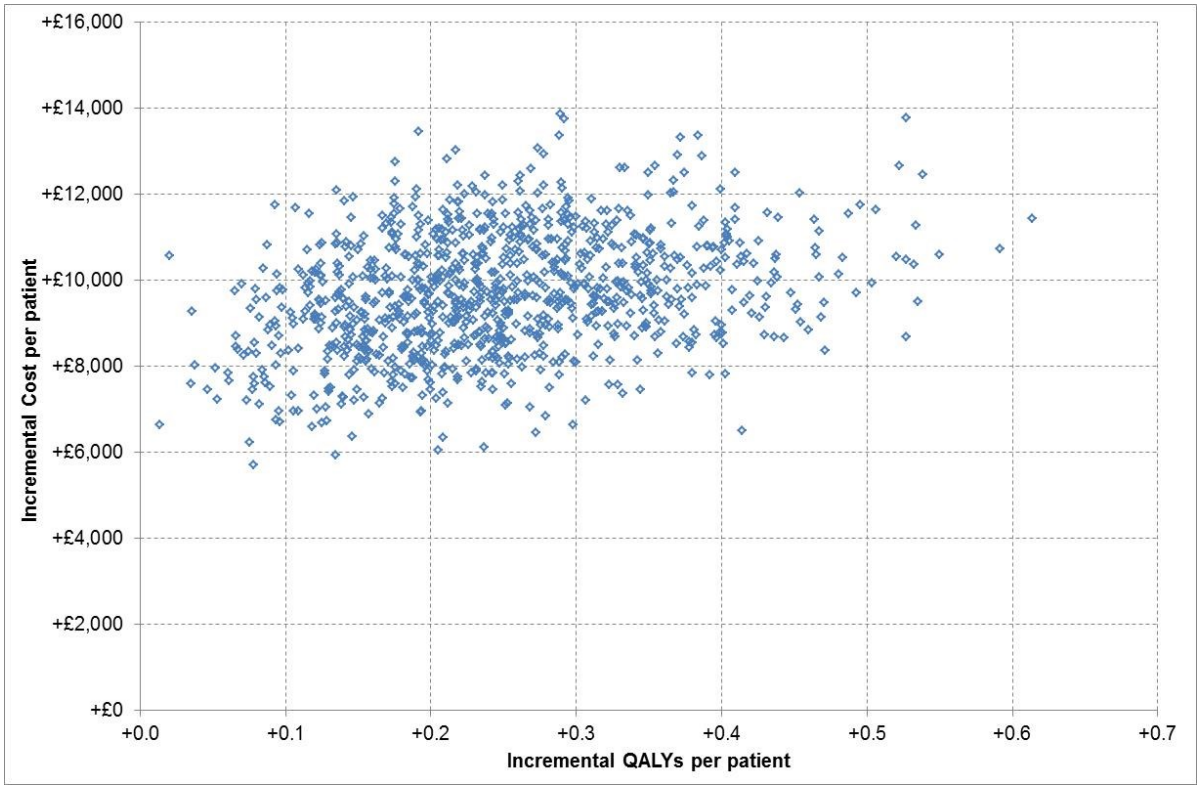


Figure 3 Cost effectiveness plane (Subgroup1)

Source: Company model

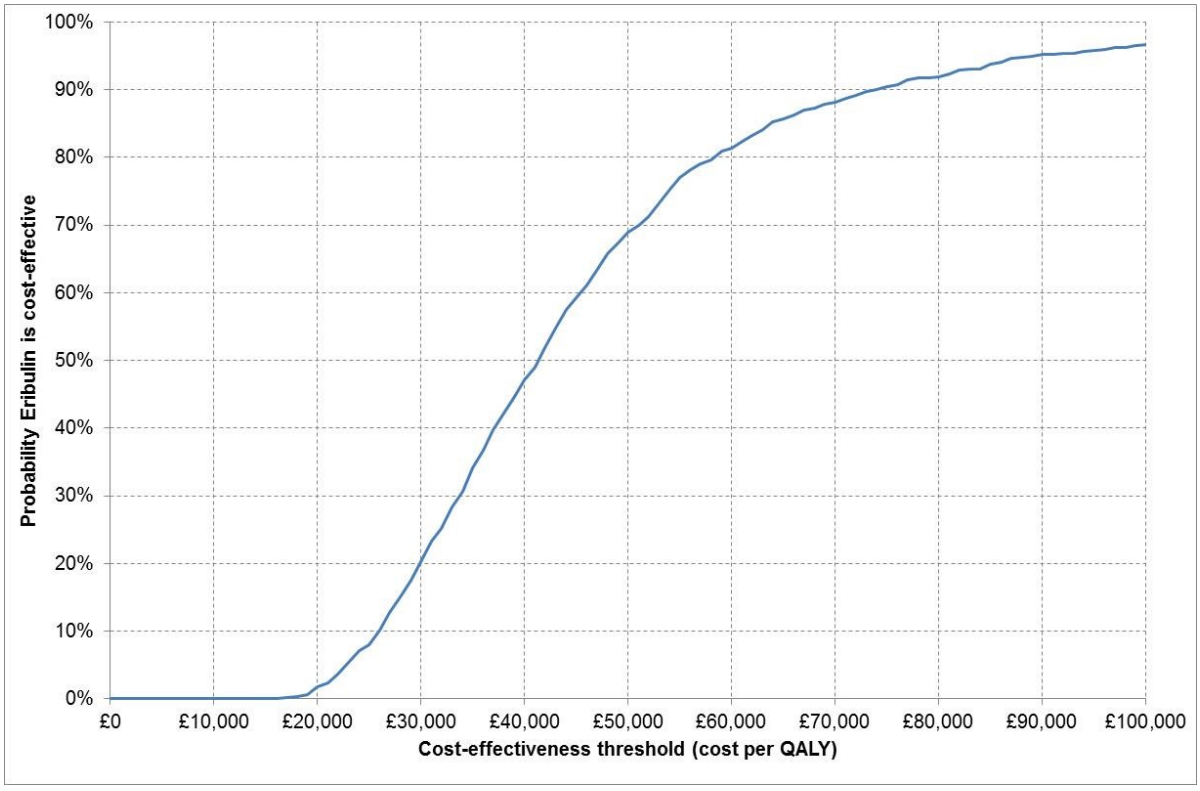


Figure 4 Cost effectiveness acceptability curve (Subgroup 1)

