NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Eribulin for the treatment of locally advanced or metastatic breast cancer

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. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Eisai
   - Breakthrough Breast Cancer
   - Joint response from NCRI/Royal College of Physicians/RCR/ACP/JCCO
   - NHS Camden
   - Commissioning Support Appraisals Service

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Additional evidence submitted by Eisai**
   - Supporting document explaining rationale for base case

5. **ERG critique of new evidence** prepared by Liverpool reviews and Implementation Group (LRiG)

6. **Vinorelbine prices**
   - National acquisition costs of vinorelbine
   - ERG results with CMU prices for vinorelbine

No comments were received on the ACD from the clinical specialists or patient experts.

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

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Eribulin for the treatment of locally advanced or metastatic breast cancer

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

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

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 may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Eisai	**Adverse Events** Eisai does not believe that the Committee's assessment of the toxicity profile of eribulin is either a reasonable interpretation of the available evidence or appropriately represents the overall safety profile of the medicinal product. At paragraph 4.3 the Committee states that it "concluded that eribulin was associated with a greater overall survival benefit compared with TPC but with a less favourable toxicity profile". The basis for this conclusion appears to be that "it heard from the clinical specialist that the trial data indicated that eribulin is less well tolerated than capecitabine and vinorelbine, and in particular is associated with peripheral neuropathy and alopecia (hair loss)". As stated in our submission, the pivotal Phase III RCT (EMBRACE) has demonstrated that eribulin is associated with a predictable and well-characterised safety profile and is generally well-tolerated, for a chemotherapeutic agent being used in heavily pre-treated metastatic breast cancer (MBC) (1-3). This is the first and only study to achieve Marketing Authorisation in this setting therefore NICE have not seen a phase III RCT in such a severe breast cancer patient population before. When assessing the overall safety profile in EMBRACE, eribulin is associated with less fatal AEs and fewer discontinuations and dose interruptions due to AEs than TPC in the EMBRACE study: • Deaths due to serious AEs were lower in the eribulin arm than the TPC arm (4.0% vs. 7.7%, respectively). • Discontinuations due to AEs were lower in the eribulin group than in the TPC group (13.3% vs. 15.4%, respectively). • Dose interruptions were lower in the eribulin group than the TPC group (5.0% vs. 10.1%, respectively). Importantly the duration of therapy in EMBRACE was longer in the eribulin arm (median: 118 days) than the TPC arm (median: 64 days for chemotherapy agents and 30 days for hormonal agents), again reflecting the acceptability of the safety profile and tolerability of this agent for the treatment of heavily pre-treated MBC. In addition as patients continue to benefit from eribulin for a longer duration than other currently	Section 3.7 of the FAD details adverse events data from the trial accurately. The Committee has taken all evidence into account, along with the views expressed by the clinical specialist and written submissions of the consultees and risks and benefits as seen from the patients's perspective. Section 4.3 also notes that the clinical specialist and patient expert stated that it is unusual for a technology to show an overall survival benefit in advanced breast cancer at this stage of the clinical pathway, and also of the importance of having a further treatment option for patients whose previous chemotherapy has failed. The Committee considered that alopecia and peripheral neuropathy were significant toxicities which apply far less to capecitabine or vinorelbine and do not resolve quickly. It is noted that, in response to consultation, patient groups have supported the view that eribulin is less well tolerated than capecitabine and vinorelbine, and can lead to side effects including peripheral neuropathy and alopecia. Patient groups agreed that these side effects have the potential to impact a patient's quality of life since the patient may have already

