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]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Company ACD comments**
   - **Additional evidence: Appendix 1**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Breast Cancer Now

   No comments were received from patient or clinical experts
   No comments were received through the NICE website consultation

4. **ERG critique response to company ACD comments**

5. **Erratum to ERG critique**

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

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

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1		Breast Cancer Now	Breast Cancer Now is disappointed by the Committee's recommendation that eribulin should not be recommended for treating locally advanced or metastatic breast cancer in those that have had only one chemotherapy regimen.	Comment noted
2		Breast Cancer Now	Metastatic breast cancer is a terminal diagnosis and any additional time, especially with a good quality of life, is extremely valuable to breast cancer patients and their families. We note that the clinical trial evidence showed a statistically significant overall survival benefit of an additional 4.6 months compared to capecitabine in those with HER2 negative disease - although given the lack of any statistically significant progression free survival, the Committee was unclear whether this was attributable to eribulin or subsequent treatments. Eribulin has a different side effect profile to other treatment options, is generally well tolerated, and is therefore an important alternative for those that cannot tolerate those other treatments.	Comment noted. During consultation the company submitted analyses of the impact of post-progression treatment on overall survival. The committee noted that these analyses suggested that overall survival with eribulin 2nd line in clinical practice (that is, followed by capecitabine) would be less effective than subgroup 1 in the clinical trial and may be no more effective than 3rd line (currently recommended in TA 423). Patients who are unable to tolerate capecitabine 2nd line would be eligible for eribulin 3rd line (TA423) or may receive other treatments such as vinorelbine or paclitaxel. The side effect profile is important but the clinical and cost effectiveness needs to be established for a positive recommendation
3		Breast Cancer Now	Eribulin is likely to be of particular value to women with 'triple negative' breast cancer: those with HER2 positive breast cancer are most likely to be treated with targeted treatments such as Perjeta and Kadcyla; and those with hormone positive breast cancer are most likely to be treated with hormone therapies as the first few lines of treatment for disease before chemotherapy, although some may have chemotherapy as a first line treatment if their disease is life threatening or requires early relief of symptoms.	Comment noted. The company did not present a case for the clinical and cost effectiveness of this subgroup in their submission

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4		Breast Cancer Now	Around 15% of all breast cancers are 'triple negative' which tend to be more aggressive, and research has shown eribulin to have particular benefits for this group. There are no targeted treatments available for 'triple negative' breast cancer which means that, without eribulin these women may have to have additional chemotherapy for which the benefits may be marginal, but the side effects significant.	Comment noted (see above)
5		Eisai Limited	**Eisai do not agree that the summary of the clinical evidence from Study 301 is a reasonable interpretation of the evidence for the reasons cited below:** **Eisai does not agree that the relevant subgroup evidence may not be sufficiently robust for decision-making.** It is important to reflect on the history of this appraisal as explanation for the choice of this subgroup and why the evidence is robust for decision making. Eisai's company submission and cost effectiveness model submitted to NICE in November 2016 focused on two subgroups in particular for the following reasons: 1. Eribulin's clinical benefit has been assessed in two phase III pivotal trials, study 305 (EMBRACE) and study 301. However, the two studies included patient populations with different characteristics and focused in slightly different disease settings. 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 figure below illustrates the overlap between the two trials and how the selection of the subgroups enables accurate cost-effectiveness assessment *[provided but not reproduced here]*. 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 and reflect unmet clinical need. Subgroup 2 was then assessed by NICE first and positive guidance issued in December 2016 (TA423). This appraisal focuses on Subgroup 1 from study 301 ie HER2-negative patients with LABC/MBC who have progressed after one prior chemotherapy regimen in the advanced setting. Study 301 was a large phase III trial in just over one thousand patients. The ERG noted that study 301 was generally well designed and well conducted with a low risk of bias. Although clinical effectiveness evidence for the Subgroup 1 population is derived from a post-hoc subgroup of the phase III study 301, it is important to note that, as stated in the company submission, study 301 was designed to further evaluate the effect of eribulin on prespecified subgroups including HER2 negative status. Therefore, patients were pre-stratified according to HER2 status. As highlighted in the ERG report, the results for all patients with HER2-negative status who were enrolled into the trial are consistent with those of Subgroup 1 ie a statistically significant gain in OS for eribulin compared to capecitabine is observed (median 15.9 months versus 13.5 months; HR=0.84, 95% CI: 0.71 to 0.98)	Comment noted. For the reasons highlighted by the company the appraisal was split into 3rd line and 2nd line.

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			In addition, analyses based on number of prior chemotherapies for advanced or metastatic disease were pre-specified. 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) were also consistent with those of the ITT population, suggesting that these patients may experience a beneficial treatment effect from eribulin in comparison to capecitabine regardless of HER2 status.	

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6		Eisai Limited	**Eisai does not agree that the overall survival (OS) benefit in the trial may not be directly attributable to eribulin alone.** As stated in the ERG report on page 40, Eisai 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 (pp115-116). Further information from the CSR regarding these analyses on the ITT population of study 301 is provided below. As per Table 4 provided in the response to clarification questions, a total of 730 patients in Study 301 received further anticancer therapy after discontinuation of study treatment: 390 (70.4%) in the eribulin group and 340 (62.0%) in the capecitabine group. As first anticancer therapy after discontinuation of study treatment, 221 (39.9%) of eribulin patients received capecitabine and 55 (10%) of capecitabine subjects received further capecitabine. Kaplan–Meier curves in five subgroups were compared: two subgroups were patients who did not receive further cytotoxic therapy after discontinuation of study treatment, in both treatment groups. The other three subgroups included patients: • originally randomised to eribulin and who immediately received capecitabine after discontinuation of study treatment • originally randomised to eribulin and who immediately received cytotoxic therapy other than capecitabine after discontinuation of study treatment • originally randomised to capecitabine and who received any subsequent cytotoxic therapy Figure 1 below shows that the OS for patients treated with eribulin or capecitabine who received chemotherapy other than capecitabine after study treatment was consistent with the OS from the primary analysis. Eribulin patients who received capecitabine after study medication had a numerically slightly worse outcome than eribulin-treated patients who received other therapies. As would be expected, patients who did not receive any further chemotherapy died earlier in both treatment groups. *[Figure 1 provided but not reproduced here]* These results show that the observed improvement in OS seen with eribulin compared with capecitabine in the primary analysis was not likely due to the subsequent treatment with capecitabine after discontinuation of eribulin and treatment with subsequent chemotherapies did not appear to alter the relationship of OS between the treatment groups. The effect of post study chemotherapy medication on the ITT population was also analysed in a separate sensitivity analysis, which is reported in the CSR on page 116. This analysis was generated by censoring subjects if they had crossed over to either eribulin or capecitabine after progression, and thus assesses whether the OS improvement observed in eribulin patients is mainly due to the effect of capecitabine as a post progression treatment. The OS benefit was conserved under this assumption (median OS 17.6 months vs 14.5 months; HR = 0.731; p = 0.0002) – see Figure 2 overleaf. The same analysis has been conducted for Subgroup 1 and shows consistent results – see Appendix 1 for further information. *[Figure 2 and Appendix 1 provided but not reproduced here]* Thus, again, the use of capecitabine following eribulin does not account for the OS differences in the primary analysis.	Comment noted. The committee considered the additional evidence on the overall survival gain of eribulin for different subpopulations of study 301. It did note however that overall survival was highly dependent on the post progression treatment received. Section 3.7 of the FAD states that 'The committee concluded that patients with disease that progresses on eribulin would be very likely to have capecitabine on progression, and the company's evidence suggested that this not likely to result in better overall survival than current clinical practice (that is, capecitabine followed by another active treatment). The committee was not persuaded that a clear benefit had been shown for offering eribulin second line compared with third line, as recommended in NICE's guidance on eribulin after 2 or more chemotherapy regimens.'
7		Eisai Limited	**Eisai do not agree that the summary of the cost effectiveness evidence is a reasonable**	Comment noted. The committee noted the continued