Source: Company model

5.3.13 Scenario analyses

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

Table 22 Scenario analysis results

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

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

5.3.14 Model validation and face validity check

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

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

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

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

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	[redacted]
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Not always	Several errors were identified (see Section 5.4)
Were costs and consequences adjusted for differential timing?	Partial	ERG corrected a minor error in method of discounting used
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Partial	Deterministic sensitivity analysis was reported, but the PSA lacked the facility to include correlated parameters
Did the presentation and discussion of study results include all issues of concern to users?	Yes	Yes; all issues of concern to users were discussed

ERG=Evidence Review Group

5.4 Detailed critique of the company's economic model

5.4.1 Design structure and implementation of the company model

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

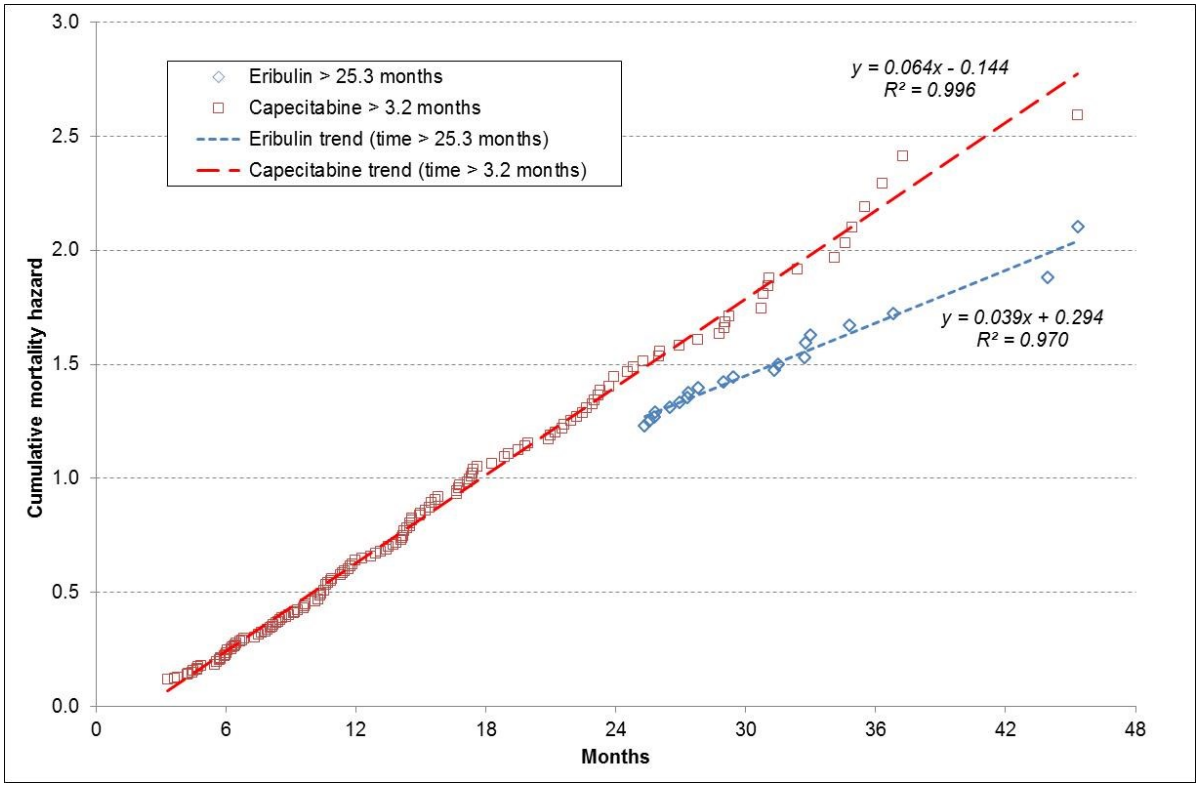
5.4.2 Patient survival and disease progression