Consultee	Comment	Response
	available therapies, as defined by TPC, it is unsurprising that patients on eribulin would experience a higher frequency of AEs than patients who stayed on TPC for half the duration. This is a function of unit time exposure for a chemotherapeutic agent. Despite these favourable results, the extended duration of therapy in patients receiving eribulin as compared with TPC resulted in a longer period for adverse events to be experienced/ reported and it is therefore likely that eribulin is even better tolerated, relative to TPC, than is suggested by these data. Again, it is important to reiterate that NICE consider the specific and unique profile of these patients for whom all other registered options have been exhausted and no evidence-based option proven to extend overall survival is available. To be able to positively impact overall survival for these patients without introducing new or severe toxicities that are not commonly addressed is an important consideration. Limited inference can be drawn from direct comparison of safety between patients treated with eribulin and those treated with TPC, as the TPC group comprises patients treated with a wide range of therapies and dosing regimens. Further, as each of the therapies in the TPC group has a distinct safety profile, and the number of patients receiving each TPC was relatively small, conclusions cannot be drawn from the comparison of incidences of specific AEs between each TPC and eribulin. Thus the view of the clinical specialist suggesting that eribulin is less well tolerated than either capecitabine or vinorelbine is not evidence-based. From clinicians who have used eribulin in their practice in the UK, we have heard quite different feedback and we would urge NICE to review such comments where available. Therefore, as direct safety comparisons using data from EMBRACE are likely to be unreliable and to underestimate adverse events associated with TPC therapies, it is important to take into account the safety data quoted in the each TPC agent's Summary of Product Characteristics (SPC), as below, when developing hypotheses as to the incidence of adverse events associated with the individual products: • Neutropenia (All grades) occurred in 49% of patients on vinorelbine in the EMBRACE trial, whereas the incidence is 71.5% in the vinorelbine SPC (4). • Peripheral neuropathy (Grades 3 & 4) occurred in less than 10% of patients in the EMBRACE trial for both eribulin and vinorelbine. This is consistent with the incidence reported in the vinorelbine SPC (4). (Please note as described in our submission that patients with pre-existing neuropathies of grade 2 or below were allowed entry to the EMBRACE study. This is in direct	experienced them earlier in the treatment pathway and not wish to experience them again. In addition, sections 4.8 and 4.10 of the FAD outlines the Committee's concern that the manufacturer's base-case model included only grade 3 and 4 adverse events that occurred in at least 10% of patients and therefore underestimated the costs and disutilities of adverse events associated with eribulin.

Consultee	Comment	Response
	reflection of the reality facing patients at this late stage of disease. Critically, eribulin was not associated with an exacerbation of this toxicity in those patients who had already been compromised by neuropathies). • The incidence of hand-foot syndrome commonly seen with certain chemotherapies, e.g. capecitabine [53%-60%] across monotherapy trials (5), occurred in only 1.4% of patients at any severity grade with eribulin. • 91% of the intended dose intensity for eribulin was achieved demonstrating the well tolerated profile of the drug. Finally the Appraisal Committee does not appear to have taken into account the submissions from patient groups in relation to the significance of the adverse event profile for eribulin. Breast Cancer Care, Breakthrough Breast Cancer and Breast Cancer Campaign described the side-effects associated with eribulin as "acceptable for a standard regime" and "likely to be manageable for patients in this setting". Side effects and their severity are clearly vital considerations. However, these must be balanced against the potential benefit to be derived from treatment. This is the realistic decision facing patients facing a new treatment option. For a patient who has exhausted all other available options and is desperate to extend her life, the opportunity to decide on the balance of known side-effects against the opportunity for extended life should be available. The current negative ACD would result in the patient in consultation with their oncologist not even having the option to make this decision. It is relevant to highlight that in their role as the authority of determining the safety and efficacy of medicines, the CHMP have stated in the European Public Assessment Report that 'Halaven's (eribulin) benefits are greater than its risks and recommend that it be given a marketing authorisation'. NICE are clearly within their right to evaluate the clinical and cost-effectiveness however drawing a different conclusion from the CHMP on the benefit/risk profile for clinical effectiveness is highly questionable. **The ACD has not adequately considered the overall safety profile of eribulin in circumstances where, despite the fact that EMBRACE was likely to underestimate adverse events in the TPC arm, the incidence of serious adverse events and adverse events leading to treatment delays or modifications and fatal adverse events were almost**	

Consultee	Comment	Response
	identical in both groups. The side effects are manageable for such a heavily pre-treated MBC population and have minimal impact on the ICER.	
	<u>Reliance on the analysis of data from Region 1 of EMBRACE</u>	Comments noted. References to the EU marketing authorisation in this

