For projector and public [redacted]

Lead team presentation
Eribulin for treating locally advanced or metastatic breast cancer after two or more prior chemotherapy regimens – STA

1st Appraisal Committee meeting

Cost Effectiveness

Committee A

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ERG: Liverpool Reviews & Implementation Group (LRiG)

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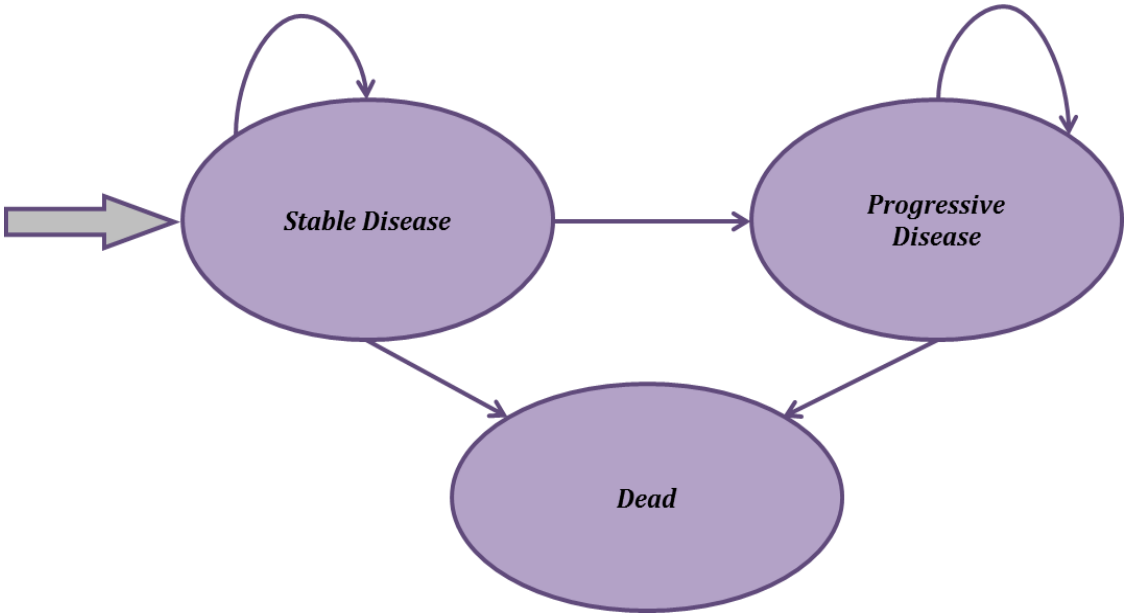
Cost effectiveness issues

- What is the Committee's view on the issues around cost-effectiveness?
  - Utility values (mapping algorithm, sources and utility value for progressive disease)
  - Dose calculations for eribulin
  - Administration costs post 6 months treatment
  - Cost calculations for the comparators
  - Cost calculations for subsequent lines of therapy
- What is the most plausible ICER?
- Does eribulin fulfil the end of life criteria?

Economic model

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



Source: Figure 26 of company submission

Structure of the model

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

Costs (I)

- Body surface area was assumed to be 1.74m^2 (CI 1.72-1.76), based on a study by Sacco et al. (2010)
- The PAS discount for eribulin has been incorporated in the model
- The model used the licensed doses of eribulin and comparators
- A dose intensity of 0.84 was used in both arms based on the dose reduction used for eribulin in EMBRACE
- Drug wastage: Doses were rounded to lessen drug wastage.
- The treatment duration for ‘Stable’ and ‘Progressive’ health states in combination is set to a maximum of 6 months. The treatment duration of secondary treatment following eribulin or TPC in the ‘Progressive’ state is linked with the treatment duration of the ‘Stable’ health state
- End of life costs were applied to the 2-week period prior to death
- Resource utilisation was based on NICE CG81 and TA250
- The cost and disutility of common AEs (all grades with a prevalence ≥10%) or serious AEs (≥3 with a prevalence ≥2%) are included within the model (for the full list of included AEs, see table 23 of the company submission)