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			interpretation of the evidence for the reasons cited below: **Eisai do not agree with modelling no progression-free survival benefit.** Eisai do not agree that lack of statistical significance justifies pooling data from both treatments into a single survival curve. It is important that the cost effectiveness evidence is reflective of the clinical evidence. As can be seen from the Figure overleaf, even though overall, there was [redacted] the PFS curves exhibit a clear and consistent separation for almost 12 months. *[Figure 3 provided but not reproduced here]*	discrepancy between the PFS estimated by the company in the revised model and the ERG. 'The committee did not consider that the 17 day improvement in progression-free survival in the model (non-significant 6 days benefit in the trial), which resulted in a large reduction in the ICER of 6,000 per QALY, was justified. The committee concluded that the most plausible ICER for eribulin compared with capecitabine, using the revised company model with the committee's preferred assumptions, is approximately £69,843 per QALY gained which does not represent a cost-effective use of NHS resources.' (FAD section 3.14)
8		Eisai Limited	**Eisai do not agree with the ERG's estimates of the costs of subsequent treatments.** We agree not all patients who enter the post progression health state will be treated with active therapy. In addition, not all patients who are treated within this health state will stay on therapy for the full time, ie remain on active treatment until death. This ERG assumption was reviewed by this same committee previously during the appraisal of subgroup 2 ie the third line setting. It is important to note that at the time, the committee considered that there is significant uncertainty about the proportion of patients who might still be on treatment after 6 months, and the duration of subsequent lines of treatment. The committee acknowledged that the subsequent treatments are a source of uncertainty in the model, which it is not possible to resolve and it concluded that although the assumptions in the company's model might have been optimistic, the ERG's assumption represents a worst-case scenario for the costs of subsequent therapy. We consider the assumption that 60% of patients will receive active therapy in the post progression state to be the worst-case scenario. As a conservative estimate, we have included a further scenario in the model which assumes that this percentage of patients will be treated for no longer than the average duration of estimated survival in the model ie 21.33 months. This is in line with the committee's decision that the life expectancy for patients in this setting is less than 24 months. Further information is provided in Appendix 1 *[provided but not reproduced here]*.	Comment noted. 'The committee agreed at its first meeting that an 8 month cap on total treatment was not clinically plausible. In its revised model the company changed the cap on the duration of treatment in both arms of the model from 8 months to 21.3 months (the average survival in the eribulin arm). The ERG noted that a substantial number of people in the eribulin arm of study 301 had more than 21 months of treatment. The committee concluded that in clinical practice patients who live longer than 21 months would still have treatment and

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				therefore it did not accept this assumption '(FAD section 3.13)
9		Eisai Limited	**Eisai do not agree that the most plausible ICER for eribulin is higher than the range normally considered cost effective.** In line with the committee's decision that the post-progression utility value is likely to be between the company's and the ERG's estimates, Eisai have submitted a scenario to reflect this, with a post progression utility value of 0.59. This changes the ICER to £69,843. As indicated above, Eisai do not agree with modelling no progression –free survival benefit and the ERG's estimates of the costs of subsequent treatments. In addition, we would like to consider the following two plausible scenarios: 1. The committee concluded that capecitabine was the most relevant comparator, but highlighted that treatment sequences in the adjuvant and advanced setting could vary in clinical practice. In line with recent clinician feedback, Eisai believe that the scenario already included in the model where 50% of patients receive capecitabine and 50% vinorelbine would be more reflective of current clinical practice. In addition, current clinical practice is that breast cancer oncologist would use the IV formulation of vinorelbine and not the oral. To reflect this, a scenario has been presented in the model and this changes the ICER to £60,479. 2. The mean dose intensity for eribulin in Subgroup 1 has been provided as additional evidence – see Appendix 1 and should be considered in the cost calculation. *[Appendix 1 provided but not reproduced here]*	Commented noted. 'The committee considered the appropriateness of all changes in the revised company model and their impact on the ICER. It considered only the updated utility value for progressive disease to be justified. The committee concluded that the most plausible ICER for eribulin compared with capecitabine, using the revised company model with the committee's preferred assumptions, is approximately £69,843 per QALY gained. This does not represent a cost-effective use of NHS resources' (FAD section 3.14)
10		Eisai Limited	**Overall Eisai does not believe that these provisional recommendations provide sound and suitable guidance to the NHS.** As recognised by the committee, having additional treatment options for advanced breast cancer would be valued by patients and their families. Eisai are disappointed that NICE has not recognised the benefits that eribulin will bring to patients in England and Wales in this earlier line setting in patients with HER2-negative disease. This is recognised as an area of unmet need, together with patients with triple-negative disease. Nominally significant findings in OS for patients in the eribulin group were observed in both of these pre-specified subgroups from study 301 with triple negative patients having an increase of 5 months (median OS for the eribulin group was 14.4 months and 9.4 months for the capecitabine group) with a HR (95% CI) of 0.702 (0.545, 0.906) and nominal P = 0.0062. As above and with the additional evidence provided, eribulin has been shown to demonstrate an overall survival benefit of at least 3 months that is attributable to the medicine itself without adversely impacting on health-related quality of life. In this group of patients, in whom life expectancy is short, this is very important. The Eisai model has been updated to include the changes highlighted above and is included separately as part of this response. The combined additional changes presented above result in a revised company base case ICER of £50,808. Further detail is provided in Appendix 1 *[provided but not reproduced here]*. This does not take into account the updated mean dose intensity for Subgroup 1. Taking the above information into account, eribulin should be considered good value for money for adoption by the NHS.	Comment noted. The company did not make a case for the clinical and cost effectiveness of patients with triple negative disease. 'The committee concluded that the most plausible ICER for eribulin compared with capecitabine, using the revised company model with the committee's preferred assumptions, is approximately £69,843 per QALY gained. This does not represent a cost-effective use of NHS resources' (FAD section 3.14)

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by 5pm on Tuesday 18 December 2017 **email:** TAComm@nice.org.uk

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Eisai Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**N/A**]
Name of commentator person completing form:	[**Cyndy Simon**]