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

Overall survival

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

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



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

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

Progression-free survival

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

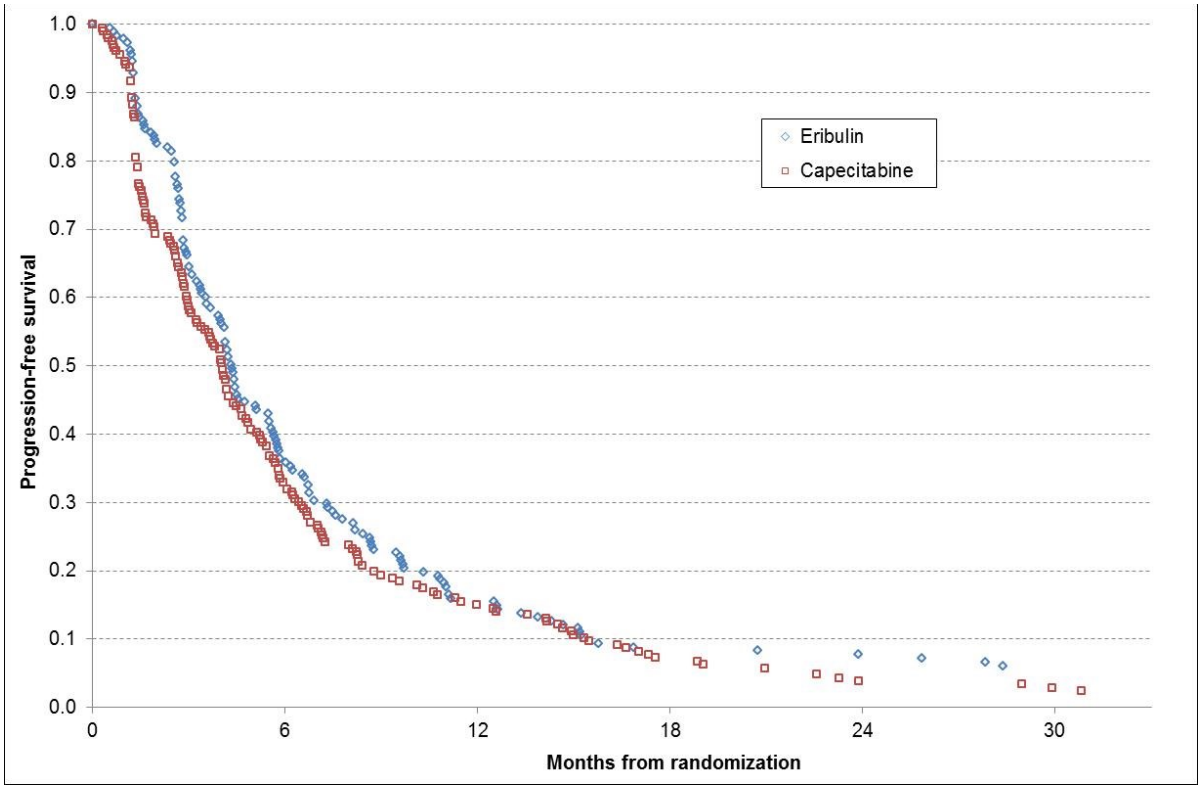
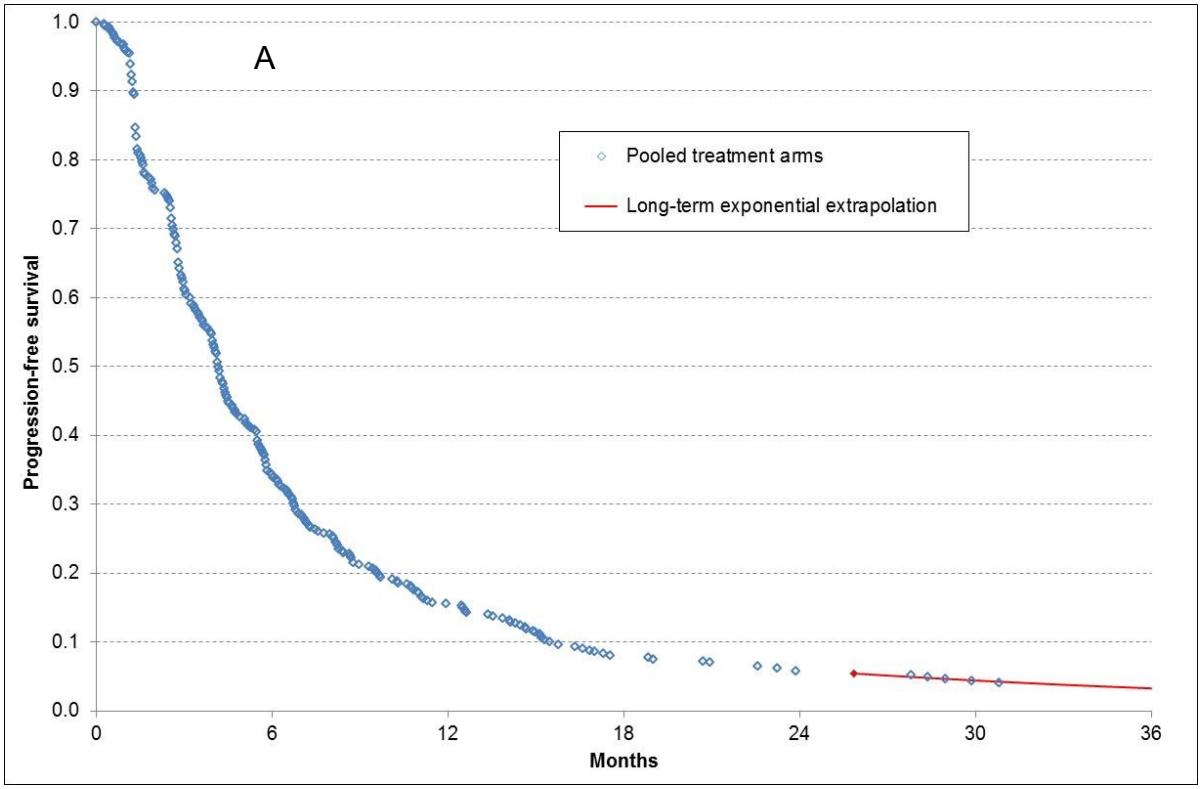


Figure 6 Progression-free survival Kaplan-Meier data from Subgroup 1 of Study 301