Costs (II) - comparators

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

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

Abbreviation: ITT, intent-to-treat

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

Utilities

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

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

Company's base case results

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

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

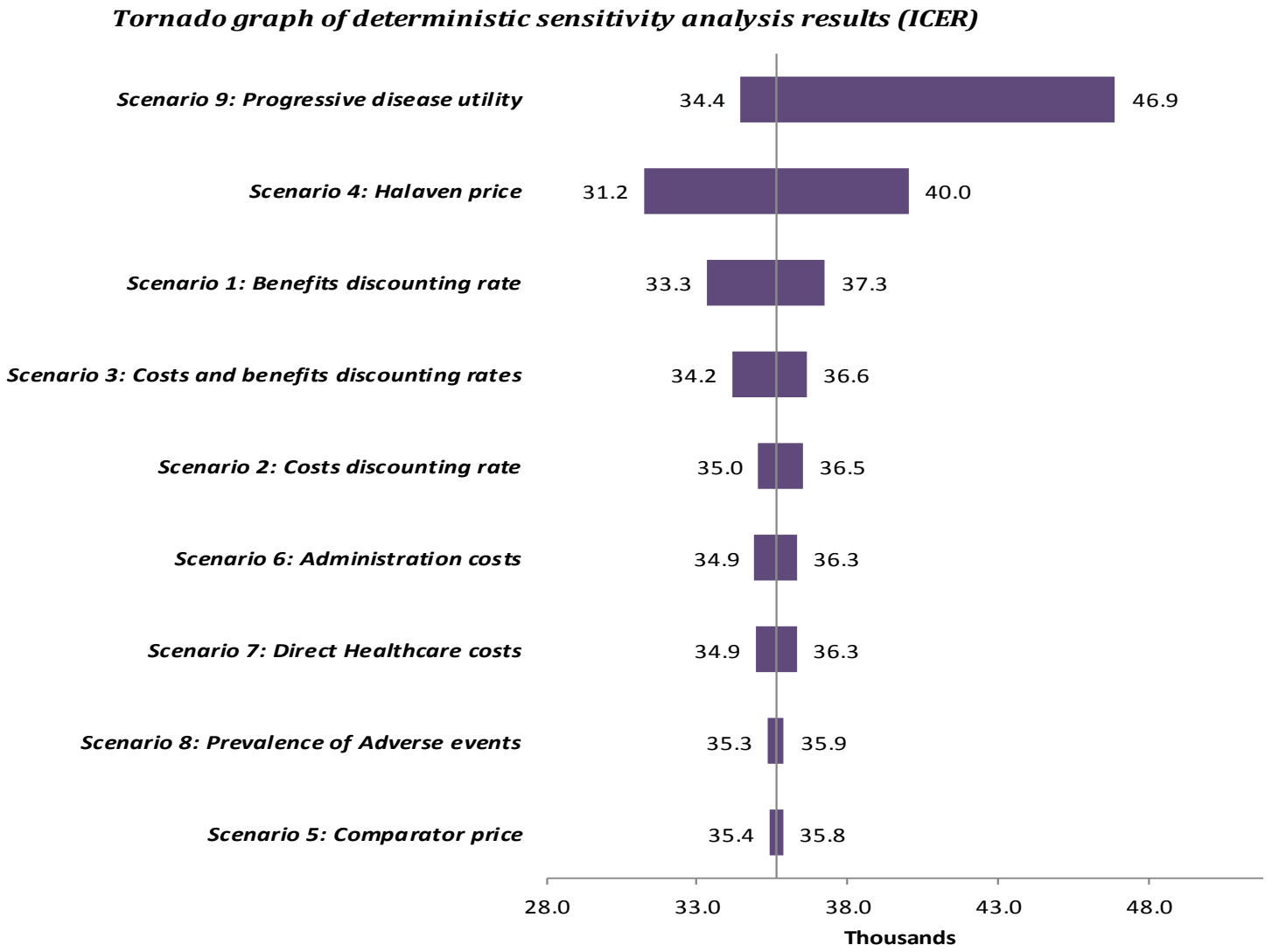
Deterministic scenario analysis

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

Abbreviation: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year

Source: Table 84 of company submission

Tornado diagram



Source: Figure 48 of company submission

ERG comments
Model structure