Comment number	Comments

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

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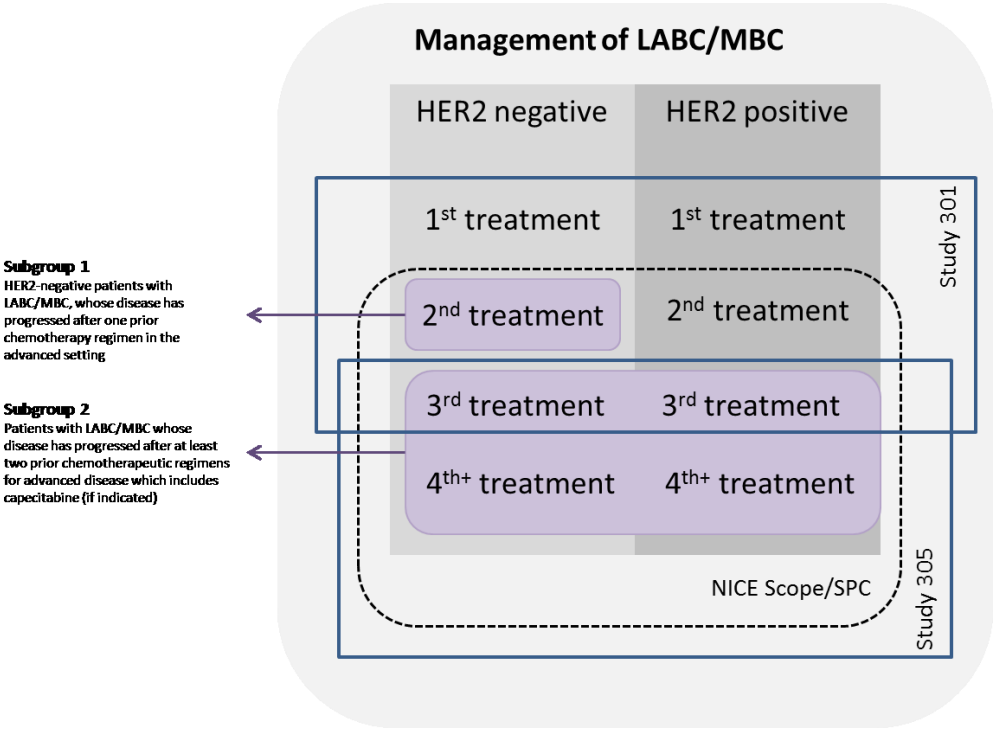
	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Eisai do not agree that the summary of the clinical evidence from Study 301 is a reasonable interpretation of the evidence for the reasons cited below:	
1	**Eisai does not agree that the relevant subgroup evidence may not be sufficiently robust for decision-making.** It is important to reflect on the history of this appraisal as explanation for the choice of this subgroup and why the evidence is robust for decision making. Eisai's company submission and cost effectiveness model submitted to NICE in November 2016 focused on two subgroups in particular for the following reasons: 1. Eribulin's clinical benefit has been assessed in two phase III pivotal trials, study 305 (EMBRACE) and study 301. However, the two studies included patient populations with different characteristics and focused in slightly different disease settings. 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 figure below illustrates the overlap between the two trials and how the selection of the subgroups enables accurate cost-effectiveness  assessment. 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

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	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 and reflect unmet clinical need. Subgroup 2 was then assessed by NICE first and positive guidance issued in December 2016 (TA423). This appraisal focuses on Subgroup 1 from study 301 ie HER2-negative patients with LABC/MBC who have progressed after one prior chemotherapy regimen in the advanced setting. Study 301 was a large phase III trial in just over one thousand patients. The ERG noted that study 301 was generally well designed and well conducted with a low risk of bias. Although clinical effectiveness evidence for the Subgroup 1 population is derived from a post-hoc subgroup of the phase III study 301, it is important to note that, as stated in the company submission, study 301 was designed to further evaluate the effect of eribulin on prespecified subgroups including HER2 negative status. Therefore, patients were pre-stratified according to HER2 status. As highlighted in the ERG report, the results for all patients with HER2-negative status who were enrolled into the trial are consistent with those of Subgroup 1 ie a statistically significant gain in OS for eribulin compared to capecitabine is observed (median 15.9 months versus 13.5 months; HR=0.84, 95% CI: 0.71 to 0.98) In addition, analyses based on number of prior chemotherapies for advanced or metastatic disease were pre-specified. 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) were also consistent with those of the ITT population, suggesting that these patients may experience a beneficial treatment effect from eribulin in comparison to capecitabine regardless of HER2 status.
2	**Eisai does not agree that the overall survival (OS) benefit in the trial may not be directly attributable to eribulin alone.** As stated in the ERG report on page 40, Eisai 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 (pp115-116). Further information from the CSR regarding these analyses on the ITT population of study 301 is provided below. As per Table 4 provided in the response to clarification questions, a total of 730 patients in Study 301 received further anticancer therapy after discontinuation of study treatment: 390 (70.4%) in the eribulin group and 340 (62.0%) in the capecitabine group. As first anticancer therapy after discontinuation of study treatment, 221 (39.9%) of eribulin patients received capecitabine and 55 (10%) of capecitabine subjects received further capecitabine. Kaplan–Meier curves in five subgroups were compared: two subgroups were patients who did not receive further cytotoxic therapy after discontinuation of study treatment, in both treatment groups. The other three subgroups included patients: • originally randomised to eribulin and who immediately received capecitabine after discontinuation of study treatment • originally randomised to eribulin and who immediately received cytotoxic therapy other than

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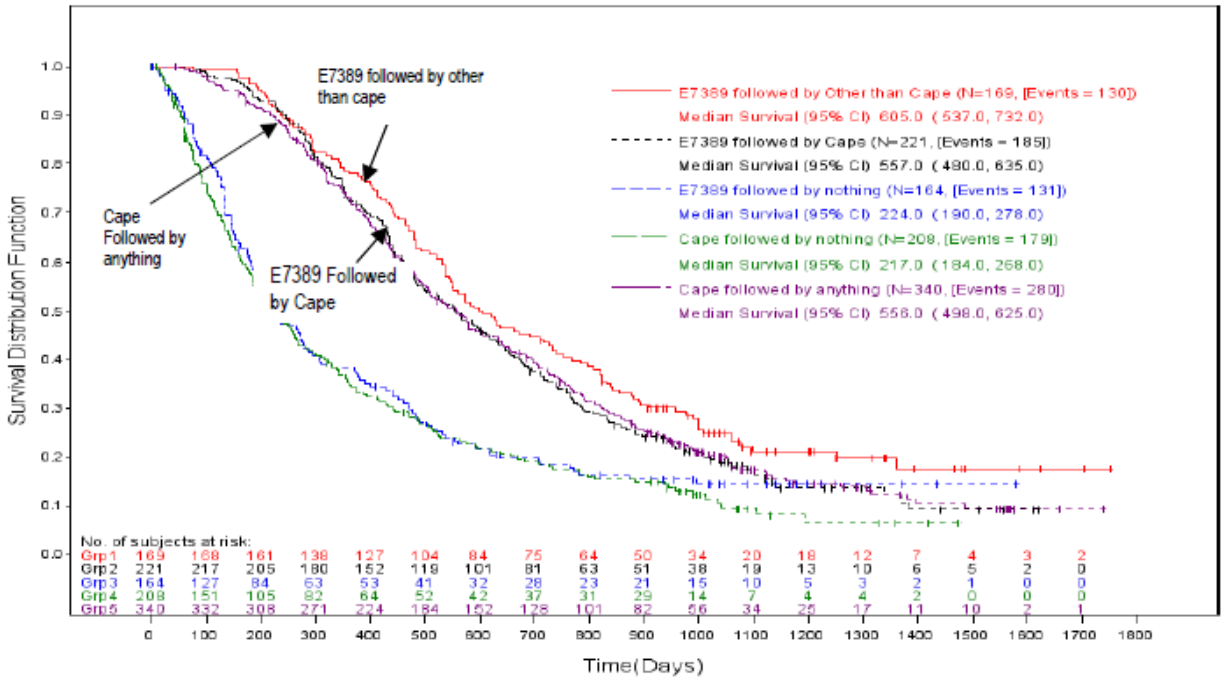
capecitabine after discontinuation of study treatment

- originally randomised to capecitabine and who received any subsequent cytotoxic therapy

Figure 1 below shows that the OS for patients treated with eribulin or capecitabine who received chemotherapy other than capecitabine after study treatment was consistent with the OS from the primary analysis. Eribulin patients who received capecitabine after study medication had a numerically slightly worse outcome than eribulin-treated patients who received other therapies. As would be expected, patients who did not receive any further chemotherapy died earlier in both treatment groups.