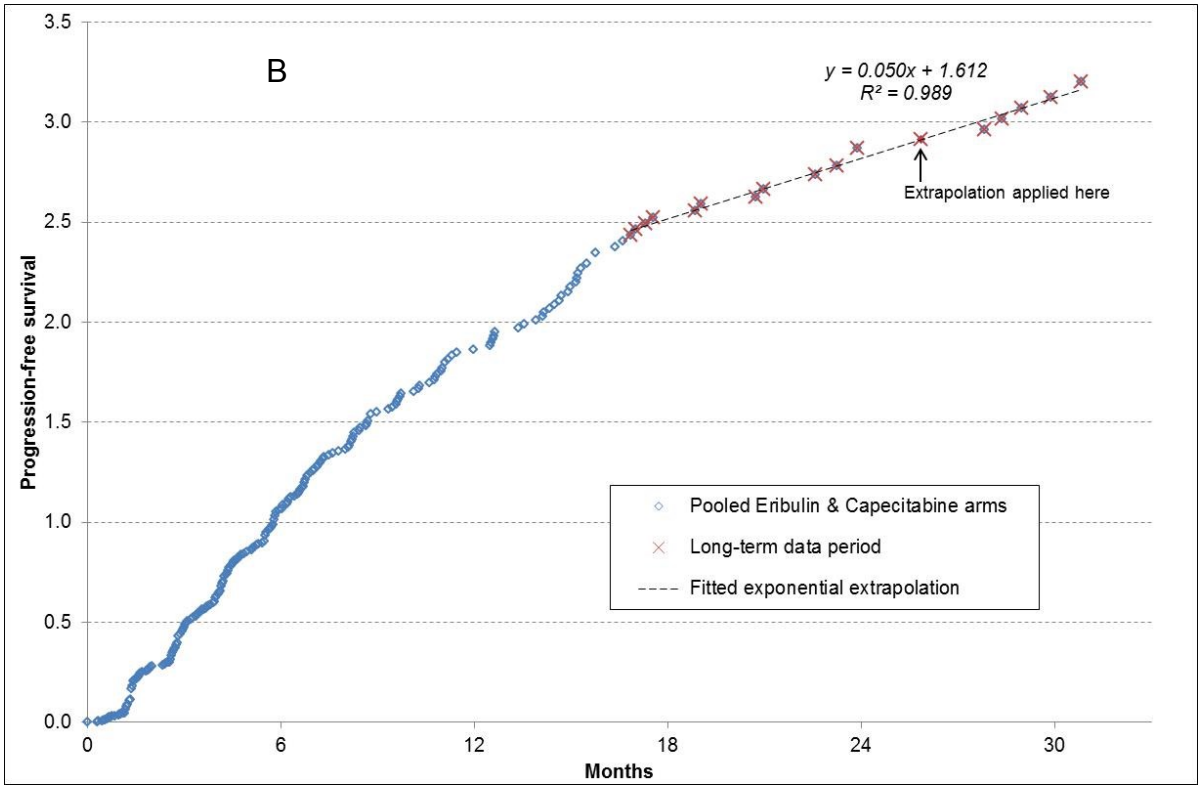


Figure 7 Pooled PFS Kaplan-Meier data from the Subgroup 1 population of Study 301, showing linear long-term hazard trend (B), and exponential extrapolation (A)

Post-progression survival

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

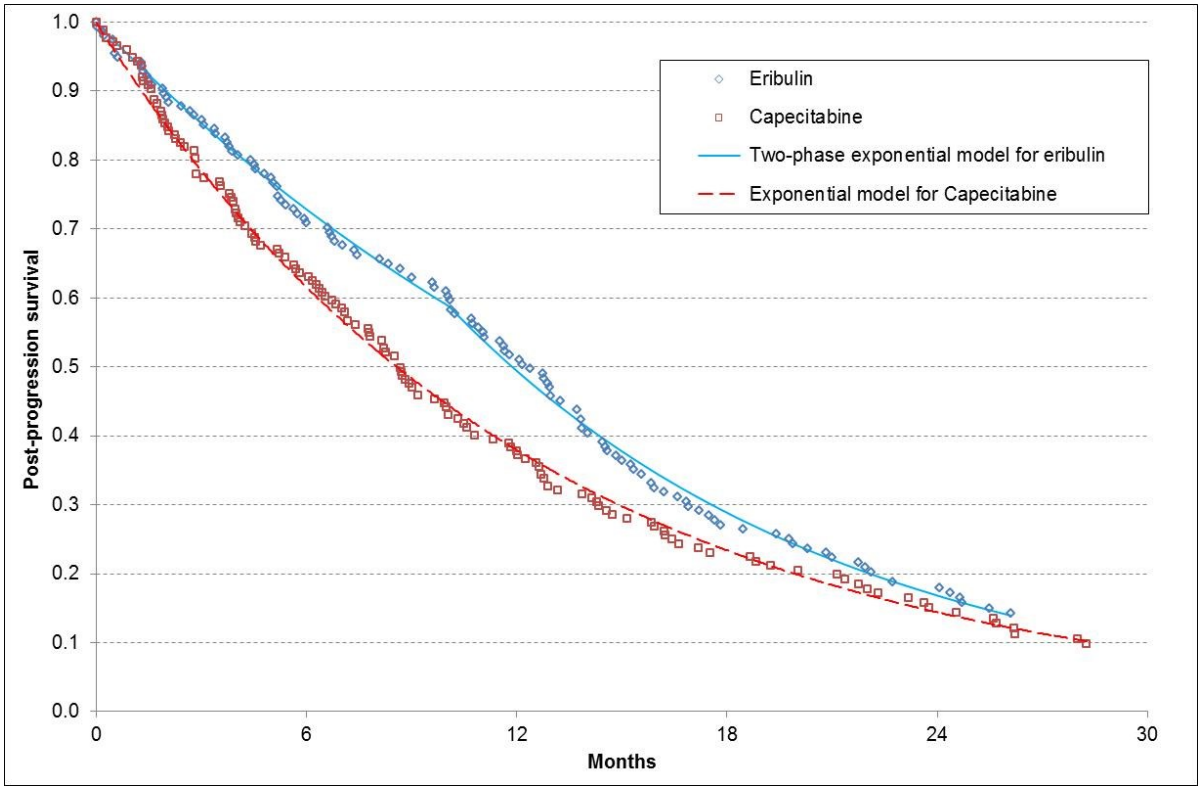


Figure 8 PPS Kaplan-Meier data from the Subgroup 1 population of Study 301, showing fitted trend lines: a simple exponential model for capecitabine and a 2-phase exponential model for eribulin