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

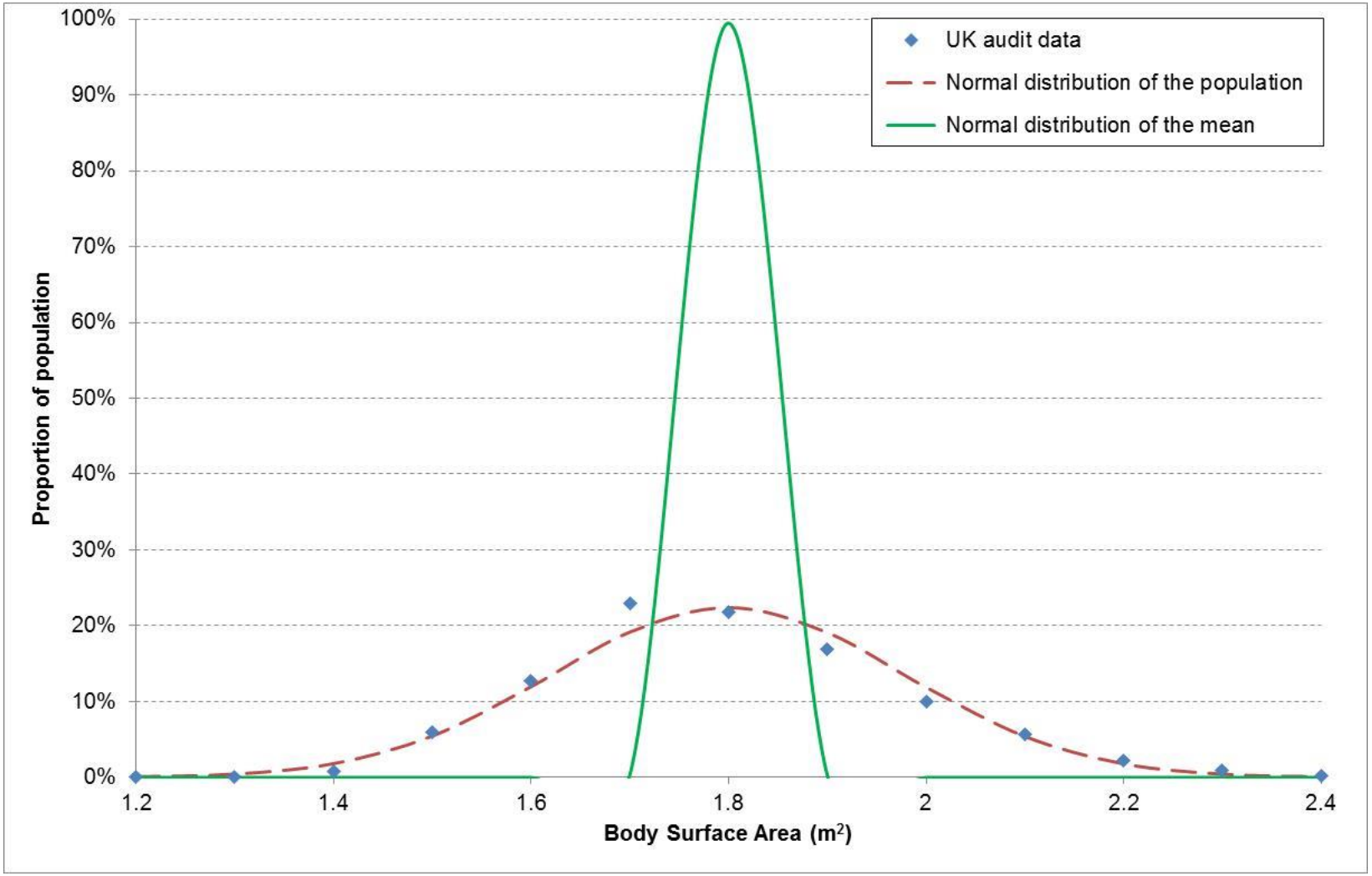
ERG comments
Costs (I)

- The way the company models subsequent lines of chemotherapy leads to anomalous results, because it limits the number of cycles of therapy, which ignores that patients who respond better to third-line treatment will continue third-line treatment longer and be more likely to receive additional lines of subsequent treatment
- The ERG identified a number of issues relating to cost calculations in the model, which have been adjusted in the its revised analyses
- For calculating treatment costs time-to-treatment discontinuation data would have been more appropriate, instead of PFS data

ERG adjustments
Costs (II)

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

ERG adjustments – calculation of BSA



ERG adjustments
Costs (III)