Figure 1: Overall Survival by subsequent therapy after discontinuation of study treatment: ITT Population



These results show that the observed improvement in OS seen with eribulin compared with capecitabine in the primary analysis was not likely due to the subsequent treatment with capecitabine after discontinuation of eribulin and treatment with subsequent chemotherapies did not appear to alter the relationship of OS between the treatment groups.

The effect of post study chemotherapy medication on the ITT population was also analysed in a separate sensitivity analysis, which is reported in the CSR on page 116.

This analysis was generated by censoring subjects if they had crossed over to either eribulin or capecitabine after progression, and thus assesses whether the OS improvement observed in eribulin patients is mainly due to the effect of capecitabine as a post progression treatment. The OS benefit was conserved under this assumption (median OS 17.6 months vs 14.5 months; HR = 0.731; p = 0.0002) – see Figure 2 overleaf. The same analysis has been conducted for Subgroup 1 and shows consistent results – see Appendix 1 for further information.

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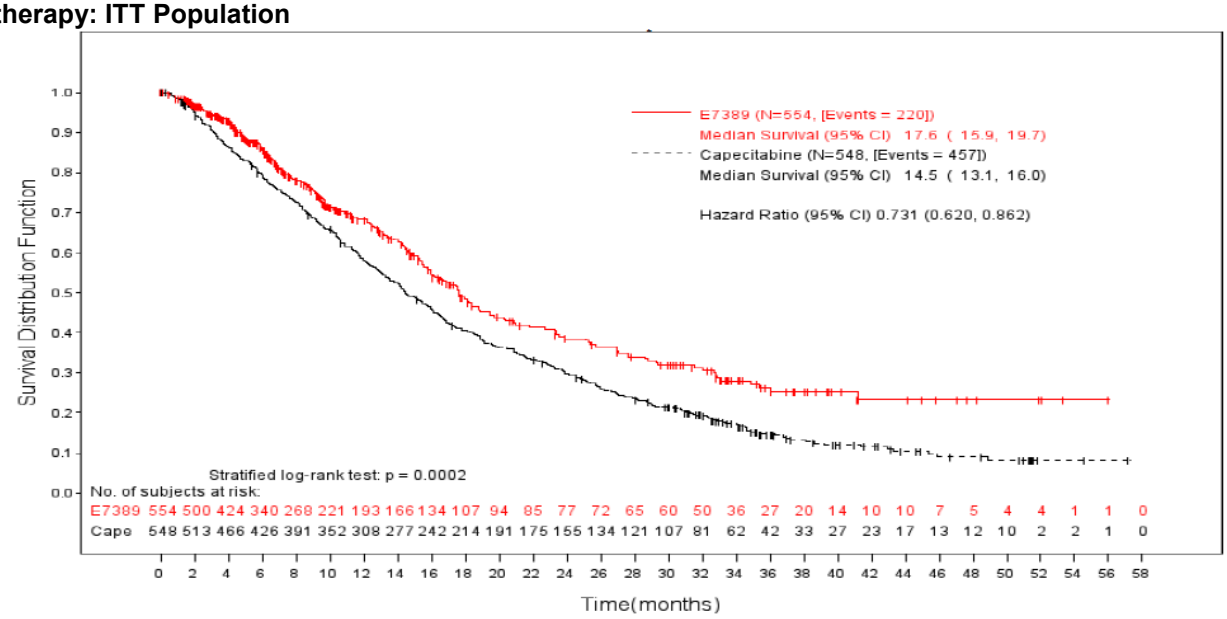
	Figure 2: Kaplan-Meier plot of OS censoring at capecitabine and eribulin as post treatment therapy: ITT Population  Thus, again, the use of capecitabine following eribulin does not account for the OS differences in the primary analysis.
Eisai do not agree that the summary of the cost effectiveness evidence is a reasonable interpretation of the evidence for the reasons cited below:	
1	**Eisai do not agree with modelling no progression-free survival benefit.** Eisai do not agree that lack of statistical significance justifies pooling data from both treatments into a single survival curve. It is important that the cost effectiveness evidence is reflective of the clinical evidence. As can be seen from the Figure overleaf, even though overall, there was [redacted], the PFS curves exhibit a clear and consistent separation for almost 12 months.

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	Figure 3: 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) Academic in confidence information removed
2	**Eisai do not agree with the ERG's estimates of the costs of subsequent treatments.** We agree not all patients who enter the post progression health state will be treated with active therapy. In addition, not all patients who are treated within this health state will stay on therapy for the full time, ie remain on active treatment until death. This ERG assumption was reviewed by this same committee previously during the appraisal of subgroup 2 ie the third line setting. It is important to note that at the time, the committee considered that there is significant uncertainty about the proportion of patients who might still be on treatment after 6 months, and the duration of subsequent lines of treatment. The committee acknowledged that the subsequent treatments are a source of uncertainty in the model, which it is not possible to resolve and it concluded that although the assumptions in the company's model might have been optimistic, the ERG's assumption represents a worst-case scenario for the costs of subsequent therapy. We consider the assumption that 60% of patients will receive active therapy in the post progression state to be the worst-case scenario. As a conservative estimate, we have included a further scenario in the model which assumes that this percentage of patients will be treated for no longer than the average duration of estimated survival in the model ie 21.33 months. This is in line with the committee's decision that the life expectancy for patients in this setting is less than 24 months. Further information is provided in Appendix 1.
3	**Eisai do not agree that the most plausible ICER for eribulin is higher than the range normally considered cost effective.** In line with the committee's decision that the post-progression utility value is likely to be between the company's and the ERG's estimates, Eisai have submitted a scenario to reflect this, with a post progression utility value of 0.59. This changes the ICER to £69,843. As indicated above, Eisai do not agree with modelling no progression –free survival benefit and the ERG's estimates of the costs of subsequent treatments. In addition, we would like to consider the following two plausible scenarios: 1. The committee concluded that capecitabine was the most relevant comparator, but highlighted that treatment sequences in the adjuvant and advanced setting could vary in clinical practice. In line with recent clinician feedback, Eisai believe that the scenario already included in the model where 50% of patients receive capecitabine and 50% vinorelbine would be more reflective of current clinical practice. In addition, current clinical practice is that breast cancer oncologist would use the IV

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	formulation of vinorelbine and not the oral. To reflect this, a scenario has been presented in the model and this changes the ICER to £60,479. 2. The mean dose intensity for eribulin in Subgroup 1 has been provided as additional evidence – see Appendix 1 and should be considered in the cost calculation.

Overall Eisai does not believe that these provisional recommendations provide sound and suitable guidance to the NHS.

As recognised by the committee, having additional treatment options for advanced breast cancer would be valued by patients and their families. Eisai are disappointed that NICE has not recognised the benefits that eribulin will bring to patients in England and Wales in this earlier line setting in patients with HER2-negative disease. This is recognised as an area of unmet need, together with patients with triple-negative disease. Nominally significant findings in OS for patients in the eribulin group were observed in both of these pre-specified subgroups from study 301 with triple negative patients having an increase of 5 months (median OS for the eribulin group was 14.4 months and 9.4 months for the capecitabine group) with a HR (95% CI) of 0.702 (0.545, 0.906) and nominal P = 0.0062.