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

Time to treatment discontinuation

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

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

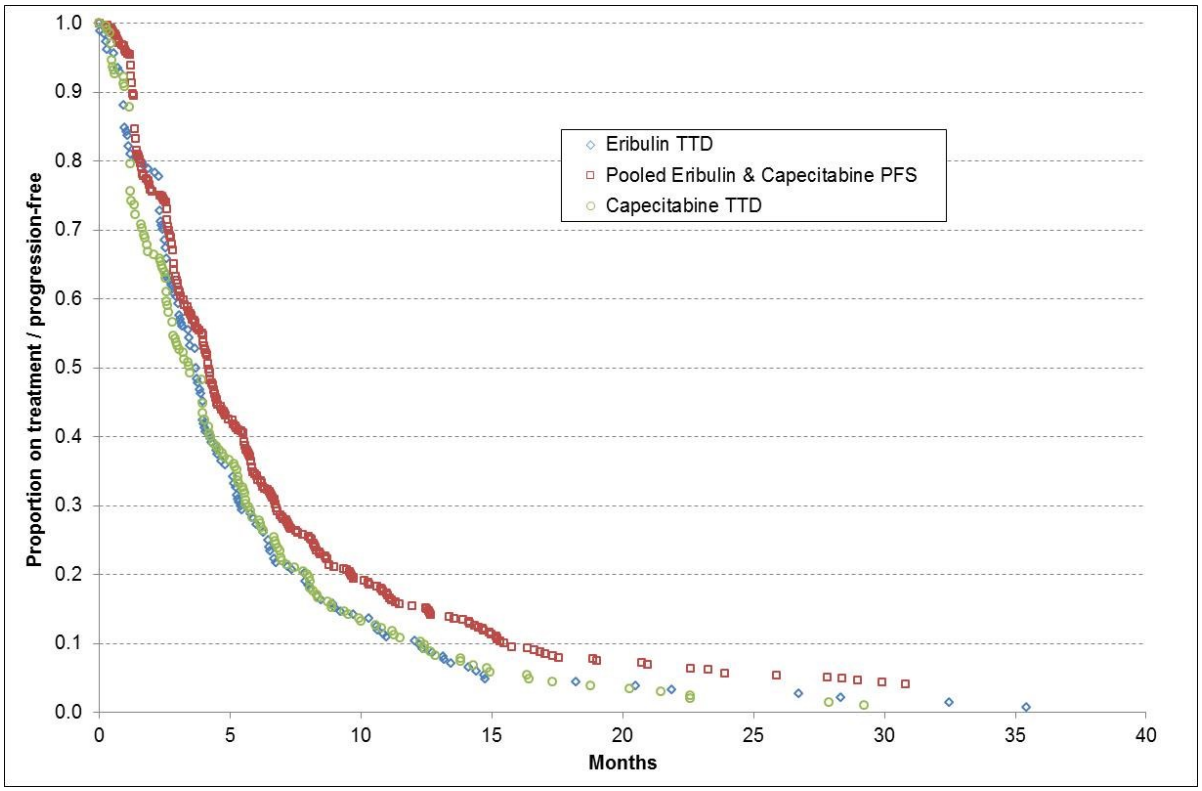


Figure 9 Comparison of PFS and TTD for estimating treatment costs

5.4.3 Logic error

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

5.4.4 Acquisition cost of chemotherapy

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

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

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

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

ERG=Evidence Review Group; IV=intravenous

5.4.5 Dose intensity and time on treatment

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

5.4.6 Probabilistic sensitivity analysis

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

5.4.7 Discounting

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

5.4.8 Health-related utility values

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

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

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

5.4.9 Subsequent lines of chemotherapy

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

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

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

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

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

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

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

5.4.10 Logic error in calculation of eribulin administration costs

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

5.5 Impact on the ICER of additional ERG analyses

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

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

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

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

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

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

5.6 Conclusions of the cost effectiveness section

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

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

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

6 END OF LIFE

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

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

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

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

7 OVERALL CONCLUSIONS

7.1 Clinical effectiveness

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

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

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

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

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

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

7.2 Cost effectiveness

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

7.3 Implications for research

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

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

8 REFERENCES

1. National Institute for Health and Care Excellence (NICE). Eribulin for the treatment of locally advanced or metastatic breast cancer. Technology appraisal guidance [TA250]. Published date: 03 April 2012. Available from: https://www.nice.org.uk/guidance/ta250. Accessed 14 August 2017.

2. National Institute for Health and Care Excellence (NICE). Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens. NICE technology appraisal guidance [TA423]. Published date: 21 December 2016 Available from: https://www.nice.org.uk/guidance/ta423/. Accessed 15 August 2017.

3. Eisai Ltd. Eribulin for treating locally advanced or metastatic breast cancer after chemotherapy [ID964]. Company evidence submission.

4. Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, Velikova G*, 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; 33:594-601.

5. Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K*, et al.* Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): A phase 3 open-label randomised study. Lancet. 2011; 377:914-23.

6. National Institute for Health and Care Excellence (NICE). Eribulin for treating locally advanced or metastatic breast cancer after one prior chemotherapy regimen. Final Scope. Issue Date: August 2016. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10094/documents. Accessed 14 August 2017.

7. Cancer Research UK. UK breast cancer incidence statistics 2013. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero. Accessed 26 April 2016.

8. Cancer Research UK. Breast cancer statistics. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero. Accessed 18 September 2017.

9. Roche H, Vahdat LT. Treatment of metastatic breast cancer: Second line and beyond. Ann Oncol. 2011; 22:1000-10.

10. Lobbezoo DJ, van Kampen RJ, Voogd AC, Dercksen MW, van den Berkmortel F, Smilde TJ*, et al.* Prognosis of metastatic breast cancer subtypes: the hormone receptor/HER2-

positive subtype is associated with the most favorable outcome. Breast Cancer Res Treat. 2013; 141:507-14.

11. National Institute for Health and Care Excellence (NICE). Advanced breast cancer: diagnosis and treatment. NICE guidelines [CG81]. Published date: February 2009. Last updated: July 2014 Available from: http://www.nice.org.uk/CG81. Accessed 11 August 2016.

12. Aranda S, Schofield P, Weih L, Yates P, Milne D, Faulkner R*, et al.* Mapping the quality of life and unmet needs of urban women with metastatic breast cancer. Eur J Cancer Care (Engl). 2005; 14:211-22.

13. National Institute for Health and Care Excellence (NICE). Gemcitabine for the treatment of metastatic breast cancer. NICE technology appraisal guidance [TA116]. Published date: 24 January 2007 London; Available from: https://www.nice.org.uk/guidance/TA116. Accessed 11 August 2016.

14. Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. J Exp Clin Cancer Res. 2008; 27:32.

15. Kowal-Podmore S, Munakata J, Tencer T, Smith T. The economic burden of adverse events associated with salvage treatment in advanced and metastatic breast cancer. ISPOR 11th Annual European Congress 8-11 November, 2008, Athens, Greece. PCN62. 2008; Available from: https://core.ac.uk/download/pdf/82075672.pdf. Accessed 18 September 2017.

16. Visovsky C, Collins M, Abbott L, Aschenbrenner J, Hart C. Putting evidence into practice: evidence-based interventions for chemotherapy-induced peripheral neuropathy. Clin J Oncol Nurs. 2007; 11:901-13.

17. Osgood CL, Chuk MK, Theoret MR, Huang L, He K, Her L*, et al.* FDA approval summary: eribulin for patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen. Clin Cancer Res. 2017.

