Public observers

Chair's presentation

Eribulin for treating locally advanced or metastatic breast cancer after 1 chemotherapy regimen

2nd Appraisal Committee meeting

Committee A

Lead team: Andrew England, Nerys Woolacott, Pamela Rees

ERG: Liverpool Reviews and Implementation Group

NICE technical team: Anna Brett, Eleanor Donegan

Company: Eisai

16 January 2018

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Eribulin (Halaven), Eisai

Marketing authorisation	Indicated in adults for treating locally advanced or metastatic breast cancer that has progressed after at least 1 chemotherapeutic regimen for advanced disease
Administration & dose	Administered intravenously
Mechanism of action	Synthetic analogue of halichondrin.B, which inhibits tubulin polymerisation. This disrupts the assembly and formation of microtubules, stopping cancer cell division.

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History of the appraisal

- 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 recommended in TA 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: focus of this appraisal.
- Not recommended at committee meeting 2nd November 2017
- The company have submitted additional evidence to support the clinical and cost effectiveness of eribulin 2nd line and address some of the concerns raised in the ACD

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Study 301 – subgroup 1

(HER2-negative disease; 1 prior therapy)

	Eribulin (n=186)	Capecitabine (n=206)
Progression-free survival (investigator-assessed)		
Median	4.2 months	4.0 months
Hazard ratio	0.86 (95% CI 0.69, 1.08) p=0.192	
Proportion of patients who progressed or died	83.9%	89.3%
Proportion of patients experiencing non-fatal progression episode	81.3%	76.1%
Overall survival		
Median	16.1 months	13.5 months
Hazard ratio	0.77 (95% CI 0.62, 0.97) p=0.026	

ITT population median OS 17.5 months in the eribulin vs 13.5 months in the capecitabine arm; HR = 0.644; p = 0.0032

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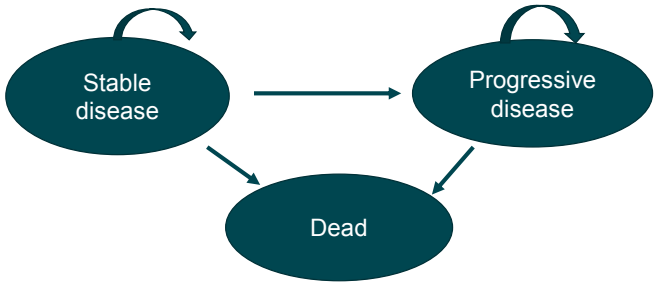
Company's economic model – subgroup 1



- 5 year time horizon partition model (10 and 20 years explored in SA)
- Enter the model in stable disease (on eribulin or capecitabine) until progression
- Capecitabine only comparator in base case model chosen to reflect study 301
- Assumed to remain in progressive state until death
- Stable disease health state can transition directly to death
- Patients receive treatment for up to a maximum of 8 months (cycles) across stable and progressive disease health states
- Transition probabilities for OS and PFS derived from Kaplan-Meier curves from Study 301, subgroup 1 results

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Company's base case results
(with PAS)

	Life years gained	Total		Incremental		ICER
		Costs	QALYs	Costs	QALYs	
Capecitabine	****	********	****			
Eribulin	****	********	****	********	****	**£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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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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ERG's base case results
(with PAS)

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

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ACD – preliminary recommendation

Eribulin is not recommended for treating locally advanced or metastatic breast cancer in adults who have had only 1 chemotherapy regimen

Committee rationale

- Post hoc subgroup (HER2 –ve/1 prior chemotherapy regimen)
- Eribulin has 4.6m OS benefit but no difference in PFS vs. capecitabine
- Patients in the eribulin arm had capecitabine post progression therefore not clear whether OS gain due to eribulin or post-progression treatments
- Most useful question to address is whether eribulin 2nd line is more clinically and cost effective than 3rd line (TA423); no trial to address this.
- Eribulin meets EOL criteria
- Estimates of cost effectiveness range from £36,244 (company base case) to £82,743 per QALY gained (ERG base case).
- Because of the uncertainty in the clinical evidence most plausible estimate is likely to be at the top of this range (not cost effective accepting EOL)