As above and with the additional evidence provided, eribulin has been shown to demonstrate an overall survival benefit of at least 3 months that is attributable to the medicine itself without adversely impacting on health-related quality of life. In this group of patients, in whom life expectancy is short, this is very important.

The Eisai model has been updated to include the changes highlighted above and is included separately as part of this response. The combined additional changes presented above result in a revised company base case ICER of **£**50,808. Further detail is provided in Appendix 1. This does not take into account the updated mean dose intensity for Subgroup 1.

Taking the above information into account, eribulin should be considered good value for money for adoption by the NHS.

Figure 1
Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- 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 confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.

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

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- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Appendix 1: Additional evidence submitted in response to ACD [ID1072]

1. Additional analyses evaluating the potential impact of poststudy anticancer therapies on overall survival

An additional analysis was conducted on the subgroup 1 population and was generated by censoring subjects if they had crossed over to either eribulin or capecitabine after progression, and thus assesses whether the OS improvement observed in eribulin patients is mainly due to the effect of capecitabine as a post progression treatment. The results which are provided in Table 1 overleaf were consistent with that seen in the ITT population: median OS 17.5 months vs 13.5 months; HR = 0.644; p = 0.0032

2. Amended subsequent treatment costs to reflect life expectancy of patients in this setting

We have included a conservative scenario in the model where the total treatment duration for eribulin and subsequent treatments is 21.33 months.

This is based on the average duration of estimated survival for eribulin in the model.

The costs are applied to 60% of of the patients who enter the post progression stage. This changes the ICER for eribulin to £62,923

3. Amended dose intensity to more accurately reflect the relevant subgroup

Please see below the updated mean dose intensity information for Subgroup 1, which should be considered in the cost calculations. Dose intensity is applicable for both scenarios assuming wastage and no wastage. We agree that some wastage is reasonable. However we have been unable to update the changes to the ICER as the ERG model currently does not incorporate dose intensity to the scenario assuming some wastage.

Eisai Protocol: E7389-G000-301 Page 2 of 3

T_NICE_REQ_A5
Exposure
Safety Population (Subgroup 1)

	E7389 (N=184) n	(%)	Capecitabine (N=205) n	(%)
Duration of treatment (days)[1]				
n	184		205	
Mean	182.1		167.9	
SD	191.23		173.99	
Median	126.0		119.0	
Min	21		21	
Max	1183		994	
Actual Dose Intensity (mg/m^2/week) [2]				
n	184		205	
Mean	0.81		10134.09	
SD	0.134		1659.851	
Median	0.88		10661.88	
Min	0.4		5047.9	
Max	1.0		12160.7	

4. Revised company base case

	ICER Eribulin vs Comparator
ERG corrected model with updated post progression utility value	**£69,843**
ERG corrected model with updated post progression utility value and company assumption for PFS	£66,630
ERG corrected model with updated post progression utility value and updated subsequent treatment assumption	£62,923
ERG corrected model with updated post progression utility value and comparator scenario	£60,479
ERG corrected model with all changes (new Eisai base case)	**£50,808**

ERG requested table (per request dated 09/01/2018)

	ICER Eribulin vs Comparator
ERG corrected model	**£82,743**
ERG corrected model with updated post progression utility value	£69,843
ERG corrected model with company assumption for PFS	£76,838
ERG corrected model with updated subsequent treatment assumption	£74,545
ERG corrected model with updated comparator scenario	£71,649
ERG corrected model with all changes (new Eisai base case)	**£50,808**

5. Company's revisions to ERG corrected model

ERG corrected model with updated post progression utility value
In line with the committee's decision that the post-progression utility value is likely to be between the company's and the ERG's estimates, Eisai have revised the model with a post progression utility value of 0.590 to reflect this decision. This changes the ICER to £69,843.

Details of this revision in the model are provided in the Table overleaf.

ERG corrected model with updated post progression utility value and company assumption for PFS

As stated in the stakeholder comments form template, Eisai do not agree with modelling no progression-free survival benefit and have submitted a scenario with the updated post progression utility value and the company assumption for PFS.

This changes the ICER from £69,843 to £66,630.

Details of this revision in the model are provided in the Table overleaf.

ERG corrected model with updated post progression utility value and updated subsequent treatment assumption.

As stated above, Eisai have included a conservative scenario in the model with the updated post progression utility value, where the total treatment duration for eribulin and subsequent treatments is 21.33 months.

This is based on the average duration of estimated survival for eribulin in the model.

The costs are applied to 60% of the patients who enter the post progression stage. This changes the ICER for eribulin from £69,843 to £62,923.

Details of this revision in the model are provided in the Table below.

ERG corrected model with updated post progression utility value and comparator scenario.

As stated in the stakeholder comments form template, in line with recent clinician feedback, Eisai have submitted a scenario with the updated post progression utility value where 50% of patients receive capecitabine and 50% IV vinorelbine. This changes the ICER for eribulin from £69,843 to £60,479.

Additional information as per ERG request of 9th January 2018

In the original company submission, a sensitivity analysis was included of a mix of 50% capecitabine and 50% vinorelbine (including both oral and IV formulation) as comparators. This scenario was validated at the time 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 clinicians were asked if vinorelbine is an appropriate comparator in second-line patients with HER2-negative disease, if the assumption that vinorelbine has equal efficacy to capecitabine is appropriate and which formulation of vinorelbine is used in clinical practice. The sensitivity analysis was then included based on the feedback received from these four clinicians.

Following the first committee meeting in November last year, Eisai sought further guidance from the clinical expert in attendance at the meeting, Dr Marina Parton, regarding current clinical practice and the relevant comparators for this group of patients. Following feedback from Dr Parton that quite a significant proportion of patients would receive vinorelbine in this setting, Eisai have revised the base case to include a 50/50 mix of capecitabine and vinorelbine to more accurately reflect current UK clinical practice. The scenario has been updated to reflect a conservative assumption of only using the IV formulation. This is in line with further feedback from

Dr Parton that for patients with breast cancer, current clinical practice would be to mainly use the IV formulation of vinorelbine, although there may be a mix of oral and IV use.

It is important to note that this comparator scenario reflects the scope and the current NICE clinical guidelines in advanced breast cancer.

Details of this revision in the model are provided in the Table below.

The revised Eisai base case ICER which incorporates all of the above changes is £50,808

Company revisions to ERG model	Implementation instructions
ERG corrected model with updated post progression utility value	In Sheet 'Results' **Change** value in S48 to 0 In Sheet 'Utility' **Replace** value in cell F29 by 0.590 **Replace** value in cell H29 by 0.590
ERG corrected model with updated post progression utility value and company assumption for PFS	In Sheet 'Results' **Change** value in S48 to 0 In Sheet 'Utility' **Replace** value in cell F29 by 0.590 **Replace** value in cell H29 by 0.590 In Sheet 'Results' **Change** value in S41 to 0
ERG corrected model with updated post progression utility value and updated subsequent treatment assumption.	In Sheet 'Results' **Change** value in S48 to 0 In Sheet 'Utility' **Replace** value in cell F29 by 0.590 **Replace** value in cell H29 by 0.590 In Sheet 'Results' **Change** value in S49 to 0 In Sheet 'Model parameters' **Replace** formula in cell RS17 by 21

Company revisions to ERG model	Implementation instructions
ERG corrected model with updated post progression utility value and comparator scenario.	In Sheet 'Results' **Change** value in S48 to 0 In Sheet 'Utility' **Replace** value in cell F29 by 0.590 **Replace** value in cell H29 by 0.590 In Sheet 'Model parameters' **Change** Comparators group - Subgroup 1 to "Capecitabine 50% and Vinorelbine 50%" In Sheet 'Model parameters' **Change** Vinorelbine formulation mix – IV proportion to "1" (100%)