18. Kantar Health. Treatment Architecture: Western Europe Breast Cancer. 2014.

19. Cancer Research UK. Breast cancer incidence by sex and UK region: Breast Cancer (C50), Number of New Cases, Crude and European Age-Standardised (AS) Incidence Rates per 100,000 Population, UK, 2013. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#UeC1YF3vQIxovH7o.99. Accessed 11 August 2016.

20. Cancer Research UK. Breast cancer incidence by stage at diagnosis: Breast Cancer (C50), Proportion of Cases Diagnosed at Each Stage, England 2013. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-

type/breast-cancer/incidence-invasive#W5VvE5PFwAPB0wvM.99. Accessed 11 August 2016.

21. Kantar Health. Cancer Mpact database.

22. Synovate Healthcare. European Oncology Monitor, market share data Q3 2010.

23. Benbow SJ, Cook BM, Reifert J, Wozniak KM, Slusher BS, Littlefield BA*, et al.* Effects of Paclitaxel and Eribulin in Mouse Sciatic Nerve: A Microtubule-Based Rationale for the Differential Induction of Chemotherapy-Induced Peripheral Neuropathy. Neurotox Res. 2016; 29:299-313.

24. Jordan MA, Kamath K, Manna T, Okouneva T, Miller HP, Davis C*, et al.* The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth. Mol Cancer Ther. 2005; 4:1086-95.

25. National Institute for Health and Care Excellence (NICE). Single technology appraisal: User guide for company evidence submission template. Process and methods [PMG24]. Published date: January 2015. Last updated: April 2017.; Available from: https://www.nice.org.uk/process/pmg24/chapter/instructions-for-companies. Accessed 18 September 2017.

26. Eisai Ltd. A phase III open label, randomized two-parallel-arm multicenter study of E7389 versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. Clinical study report. End date: 12 March 2012.

27. Twelves C, Cortes J, Olivo M, Awada A. Efficacy of eribulin in patients (pts) with metastatic breast cancer (MBC): A pooled analysis by HER2 and ER status. J Clin Oncol. 2014; 32(Suppl 5):Abstr 631.

28. Twelves C, Cortes J, Vahdat L, Olivo M, He Y, Kaufman PA*, et al.* Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies. Breast Cancer Res Treat. 2014; 148:553-61.

29. Twelves C, Cortes J, Vahdat L, Olivo M, He Y, Kaufman PA*, et al.* Efficacy of eribulin in patients (pts) with metastatic breast cancer (MBC): A pooled analysis by HER2 and ER status. J Clin Oncol. 2014; 32(15_suppl):631-.

30. Twelves C, Cortes J, Vahdat L, Olivo M, He Y, Kaufman PA*, et al.* Erratum to: Efficacy of eribulin in women with metastatic breast cancer: a pooled analysis of two phase 3 studies. Breast Cancer Res Treat. 2015; 149:313.

31. Vahdat LT, Garcia AA, Vogel C, Pellegrino C, Lindquist DL, Iannotti N*, et al.* Eribulin mesylate versus ixabepilone in patients with metastatic breast cancer: a randomized Phase II study comparing the incidence of peripheral neuropathy. Breast Cancer Res Treat. 2013; 140:341-51.

32. Eisai Ltd. OS/PFS Analysis for 2nd Line Patients. Protocol Number: E7389-G000-301. A Phase III Open Label, Randomized Two-Parallel-Arm Multicenter Study of E7389 versus Capecitabine in Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes. Version: 1.0. Date: 11 June 2015 (Eisai Ltd data on file).

33. Vahdat LT, Pruitt B, Fabian CJ, Rivera RR, Smith DA, Tan-Chiu E*, et al.* Phase II study of eribulin mesylate, a halichondrin B analog, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2009; 27:2954-61.

34. Twelves C, Awada A, Cortes J, Yelle L, Velikova G, Olivo MS*, et al.* Subgroup analyses from a phase 3, open-label, randomized study of eribulin mesylate versus capecitabine in pretreated patients with advanced or metastatic breast cancer. Breast Cancer (Auckl). 2016; 10:77-84.

35. Pivot X, Marme F, Koenigsberg R, Guo M, Berrak E, Wolfer A. Pooled analyses of eribulin in metastatic breast cancer patients with at least one prior chemotherapy. Ann Oncol. 2016; 27:1525-31.

36. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. NICE Process [PMG9]. Published date: April 2013. London; Available from: https://www.nice.org.uk/process/pmg9/chapter/1-foreword. Accessed 11 August 2016.

37. Eisai Ltd. A phase III open label, randomized two-parallel-arm multicenter study of E7389 versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. Clinical study report. Statistical analysis plan. 7 February 2012.

38. Tremblay G, Majetha U, Kondtoudis I, De Rosendo J. Cost effectiveness analysis of eribulin mesylate as a treatment for metastatic breast cancer in Spain: management in the later line of therapy. JHEOR. 2015; 3:14.

39. Wan Y, Copher R, Corman S, Abouzaid S, Gao X. Indirect costs among metastatic breast cancer patients receiving eribulin. 2015; Available from: https://www.ispor.org/ScientificPresentationsDatabase/Presentation/56065. Accessed 18 September 2017.

40. Dranitsaris G, Beegle N, Kalberer T, Blau S, Cox D, Faria C. 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. 2014; 21:170-7.

41. Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. Eur J Health Econ. 2010; 11:427-34.

42. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997; 35:1095-108.

43. Curtis L, Burns A. Unit Costs of Health and Social Care 2015. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php. Accessed 11 August 2016.

44. MIMS online. Database of prescription and generic drugs, clinical guidelines. Available from: http://www.mims.co.uk/. Accessed 12 August 2016.

45. Department of Health. Drugs and pharmaceutical electronic market information (eMit). First published: 16 March 2011. Last update: 4 May 2016.; Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Accessed 12 August 2016.

46. Department of Health. NHS reference costs 2014 to 2015. First published: 18 November 2015. Last updated: 27 November 2015. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015. Accessed 12 August 2016.

47. Latimer N. NICE DSU technical support document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Report by the Decision Support Unit. June 2011 (last updated March 2013). Available from: http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf. Accessed 12 August 2016.

48. Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. PLoS One. 2010; 5:e8933.

49. Supporting Information. Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. PLoS One. 2010; 5:e8933 Available from: http://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0008933#s5. Accessed 23 August 2016.