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

ERG comments and adjustments Utilities

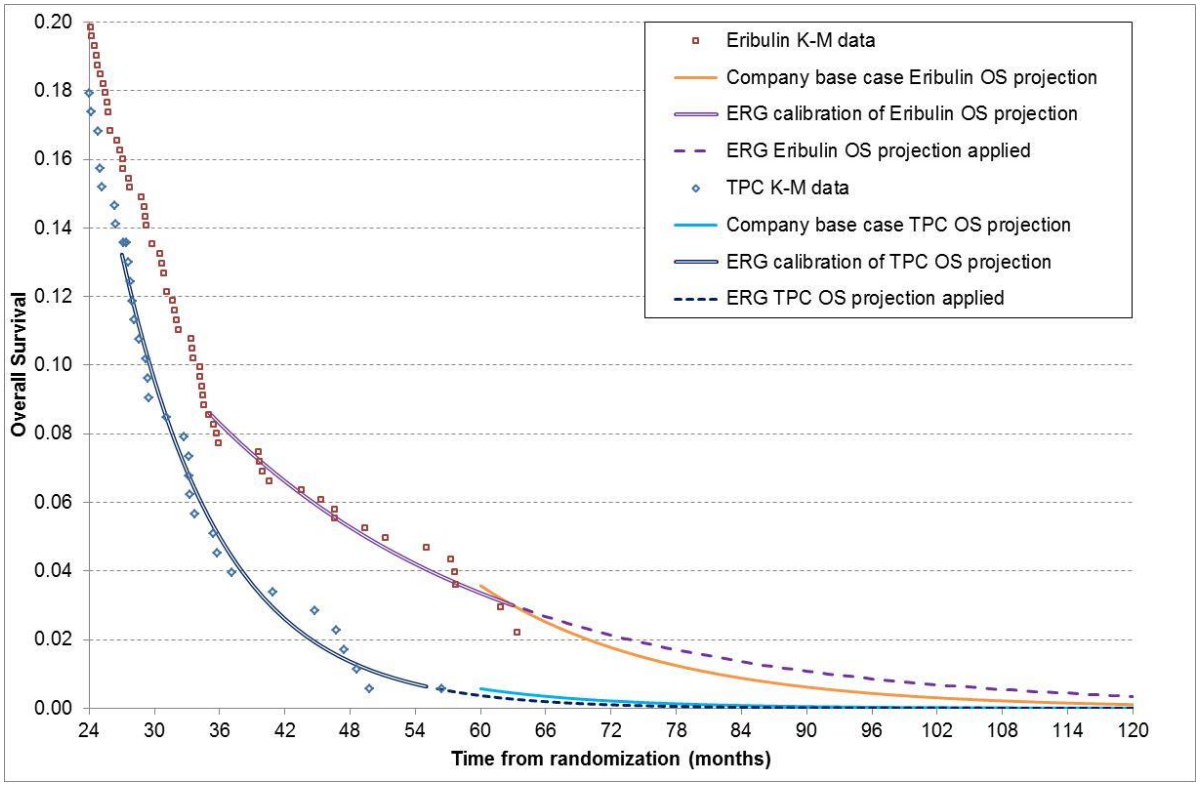
- The mapping algorithm used by the company (Crott and Briggs, 2010) to estimate EQ-5D values from QLQ-C30 results from Study 301 was inappropriate as it was based on trial results from untreated LABC with good performance status
- The ERG considered as an alternative the Standard Gamble mixed model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

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

ERG adjustments - Modelling OS
(Not a decision driver)