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Committee's considerations

Issue	Committee's conclusion
Comparator	Capecitabine (for most people)
Trial results	Post-hoc subgroup analysis may not be robust for decision-making
PFS	Little, if any, benefit shown
OS	Benefit shown, but may not be attributable to eribulin alone, because most survival gain occurs post-progression and most patients had capecitabine after progression
Modelling PFS	PFS is uncertain: company modelled 0.57 months benefit; ERG no difference – increases ICER significantly
PD utility	Most plausible value likely to lie between company (Crott & Briggs) and ERG (Lloyd) estimates
Subsequent treatment costs	Company's 8 month cap on total treatment not plausible – most people likely to be having active treatment after 8 months Actual costs likely to be nearer ERG's estimate (no cap; 60% patients having subsequent treatments after progression)
ICERs	Nearer ERG base case of £82,743 than company base case of £36,244 per QALY gained

ACD consultation responses

- Consultee comments from:
  - Breast Cancer Now
  - Eisai Limited
- No commentator comments received
- No web comments received

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Comments from Breast Cancer Now

- Very disappointed that eribulin is not recommended
- Metastatic breast cancer is terminal, and additional time, especially with good quality of life, is extremely valuuable to patients and their families
- Eribulin has a different side effect profile to other treatments, is generally well tolerated and is an important alternative option for those who cannot tolerate other treatments
- Eribulin is particularly valuable to women with 'triple negative' disease of the all breast cancer (ER-, HER2-, PR-), who cannot have targeted treatments or hormonal therapies
- Triple negative breast cancer accounts for 15% of all breast cancers and tends to be more aggressive; eribulin shown to have benefits in this group, who would otherwise only have chemotherapy, which may give marginal benefit but is also associated with significant side effects

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Comments from the company (1)

- The relevant subgroup evidence is robust for decision-making – reflects greatest clinical benefit and unmet clinical need, HER2 status and line of therapy were pre-specified (separately) and results are consistent across subgroups
- OS benefit can be considered attributable to eribulin (see new supporting analyses on the impact of different post-progression treatments on OS and analysis of censoring at subsequent treatment)
- PFS modelling should reflect clinical evidence showing separation of curves for 12 months – a single PFS curve for both treatments is not appropriate
- Not all patients having active therapy post-progression will have it until death – assumed 21 months based on average estimated survival in eribulin arm
- Current practice has changed so that the most appropriate comparator now is a 50-50% split of vinorelbine (IV) and capecitabine

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Comments from the company (2)

- Dose intensity for eribulin (approximately 80%) should be considered in the cost calculation (although not included in company's revised base case)
- Additional treatment options valued by patients and their families
- Triple negative disease also an area of unmet need; nominally significant findings in OS for eribulin in this group (median 14.4 months vs. 9.4 months; HR 0.702 [95% CI 0.545, 0.906] p=0.0062).
- Eribulin shows OS benefit of at least 3 months without adversely impacting on health-related quality of life

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Additional analyses from the company (1)

Impact of subsequent treatments on overall survival

- The OS benefit in subgroup 1 is consistent with that in the whole HER2 – ve population (median 15.9 vs.13.5 m; HR=0.84, 95% CI: 0.71 to 0.98)
- Potential impact of post-study anticancer therapies on OS assessed by subgroup analyses of study 301 ITT population (on the next slide):
  - Patients not having further cytotoxic therapy (eribulin and capecitabine arms)
  - Patients in eribulin arm having capecitabine next
  - Patients in eribulin arm having cytotoxic therapy other than capecitabine next
  - Patients in capecitabine arm having any cytotoxic therapy next
- Effect of post-study chemotherapy on ITT population and subgroup 1 also analysed by censoring patients who crossed over to either eribulin or capecitabine after progression (appendix 1).
- Results of subgroup 1 with censoring: median OS 17.5 months vs. 13.5 months; HR 0.644; p=0.0032

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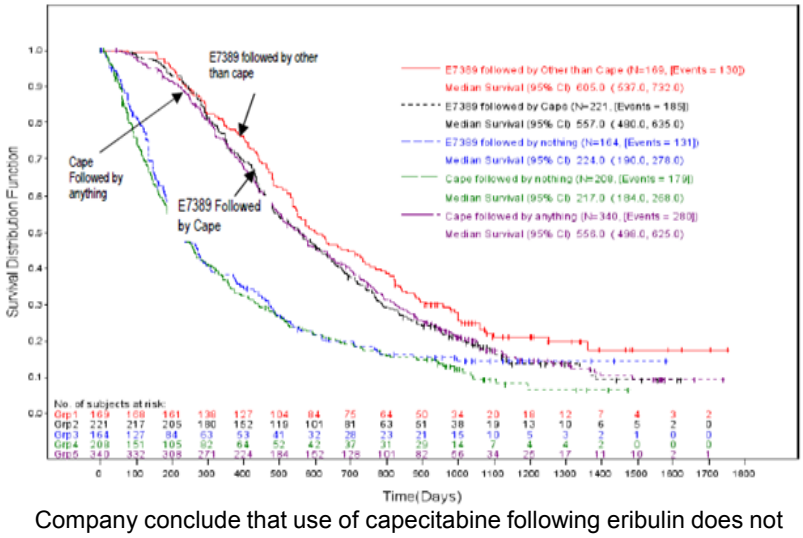
Additional analyses from the company (2)