50. Therasse P, Mauriac L, Welnicka-Jaskiewicz M, Bruning P, Cufer T, Bonnefoi H*, et al.* Final results of a randomized phase III trial comparing cyclophosphamide, epirubicin, and fluorouracil with a dose-intensified epirubicin and cyclophosphamide + filgrastim as neoadjuvant treatment in locally advanced breast cancer: an EORTC-NCIC-SAKK multicenter study. J Clin Oncol. 2003; 21:843-50.

51. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006; 95:683-90.

9 APPENDICES

9.1 Additional tables for Study 301

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

Outcome and definition	Assessment Measures	Statistical analysis methodology
OS Defined as the time from the date of randomisation until date of death from any cause or the last date the subject was known to be alive	Survival was recorded during the study and following treatment discontinuation for any reasons other than consent withdrawal. Follow-up for survival was assessed at three-monthly intervals until death	• OS was compared between the randomised treatment arms in the ITT population, using a two-sided log-rank test (stratified by HER2 status and geographical region) at a significance level of 0.04. • K-M survival curves were used to summarise OS, using 95% limits at selected time points. • K-M estimates of the median survival time, and first and third quartiles were presented with 95% CIs. • HR was computed together with the two-sided 95% CI using Cox regression model and was stratified according to the type of treatment received, HER2 status and geographical region. • An additional Cox regression model was fitted in which the HR was also adjusted for the number of prior chemotherapies for advanced or metastatic disease and time to progression after the last chemotherapy. • For participants for whom a date of death was not recorded, i.e., those who were lost to follow-up or who were alive at the date of data cut-off, time to death was censored at the time of last contact
PFS Defined as the time from the date of randomisation to the date of recorded progression of the disease or the death of the subject from any cause, whichever occurred first	Tumour assessment was performed according to the RECIST methodology. Baseline tumour assessments were performed within 28 days of the start of treatment, consisting of: CT or MRI scans of the chest, abdomen, pelvis, and any other areas of suspected disease; photographs of skin lesions (if present); and bone scans. Tumour assessments were performed in all participants every second cycle (starting Cycle 2) between Days 15 and 21, or sooner if there was evidence of disease progression. Scans and photography were performed in those areas where disease was found at baseline, and in any new areas of suspected disease. If subjects remained on study for more than 12 cycles after starting treatment, the assessments described above were performed every three cycles until disease progression. Bone scans were repeated every sixth cycle (starting Cycle 6) between Day 15 of the sixth cycle and Day 7 of the following cycle.	• Analyses were conducted based on both the investigator's assessment of disease (imaging data and clinical examination) and an independent blinded review of imaging data • K-M plots and the K-M estimates of the medians, and first and third quartiles were presented with the 95% CI for PFS • PFS was compared between the treatment arms using a two-sided 0.01 level stratified log-rank test • HR was computed together with the two-sided 95% CI using Cox regression model and was stratified according to the type of treatment received, HER2 status and geographical region • Participants who had not progressed on the data cut-off date or who were lost to follow-up, were censored at that date

Outcome and definition	Assessment Measures	Statistical analysis methodology
	Tumour responses were confirmed by a second assessment ≥ 4 weeks later. Participants with CR/PaR or SD* who withdrew from treatment before disease progression, continued to have tumour assessments every 3 months until progressive disease or the start of a new anticancer treatment. Tumour assessments were made by investigators via imaging data and clinical examinations. Imaging data was independently reviewed (CT, MRI, bone scans, x-rays, and photographs) in a blinded fashion at a central facility. Analyses were conducted based on the investigator's assessment of disease (imaging data and clinical examination) and an independent blinded review of imaging data	

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

Table 27 Patient disposition in Study 301

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

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

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

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

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

9.2 ERG Revisions to company's model

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

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

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

.

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

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

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

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

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

ERG REPORT ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/148/12

Erratum completed 18 October 2017

CONTAINS IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company identified seven overall issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. Six were considered by the ERG to require minor changes to the text. The pages of the report affected are presented here.

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

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

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

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

4.6.2 Safety data

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

Adverse events reported by all patients in Study 301

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

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

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

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

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

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

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

4.6.3 Health-related quality of life data

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

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

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

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

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

4.8 Conclusions of the clinical effectiveness section

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

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

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

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

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

Wastage

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

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

5.3.6 Perspective, time horizon and discounting

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

5.3.7 Treatment effectiveness and extrapolation

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

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

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Direct medical costs

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

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

Table 18 Direct medical costs

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

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

7 OVERALL CONCLUSIONS

7.1 Clinical effectiveness

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

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

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

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

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

ERG Results Table Row Title	Associated detail	Implementation instructions
R3. Discounting method (Binary switch Mod_3)	None	In Sheet 'Appendix Transition', **Replace** formula in cell K19 by =IF(Mod_3=1,1/((1+Discounting_cost)^(12*INT(D19))), 1/((1+Discounting_cost)^(B19))) **Replace** formula in cell L19 by =IF(Mod_3=1,1/((1+Discounting_ben)^(12*INT(D19))), 1/((1+Discounting_ben)^(B19))) **Replace** formula in cell M19 by =IF(Mod_3=1,1/((1+Discounting_ben)^(12*INT(D19))), 1/((1+Discounting_ben)^(B19))) **Copy** range K19:M19 **Paste** to range K20:M259 and to range K272:M512
R10. Correct logic error in oral vinorelbine costing (Binary switch Mod_7)	None	In Sheet 'Appendix dose and BSA', **Replace** formula in cell S76 by =IF(Mod_7=1,S75*$J$53, S75*$F$53) **Replace** formula in cell S77 by =IF(Mod_7=1, S76*$J$54, S76*$F$54) **Replace** formula in cell S78 by =IF(Mod_7=1,P78*$H$60+R78*$J$60+$I$60*Q78, P78*$K$60+R78*$M$60+$L$60*Q78) **Copy** cell S78 **Paste** to range S79:S138
R5. ERG estimated eribulin unit costs (Binary switch Mod_5)	1072 eribulin 2 ReworkedDrugCosts (ERG).xlsx	In Sheet 'Appendix dose and BSA', **Replace** formula in cell H75 by =SUMPRODUCT(($D$78:$D$138)*(H$78:H$138))*IF(Mod_5=1.167927,1) **Replace** formula in cell I75 by =SUMPRODUCT(($D$78:$D$138)*(I$78:I$138))*IF(Mod_5=1.167927,1)
R4. (Binary switch Mod_4)	ERG_TTD/PFS data for drug use and admin costs are included as new columns L and M in worksheet 'ERG_survival'	In Sheet 'Appendix – transition' **Replace** formula in cell AB19 by =IF(Mod_4=1,ERG_survival!L4,$F19)*'Model parameters'!$P$77 **Copy** cell AB19 **Paste** to range AB20:AB259 **Replace** formula in cell AB272 by =IF(Mod_4=1,ERG_survival!M4,$F272)*'Model parameters'!$P$90 **Copy** cell AB272