Table 1
Sensitivity Analysis of OS censoring at capecitabine and eribulin as post treatment therapy
HER2 negative and 2nd Line patients

		E7389 (N=186)	Capecitabine (N=206)
Number of subjects	Died, n(%)	63 (33.9%)	179 (86.9%)
	Censored before Database cut-off, n(%)	112 (60.2%)	5 (2.4%)
	Censored at Database cut-off, n(%)	11 (5.9%)	22 (10.7%)
Overall Survival (days)	Median (95% CI)	532.0 (463.0, 599.0)	411.0 (331.0, 454.0)
	1st Quartile (95% CI)	283.0 (210.0, 411.0)	205.0 (174.0, 256.0)
	3rd Quartile (95% CI)	NE (727.0, NE)	708.0 (635.0, 882.0)
Overall Survival (months)	Median (95% CI)	17.5 (15.2, 19.7)	13.5 (10.9, 14.9)
	1st Quartile (95% CI)	9.3 (6.9, 13.5)	6.7 (5.7, 8.4)
	3rd Quartile (95% CI)	NE (23.9, NE)	23.3 (20.9, 29.0)
Stratified log-rank test	p-value	0.0032	
Hazard ratio (95% CI)	E7389 vs. Capecitabine	0.644 (0.480, 0.865)	
Overall Survival Rate	1-year (95% CI)	0.720 (0.639, 0.802)	0.525 (0.457, 0.594)
	p-value	0.0008	
	2-year (95% CI)	0.352 (0.238, 0.466)	0.235 (0.176, 0.293)
	p-value	0.0529	
	3-year (95% CI)	0.257 (0.141, 0.372)	0.115 (0.066, 0.164)
	p-value	0.0111	

Stratified by Geographic region

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

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Breast Cancer Now
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Melanie Sturtevant

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

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Breast Cancer Now is disappointed by the Committee's recommendation that eribulin should not be recommended for treating locally advanced or metastatic breast cancer in those that have had only one chemotherapy regimen.
2	Metastatic breast cancer is a terminal diagnosis and any additional time, especially with a good quality of life, is extremely valuable to breast cancer patients and their families. We note that the clinical trial evidence showed a statistically significant overall survival benefit of an additional 4.6 months compared to capecitabine in those with HER2 negative disease - although given the lack of any statistically significant progression free survival, the Committee was unclear whether this was attributable to eribulin or subsequent treatments. Eribulin has a different side effect profile to other treatment options, is generally well tolerated, and is therefore an important alternative for those that cannot tolerate those other treatments.
3	Eribulin is likely to be of particular value to women with 'triple negative' breast cancer: those with HER2 positive breast cancer are most likely to be treated with targeted treatments such as Perjeta and Kadcyla; and those with hormone positive breast cancer are most likely to be treated with hormone therapies as the first few lines of treatment for disease before chemotherapy, although some may have chemotherapy as a first line treatment if their disease is life threatening or requires early relief of symptoms.
4	Around 15% of all breast cancers are 'triple negative' which tend to be more aggressive, and research has shown eribulin to have particular benefits for this group. There are no targeted treatments available for 'triple negative' breast cancer which means that, without eribulin these women may have to have additional chemotherapy for which the benefits may be marginal, but the side effects significant.
5	
6	

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

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Response to ACD Comments

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

ERG response to ACD comments and evidence submitted by Eisai

This response is part of a project commissioned by the NIHR HTA Programme as project number 15/148/12

11 January 2018

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Evidence Review Group response to ACD comments and evidence submitted by Eisai

1 EISAI DOES NOT AGREE THAT THE RELEVANT SUBGROUP EVIDENCE MAY NOT BE SUFFICIENTLY ROBUST FOR DECISION-MAKING

The ERG concurs with the company that:

- Study 301 was designed to further evaluate the effect of eribulin on prespecified subgroups including HER2-negative status and therefore patients were pre-stratified according to HER2 status.

- As highlighted in the ERG report, the results for all patients with HER2-negative status who were enrolled into the trial are consistent with those of Subgroup 1 i.e. a statistically significant gain in OS for eribulin compared to capecitabine is observed (median 15.9 months versus 13.5 months; HR [Hazard ratio]=0.84, 95% CI [confidence interval]: 0.71 to 0.98).

In the ERG report (p44), the ERG also noted:

- 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)

Summary

The ERG concluded (p46):

- Overall, therefore, the findings … 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.

2 EISAI DOES NOT AGREE THAT THE OVERALL SURVIVAL (OS) BENEFIT IN THE TRIAL MAY NOT BE DIRECTLY ATTRIBUTABLE TO ERIBULIN ALONE

In its original report, the ERG noted (p39) that with the exception of additional capecitabine, the types of treatment and the proportion of patients receiving these subsequent treatments were similar in both arms. Capecitabine was an additional treatment option for patients in both arms but perhaps unexpectedly, more patients randomised to receive eribulin received subsequent capecitabine than did patients randomised to receive capecitabine. The receipt of subsequent eribulin was rare in either arm. The data are reproduced here in Table 1.

Table 1 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), also reproduced in original ERG report (Table 12)

As stated in the ERG report (p40), Eisai 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 (pp115-116). In its comments on the ACD, the company has made publicly available some of this evidence from the CSR, namely the results from the following analyses:

1. Patients who did not receive further cytotoxic therapy after discontinuation of study treatment in both arms of the trial.

2. Patients originally randomised to eribulin and who immediately received capecitabine after discontinuation of study treatment.

3. Patients originally randomised to eribulin and who immediately received cytotoxic therapy other than capecitabine after discontinuation of study treatment.

4. Patients originally randomised to capecitabine and who received any subsequent cytotoxic therapy.

5. Censoring subjects if they had crossed over to either eribulin or capecitabine after disease progression.

It should be noted that analyses #1 to #4 are available only for the whole trial ITT population i.e., a population which includes patients with HER2-positive disease (15% of the ITT population) and unknown HER2 status (16%) and who received treatment first-line (20%), second-line (as per the NICE scope, 52%) or third-line (28%). Analysis #5 has been conducted for both the ITT (100%) and Subgroup 1 populations (36%).

Regarding analysis #1, fewer patients did not receive subsequent treatment on disease progression in the eribulin arm (n=164 [30%] than in the capecitabine arm (n=208 [38%]. The ERG notes that for analysis #2, the number of patients originally randomised to eribulin and who immediately received capecitabine after discontinuation of study treatment is 221 (40%) whereas as is evident from Table 1, 275 (50%) were previously cited by the company to receive subsequent capecitabine. For analysis #3, the number of patients originally randomised to eribulin and who immediately received cytotoxic therapy other than capecitabine after discontinuation of study treatment is 169 (31%, i.e. 390 minus 221). For analysis #4, patients originally randomised to capecitabine and who received any subsequent cytotoxic therapy (n=340 [62%]), includes patients who received capecitabine again (16% according to Table 1). While patients who crossed over are censored in analysis #5, those who received any other subsequent treatment are not censored.

The results from the analyses were provided by the company in the text and Figures 1 and 2 of the company's ACD comments and in the text and Table 1 of the company's appendix. These have been tabulated by the ERG in Table 2 and Table 3 of this document.