OS subgroup analyses – subsequent treatment (ITT)



Company conclude that use of capecitabine following eribulin does not account for OS differences in the primary analysis

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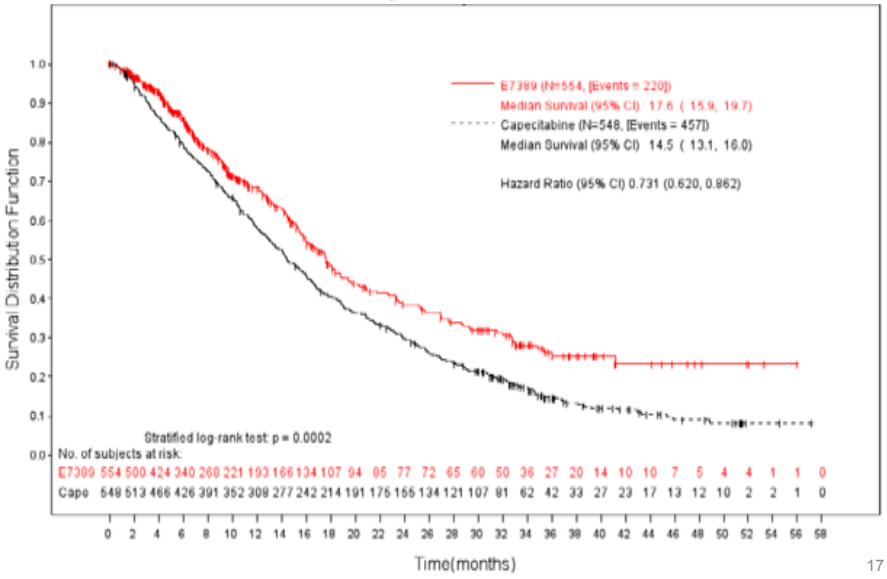
Additional analyses from the company (3)

OS crossover adjusted (censored) - ITT



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Company response to modelling PFS

- Even though overall, there was [redacted]
  PFS curves exhibit a clear and consistent separation for almost 12 months.

[redacted]

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Additional analyses from the company (4)
Subsequent treatment costs

- Agree not all patients in post-progression state will have active therapy
- Of those who do, not all will remain on active treatment until death
- Committee's conclusions in TA423 were that the proportion of patients still on treatment after 6 months was uncertain, as was the duration of subsequent lines of treatment
- Consider ERG's assumption of 60% patients in post-progression state having subsequent treatments to be a 'worst-case scenario' for subsequent treatment costs, but include this proportion in the revised base case
- In **revised base case estimate**, assume a cap on total treatment duration (eribulin and subsequent treatments) of 21.33 months, based on the **average** duration of survival of patients in the eribulin arm of the trial, and life expectancy of patients in this setting (less than 24 months)

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Company revised model – updated comparator

- In the original base case capecitabine was the only comparator with 50-50% split between capecitabine and vinorelbine (oral and IV) used in a sensitivity analysis (based on telephone interview with 4 NHS based clinical specialists in MBC):
  - 'Is vinorelbine is an appropriate comparator in second-line patients with HER2-negative disease,
  - Is the assumption that vinorelbine has equal efficacy to capecitabine is appropriate
  - Which formulation of vinorelbine is used in clinical practice.'
- Following the first committee meeting the company contacted the clinical expert in attendace who advised that 'quite a significant proportion of patients would receive vinorelbine in this setting'
- The comparator in the revised based case model has therefore been changed to a 50-50% split of vinorelbine (IV) and capecitabine.