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 one prior chemotherapy regimen [ID1072]

You are asked to check the ERG report from Liverpool Reviews and Implementation Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Friday 13 October 2017** 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 Incorrect figures reported for fatal adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 10 of the ERG report it is stated: "Fatal AEs were reported by 4.8% of patients treated with eribulin and **6.4**% of patients treated with capecitabine."	"Fatal AEs were reported by 4.8% of patients treated with eribulin and **6.6**% of patients treated with capecitabine."	This is a typographical error and is not consistent with the company submission (CS).	Apologies for this typographical error. Text amended on page 10.

Issue 2 Incorrect figures reported for leucopenia

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 10 and 41 of the ERG report it is stated: "In the Subgroup 1 population, compared with capecitabine, neutropenia (53.3% versus 14.6%), leucopenia (31.0% versus **19.3**%)…"	"In the Subgroup 1 population, compared with capecitabine, neutropenia (53.3% versus 14.6%), leucopenia (31.0% versus **9.3**%)…"	This is a typographical error and is not consistent with the company submission (CS).	Apologies for this typographical error. Text amended on pages 10 and 40 (which is where the error appears to be, not page 41).

Issue 3 Description of "peripheral neuropathy"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 10, 41, 48 and 85 of the ERG report refer to peripheral neuropathy	Eisai would like the ERG to amend "peripheral neuropathy" to "peripheral sensory neuropathy".	This is a factual inaccuracy and it is important to amend as the definition of "peripheral neuropathy" differed between the two phase III trials for eribulin.	Apologies for this omission. Text amended on pages 10, 40, 47 and 83 (the ERG believes the last three page numbers are the correct pages where the error occurred, not pages 41, 48 and 85).

Issue 4 Comparisons of adverse event data from Study 301 with data from Study 305

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42 of the ERG report provides a summary comparing adverse event data versus capecitabine from Study 301 with data obtained from Study 305 (EMBRACE)	Eisai would like the ERG to add the following statement: "It is important to note that the number of patients taking capecitabine in Study 305 (EMBRACE) is small ie 44 and therefore any comparisons should be interpreted with caution."	Eisai would like the ERG to provide a statement highlighting the uncertainty with comparing adverse events with Study 305 (EMBRACE) due to the small patient numbers.	A statement highlighting the uncertainty with comparing adverse events with Study 305 (EMBRACE) due to the small patient numbers added on page 41 (which is where the error appears to be, not page 42).

Issue 5 Acquisition costs of chemotherapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 75 and 76 of the ERG report, the ERG identified an error in modelling the distribution of body surface area where standard error was used instead of standard deviation. In addition the more relevant mean BSA value of 1.7448 proposed by the ERG is used, instead of 1.7400. However, the spreadsheet edits implemented by the ERG appear to adjust the average costs per dose calculated using the updated values of BSA and standard deviation. This recalculated cost per dose is then applied to the default (inaccurate) BSA distribution in the model.	Eisai propose that instead of changing the average cost per dose, the updated model uses the correct values of BSA and standard deviation calculated by the ERG (0.1785).	Eisai are unable to respond to the method of calculation used by the ERG, as the required details provided in the report are referenced to an additional spreadsheet which has not been provided. (ERG_Reworked_Drug_Costs(final).xlsx) If the new cost multiplier is applied to the incorrect BSA distribution potential double counting can occur and wastage may not be accurately calculated.	The ERG calculation Excel worksheet was provided by the ERG to NICE together with the modified version of the company's model, and the ERG report. Please request a copy of this file from NICE. Please note: filename of the spreadsheet submitted to NICE by the ERG differed slightly and so has been corrected in appendices to ERG report (page 96) Applying the ERG re-estimated average cost per dose of each medication is a simple and accurate method of evaluating the effect on cost-effectiveness of introducing into the company model the ERG method of estimating acquisition costs of different treatments. The ERG has used this approach successfully and without comment or question since STAs were first introduced by NICE.

Issue 6 Supportive palliative care costs and "Community nurse home visits"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 62 of the ERG report, in Table 18, no information is included in the usage column for "Community nurse home visits"	Eisai would like the ERG to add the following statement: "67% usage is assumed"	This is a factual inaccuracy and is not consistent with the company submission (CS).	Apologies for this omission. Text amended on page 61 (which is where the error appears to be, not page 62).

Issue 7 Medical costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 56 of the ERG report it is stated: "Medical costs following disease progression are only included in the period prior to death."	"Medical costs are included in stable disease and following disease progression."	This is a factual inaccuracy and is not consistent with the company submission (CS). Medical costs both in Stable Disease and in Progressive Disease are included and combined under Resource Use Regular (Sheet Appendix – transition, Column Y).	Apologies for this error. Text amended on page 55 (which is where the error appears to be, not page 56).

Issue 8 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The first paragraph of page 43 of the ERG report refers to QLG-C30 and QLG-BR23 On page 43 of the ERG report it is stated: "The company cautions that, due to the smaller sample sizes, the results of HRQoL analyses that were carried out **at** 6 months should be interpreted with caution."	To amend to QLQ-C30 and QLQ-BR23 "The company cautions that, due to the smaller sample sizes, the results of HRQoL analyses that were carried out **after** 6 months should be interpreted with caution."	Typographical errors	Apologies for this typographical error. Text amended on page 42 (which is where the error appears to be, not page 43).