Table 2 Overall survival results from Study 301 for the whole trial population

Analysis	Eribulin			Capecitabine			Comparison
	N	Events	Median (95% CI)	N	Events	Median (95% CI)	HR (95% CI)
ITT population	554	446	15.9 (15.2 to 17.6)	548	459	14.5 (13.1 to 16.0)	0.88 (0.77 to 1.00)
Subsequent treatment:							
#1 Nothing	164	131	7.4 (6.2 to 9.1)	208	179	7.1 (6.0 to 8.8)	NR
#2 Capecitabine	221	185	18.3 (15.8 to 20.8)	NA	NA	NA	NA
#3 Cytotoxic therapy other than capecitabine	169	130	19.9 (17.6 to 24.0)	NA	NA	NA	NA
#4 Anything	NA	NA	NA	340	280	18.3 (16.4 to 21.2)	NA
#5 Censoring subjects if they crossed over	554	220	17.6 (15.9 to 19.7)	548	457	14.5 (13.1 to 16.0)	0.73 (0.62 to 0.86)

CI=confidence interval; ITT=intention-to-treat; NA=not available (analysis not conducted)

Table 3 Overall survival results from Study 301 for the Subgroup 1 population

Analysis	Eribulin			Capecitabine			Comparison
	N	Events	Median (95% CI)	N	Events	Median (95% CI)	HR (95% CI)
Subgroup 1 population (ITT analysis)	186	148	16.1 (15.2 to 18.6)	206	180	13.5 (10.9 to 14.9)	0.77 (0.62 to 0.97)
Censoring subjects if they crossed over	186	63	17.5 (15.2 to 19.7)	206	179	13.5 (10.9 to 14.9)	0.64 (0.48 to 0.87)

CI=confidence interval; ITT=intention-to-treat

The results show:

- As noted by the company, patients who did not receive any further chemotherapy died earlier in both treatment groups ("as would be expected"). Median OS in the eribulin arm was 7.4 months and in the capecitabine arm was 7.1 months (compared to 15.9 months and 14.5 months for all patients in the respective arms of the ITT population).

- The median OS in the eribulin arm who received subsequent capecitabine (18.3 months) was the same as the median OS for patients who initially received capecitabine and received any subsequent therapy (18.3 months).

- Median OS for eribulin patients subsequently treated with cytotoxic therapy other than capecitabine (19.9 months) was higher than for patients subsequently treated with capecitabine (18.3 months).

- Regardless of whether patients were subsequently treated with capecitabine or other cytotoxic therapy, median OS for patients in the eribulin (18.3 months and 19.9 months, respectively) and capecitabine arms (18.3 months) was higher than for the respective arms of the ITT population as a whole (15.9 and 14.5 months, respectively). This is not unexpected given the ITT analysis included patients who were not subsequently treated.

- Censoring subjects if they had crossed over to either eribulin or capecitabine after disease progression resulted in improved results for eribulin versus capecitabine compared to the uncensored analysis for the whole trial (17.6 months versus 14.5 months, hazard ratio [HR]=0.73 as opposed to 15.9 months versus 14.5 months, HR=0.88) and Subgroup 1 populations (17.5 months versus 13.5 months, HR=0.64 as opposed to 16.1 months versus 13.5 months, HR=0.77).

Summary

The ERG considers it is difficult to draw any firm conclusions as to 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.

- With regard to the receipt of capecitabine following eribulin, median OS appears to be similar to median OS for capecitabine followed by anything else. Compared to patients receiving no treatment, and compared to the ITT population as a whole, patients who received subsequent treatment after either eribulin or capecitabine appear to have improved OS. However, the data

only show receiving additional treatment is associated with improved OS, not that it is the cause of improved OS. For example, a patient's physical condition at the time of disease progression is likely to also be a factor as to whether a patient receives subsequent treatment and this may be the key factor resulting in improved OS.

- Censoring subjects if they crossed over shows OS is statistically significantly improved for patients who received eribulin compared to patients who received capecitabine. However, a large proportion of patients treated with eribulin crossed over to receive capecitabine (≥50%) but very few patients actually crossed over from capecitabine to eribulin (<1%). Furthermore, patients in both arms did also receive other subsequent treatment.

3 EISAI DO NOT AGREE THAT THE SUMMARY OF THE COST EFFECTIVENESS EVIDENCE IS A REASONABLE INTERPRETATION OF THE EVIDENCE

Eisai provided a modified version of the decision model which had been amended by the ERG prior to the first meeting of the Appraisal Committee. Reconciling the two model versions has proved to be very demanding. The different changes by Eisai at this stage are summarised below:

1. The patient utility value assigned to the post-progression health state has been amended to 0.59 (midway between the Eisai preferred value and the ERG value).

2. The ERG PFS estimates have not been accepted by Eisai.

3. The maximum duration of patient treatment (both primary and subsequent) has been modified to 21 cycles (previously 8 cycles preferred by Eisai and unlimited by ERG).

4. The comparator treatment has been changed from 100% capecitabine to 50% capecitabine and 50% vinorelbine.

5. The mode of delivery of vinorelbine treatment has been set to 100% intravenous.

Change 1 is a reasonable interpretation of the uncertainty expressed by Appraisal Committee members with respect to the post-progression utility.

Eisai and the ERG continue to differ concerning the interpretation and modelling of the trial PFS data. (Change 2). It is suggested by Eisai that the survival curves for the two trial arms separate in the early months before converging in the long term, and if this temporary difference is masked by pooling the two treatment arms then the cost-effectiveness of eribulin is misrepresented.

Figure 1 illustrates the development of cumulative time spent in PFS during the first 24 months of the clinical trial. A small difference appears after 3 months but disappears after 17 months. The separation never exceeds 3 days at any time.

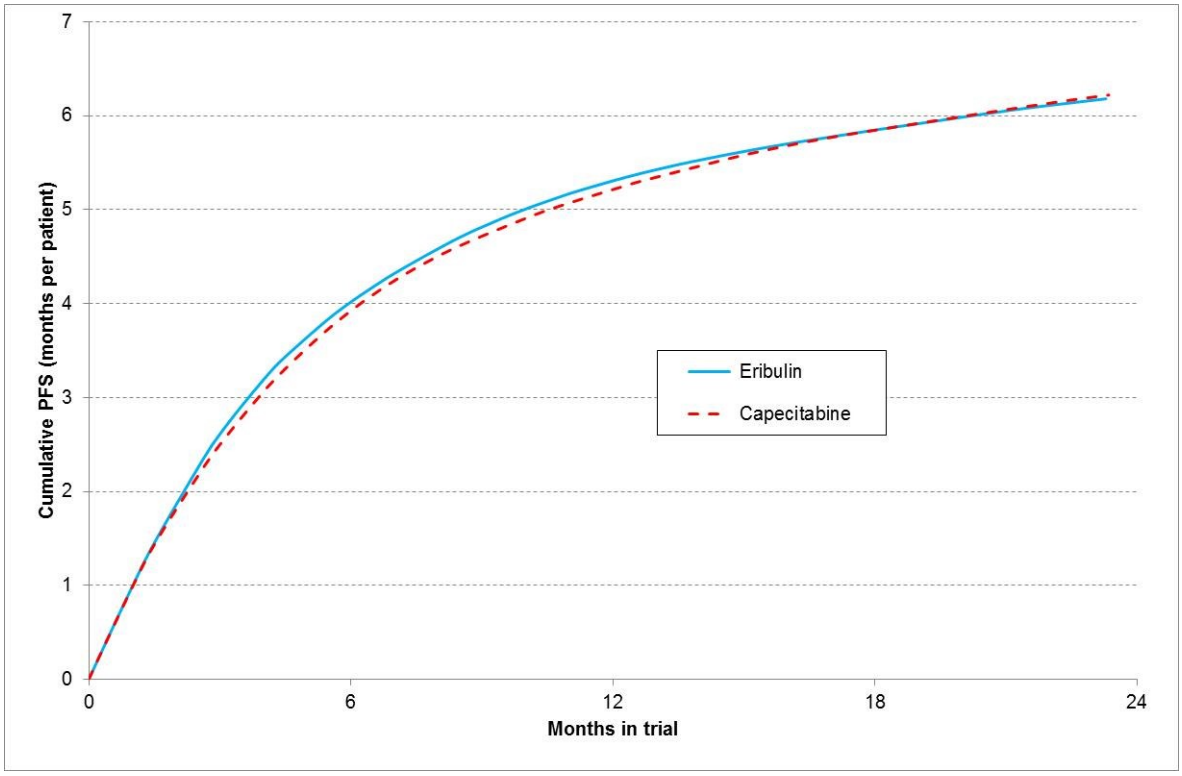

Figure 1 Comparison of cumulative PFS in the two arms of the clinical trial using the Area Under Curve (AUC) method