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Summary of company's response to committee's conclusions

Issue	Committee's conclusion	Company's revised base case
Comparator	Capecitabine (for most people)	50% capcitabine; 50% IV vinorelbine
PFS	Little, if any, benefit shown	0.57 month mean PFS benefit from trial should be modelled
OS	Benefit shown, but may not be attributable to eribulin alone	Additional subgroup and crossover-adjusted analyses to show OS benefit is attributable to eribulin
PD utility	Most plausible value likely to lie between company (Crott & Briggs) and ERG (Lloyd) estimates	Accepted mid-point estimate; applied PD utility value of 0.59 in revised base case
Subsequent treatment costs	Company's 8 month cap on total treatment not plausible Actual costs likely to be nearer ERG's estimate (no cap; 60% patients having subsequent treatments after progression)	Applied 21.33 month cap on total treatment duration to reflect average estimated survival in model; 60% patients having subsequent treatment after progression

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Company's revised base case
(with PAS)

	ICER
Company's original base case	**£36,244**
ERG's changes accepted by company: • OS estimates • Annual discounting instead of continuous • Time to treatment discontinuation used for costs • Unit cost: eribulin • Unit cost: other chemotherapies • Logic error: eribulin administration costs • Logic error: oral vinorelbine costs	
ERG corrected model	£82,743
ERG's corrected model - updated post-progression utility (mid-point)	£69,843
ERG corrected model - company assumption for PFS (mean 0.57m)	£76,838
ERG corrected model - updated subsequent treatment duration (21m cap)	£74,454
Company's new comparator (50% capecitabine 50% vinorelbine)	£71,649
Company's revised base case	**£50,808**

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ERG critique (1)

- Difficult to determine whether the improved OS for patients treated with eribulin compared to those treated with capecitabine is a result of treatment received subsequent to disease progression since:
  - For those who received no subsequent treatment, median OS is very similar in both arms (7.4m eribulin and 7.1m capecitabine)
  - Median OS for erbulin followed by capecitabine (18.3 months, 95%CI 15.8 to 20.8) to be similar to median OS for capecitabine followed by anything else (18.3, 95% CI 16.4 to 21.2)
  - Patients who received subsequent treatment after either eribulin or capecitabine appear to have improved OS vs. ITT population or those who receive no treatment. BUT this does not necessarily that subsequent treatment is the cause of improved OS which may be another key factor (e.g. physical condition of the patient).
  - OS is statistically significantly improved for patients who received eribulin vs. capecitabine when those who cross over are censored (50% cross over in the eribulin arm vs. 1% in the capecitabine arm).

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ERG (2) – revised company model

ERG model + amendment	ERG critique
Post progression utility 0.59	Reasonable interpretation of the uncertainty expressed by Appraisal Committee members with respect to the post-progression utility
PFS benefit of 0.57 months – separation of KM curves to 12 months	Do not agree that this is justified. AUC of PFS shows small difference in the eribulin and capecitabine arm from 3 to 17 months (never exceeds 3 days at time)
21 m treatment duration	A cap on primary or total treatment not justified. Inappropriate reliance on mean treatment duration – substantial number of people had over 21 cycles.
Comparator (50% capecitabine 50% vinorelbine)	Trial comparator was capecitabine. In appropriate to assume equal efficacy of capecitabine and vinorelbine (no evidence presented)
Vinorelbine 100% intravenous	This change (from 50% oral and 50% IV in the original model) alters costs in favour or Eribulin (impact on patients?
Eribulin dose intensity	The company note an absolute dose intensity of approximately 80% which is compatible with the relative dose intensity of 87% used in the model

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ERG critique (3)

- ERG does not believe there is good reason to accept any of the model changes proposed by Eisai. However, two sensitivity analyses have been explored by the ERG:
  - Amending the post-progression patient utility value from 0.496 to 0.59 reduces the estimated ICER of £12,900 per QALY gained.
  - Applying Kaplan-Meier PFS data for the two trial arms for the first 17 months, followed by a pooled extrapolation beyond 17 months reduces the estimated ICER by only £408 per QALY gained.
- Thus, the ERG best estimated ICER is £82,743 per QALY gained.
- If both these sensitivity analyses changes are applied together the ICER falls to £66,272 per QALY gained.

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Key issues for consideration

Key issues	
Comparator	Is the relevant comparator capecitabine or an even split between capecitabine and IV vinorelbine?
Attribution of OS benefit	Do the results of the subgroup and crossover-adjusted analyses support the company view that OS benefit can be attributed to eribulin and not subsequent treatments?
PD utility	Is 0.59 utility for progressive disease acceptable (midpoint of 0.679 and 0.496 in the original submission and ERG report)
PFS	Should a PFS benefit be included in the model?
Subsequent treatment costs	Is a cap of 21 months on total treatment acceptable?

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