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

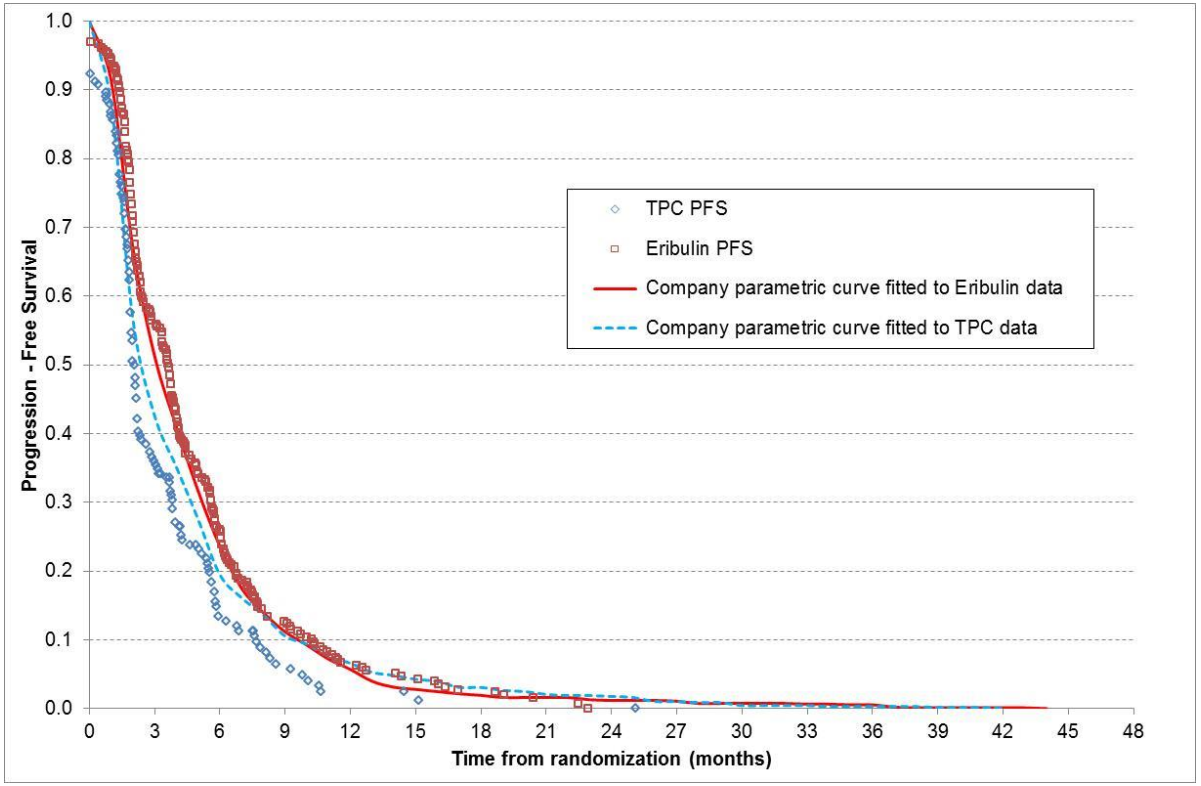
(i.e. month 35 on the eribulin arm and month 27 on the TPC arm)



Source: Figure 5 of ERG report

ERG adjustments - modelling PFS
(Not a decision driver)

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



Source: Figure 6 or ERG report

ERG comments - Modelling PPS
(Not a decision driver)

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

ERG exploratory analyses

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

Source: Table 35 of the ERG report

Evidence Review Group (ERG) exploratory analyses

Model scenario ERG revision	Eribulin		TPC		Incremental		ICER	ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	Per QALY gained	Change
A. Company base case	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	**£35,624**	**-**
R5) ERG estimated eribulin unit costs	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£45,418	**+£9,793**
R6) ERG estimated comparator unit costs (combined with R4)	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£30,106	**-£5,518**
R7) ERG preferred progression utility value	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£46,912	**+£11,288**
R8) ERG alternative method of costing subsequent lines of therapy	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£45,435	**+£9,811**
R9) Correct logic error on eribulin administration costs	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	£39,737	**+£4,113**
B. ERG revised base case A+R1 to R9	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	**£62,672**	**+£27,047**

Source: Table 35 of the ERG report

End of life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months, **and**	TPC arm of the EMBRACE study: **Median OS 10.6 months Mean OS 13.53 months** (95% CI 11.87 to 15.19 months)
There is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.	The results of the cost-effectiveness analysis in patients with LABC/MBC whose disease has progressed after at least two prior chemotherapeutic regimens for advanced disease which includes capecitabine (subgroup 2): • **mean OS benefit of 3.04 months** for eribulin compared with TPC The results of the EMBRACE trial show an **extension in median survival of 2.9 months** with eribulin compared with TPC. The **mean OS benefit is 3.39 months** (95% CI 0.83 to 5.96 months) in the ERG's revised model.

Innovation

- How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?
- Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?

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

Potential equality issues

- No equality issues were raised by the company or consultees.

Key decision points

- What is the Committee's view on the issues around cost-effectiveness?
  - Utility values (mapping algorithm, sources and utility value for progressive disease)
  - Dose calculations for eribulin
  - Administration costs post 6 months treatment
  - Cost calculations for the comparators
  - Cost calculations for subsequent lines of therapy
- What is the most plausible ICER?
- Does eribulin fulfil the end of life criteria?