The ERG continue to consider that imposing a cap on the duration of the primary treatments, or an overall cap on the combined duration of primary and subsequent lines of treatment is not justified (Change 3). In particular, reliance on an average (mean) statistic from a survey as the basis for determining the end of all treatments is illogical. An average figure indicates that there must have been a substantial number of survey patients receiving treatment for *more* than 21 cycles, directly contradicting the crude cessation of all subsequent treatment costs at 21 months.

Changing the comparator treatment to a mix of capecitabine and vinorelbine (Change 4) introduces a serious violation of the primary trial data on which the Eisai submission is based. The trial outcomes for the comparator arm are derived solely from treatment with capecitabine. The assumption that the two treatments have equal efficacy on all patients, and the same adverse event profiles lacks any factual foundation, but does alter the balance of treatment-related costs in favour of eribulin.

In addition, altering the mode of administration of vinorelbine from 50% intravenous and 50% oral to 100% intravenous (Change 5) again assumes that there are no positive or negative effects of this change on patients. This alteration also alters the costs of treatment in favour of eribulin.

A further issue raised by Eisai (though not incorporated in the model) is a claim that an updated estimate of eribulin dose intensity is available and should be considered as indicating a lower cost of treatment.

However, comparison with the absolute dose intensity reported in the Clinical Study Report (Table 30) shows the same figures as those now cited by Eisai. The model parameter for relative dose intensity in the decision model (0.87) is also the same as in Table 30, so there are no 'new data' on which to amend the model.

Summary

Having considered carefully all the above issues raised by Eisai, the 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 results in a reduction in the estimated ICER of £11,431 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. This reduces the estimated ICER by only £52 per QALY gained.

Thus, the ERG best estimated ICER is £73,317 per QALY gained. If both these sensitivity analyses changes are applied together the ICER falls to £61,861 per QALY gained.

ERG Response to ACD Comments (erratum)

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Erratum to ERG response to ACD comments and evidence submitted by Eisai

Confidential until published

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

Erratum completed 19 January 2018

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Following the second appraisal committee meeting the Evidence Review Group (ERG) has added two sentences to add clarity to its response that the overall survival (OS) benefit in the trial may not be directly attributable to eribulin alone.

The ERG has also modified its response in relation to whether the summary of the cost effectiveness evidence is a reasonable interpretation of the evidence. This is because the ERG identified transcription errors made as a result of copying and pasting information from the model into its response document (including the figure originally inserted).

The pages of the ERG's response that are affected by these modifications are presented here.

2. Patients originally randomised to eribulin and who immediately received capecitabine after discontinuation of study treatment.

3. Patients originally randomised to eribulin and who immediately received cytotoxic therapy other than capecitabine after discontinuation of study treatment.

4. Patients originally randomised to capecitabine and who received any subsequent cytotoxic therapy.

5. Censoring subjects if they had crossed over to either eribulin or capecitabine after disease progression.

It should be noted that analyses #1 to #4 are available only for the whole trial ITT population i.e., a population which includes patients with HER2-positive disease (15% of the ITT population) and unknown HER2 status (16%) and who received treatment first-line (20%), second-line (as per the NICE scope, 52%) or third-line (28%). Analysis #5 has been conducted for both the ITT (100%) and Subgroup 1 populations (36%).

Regarding analysis #1, fewer patients did not receive subsequent treatment on disease progression in the eribulin arm (n=164 [30%] than in the capecitabine arm (n=208 [38%]. The ERG notes that for analysis #2, the number of patients originally randomised to eribulin and who immediately received capecitabine after discontinuation of study treatment is 221 (40%) whereas as is evident from Table 1, 275 (50%) were previously cited by the company to receive subsequent capecitabine. This is because as *first anticancer therapy* after discontinuation of eribulin, 221 patients received capecitabine. For analysis #3, the number of patients originally randomised to eribulin and who immediately received cytotoxic therapy other than capecitabine after discontinuation of study treatment is 169 (31%, i.e. 390 minus 221). For analysis #4, patients originally randomised to capecitabine and who received any subsequent cytotoxic therapy (n=340 [62%]), includes patients who received capecitabine again. It is noted by the company that as first anticancer therapy after discontinuation of capecitabine, 55 [10%] of patients received further capecitabine. While patients who crossed over are censored in analysis #5, those who received any other subsequent treatment are not censored.

The results from the analyses were provided by the company in the text and Figures 1 and 2 of the company's ACD comments and in the text and Table 1 of the company's appendix. These have been tabulated by the ERG in Table 2 and Table 3 of this document.

3 EISAI DO NOT AGREE THAT THE SUMMARY OF THE COST EFFECTIVENESS EVIDENCE IS A REASONABLE INTERPRETATION OF THE EVIDENCE

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5. The mode of delivery of vinorelbine treatment has been set to 100% intravenous.

Change 1 is a reasonable interpretation of the uncertainty expressed by Appraisal Committee members with respect to the post-progression utility.

Eisai and the ERG continue to differ concerning the interpretation and modelling of the trial PFS data. (Change 2). It is suggested by Eisai that the survival curves for the two trial arms separate in the early months before converging in the long term, and if this temporary difference is masked by pooling the two treatment arms then the cost-effectiveness of eribulin is misrepresented.

The ERG continue to consider that imposing a cap on the duration of the primary treatments, or an overall cap on the combined duration of primary and subsequent lines of treatment is not justified (Change 3). In particular, reliance on an average (mean) statistic from a survey as the basis for determining the end of all treatments is illogical. An average figure indicates that there must have been a substantial number of survey patients receiving treatment for *more* than 21 cycles, directly contradicting the crude cessation of all subsequent treatment costs at 21 months.

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based. The trial outcomes for the comparator arm are derived solely from treatment with capecitabine. The assumption that the two treatments have equal efficacy on all patients, and the same adverse event profiles lacks any factual foundation, but does alter the balance of treatment-related costs in favour of eribulin.

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A further issue raised by Eisai (though not incorporated in the model) is a claim that an updated estimate of eribulin dose intensity is available and should be considered as indicating a lower cost of treatment. However, comparison with the absolute dose intensity reported in the Clinical Study Report (Table 30) shows the same figures as those now cited by Eisai. The model parameter for relative dose intensity in the decision model (0.87) is also the same as in Table 30, so there are no 'new data' on which to amend the model.

Summary

Having considered carefully all the above issues raised by Eisai, the 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 results in a reduction in 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. This 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.