Consultee	Comment	Response
	Eisai does not agree that the results from the overall ITT population are more applicable to the UK than the Region 1 population. There is extensive research proving that regional differences play an important role in impacting patient outcomes. Differences occur for various reasons including availability of treatments, national screening policies, social and economic conditions. When conducting a global study, treatment differences can exist particularly when using TPC and for this reason the geographical regions were included as a pre- planned stratification factor in EMBRACE. Region 1 (the EU, North America and Australia) was identified as being most likely to reflect the UK population and an analysis of the data from these participants specified in the trial protocol was used to inform a comparison of the relative benefits of eribulin against standard therapies in this region. NICE has regularly requested manufacturers to present data for the local population where available for understandable reasons. Eisai, in discussion with Global regulatory authorities, therefore ensured that such an analysis was pre-planned to avoid bias and demonstrate any differences in how therapy takes effects in different regions given this is not uncommon. The ERG has only looked at the mean survival between the three regions. Means are misleading when reporting survival data. In addition a non-significant p value does not mean that there is not a meaningful difference between the groups. This draft guidance failed to acknowledge how patients were managed within the regions and this is what determines outcomes. When considering the generalisability of the ITT population from EMBRACE versus the population from Region 1, the ERG states that the results from Region 1 should not be preferred to the ITT population as a result of (a) its conclusion that the patient characteristics in Region 1 do not differ from those in the remainder of the trial population; and (b) the fact that the EU marketing authorisation for eribulin was based on the results of the overall EMBRACE population (pages 36-37 ERG report). The Appraisal Committee's reasons for preferring the analysis based on the ITT population are: (a) the differences in survival between Region 1 and the overall ITT population are evident only for the comparator arm; (b) patients in Region 1 did not differ in terms of overall prognosis from the remainder of the trial population; (c) the advice of the clinical specialist "that UK practice in the management of advanced breast cancer differs considerably from some areas of Region 1"	regard and the clinical specialist's comment regarding the reimbursement incentive determining clinical decision making by oncologists in North America have been removed from the FAD (section 4.4). Further consideration on the use of region 1 data for the subgroup analyses submitted in response to consultation is presented in section 4.15.

Consultee	Comment	Response
	(e.g. in North America there is a greater reimbursement incentive for drugs that are administered intravenously, resulting in greater use of vinorelbine relative to capecitabine than in the UK); and (d) the EU marketing authorisation for eribulin was based on the results of the overall EMBRACE population. **Eisai believes these explanations are either invalid or do not provide a proper basis for reliance on the ITT population rather than the analysis based on patients from Region 1.** The reason for the pre-specified geographical stratification in EMBRACE was Eisai's concern that the particular therapies included in the TPC arm of the study would not be consistent across all regions, as was subsequently demonstrated by the trial data. Reasons (a) and (b) above are accordingly consistent with differences in overall survival between the Region 1 and the ITT populations being attributable to the particular TPC used in the different regions and the associated effect on outcomes. Furthermore, there were differences in baseline characteristics between patients in Region 1 and the other two regions, which do not appear to have been taken into account by the ERG in reaching its conclusions: • Region 2 and 3 contained higher proportion of patients with less than 3 prior chemotherapy regimens. This implies that patients in these regions had received less intensive treatment and any new anti-cancer therapy would result in improvement (as the patients' baseline condition represents a condition that had received minimal intervention). • In all geographic regions Her2 negative patients comprised the bulk of the patient population. However Her2 unknown patients comprised a larger percentage of the Eastern Europe (~20%) and Latin America (~20%) regions as compared with North America/Western Europe (~4%). [~75% of all Her2 unknown patients were from region 2 and 3]. Across all regions the most commonly prescribed TPC treatments were: vinorelbine, gemcitabine and capecitabine. However, hormonal medications were predominantly prescribed in Eastern Europe (71% of total hormonal anti-cancer use for the study) whereas in Region 1, it was 19%. Vinorelbine use in Region1 accounted for 74% of total anti-cancer use for the study and only 14% in Region 2. Capecitabine use was more balanced with Region 1 accounting for 44% and Region 2 for 45% of total use but gemcitabine was 53% in Region 1 and 30% in Region 2.	

Consultee	Comment	Response
	Thus one can see that the mix of therapies used as TPC in Region 2 is not therefore in keeping with UK practice. The current NICE guidelines on advanced breast cancer recommend vinorelbine or capecitabine in patients with advanced metastatic breast cancer that have been treated with previous lines of treatment and thus Region 1 best reflects the current management and therapies of those patients with advanced metastatic breast cancer in England and Wales. In addition, the results in Region 1 are most impressive as this is the region that had the greatest choice in treatment and consisted of patients who were more heavily pre-treated. Actually it is more difficult to demonstrate a benefit in such a late stage heavily pre-treated patient population. Reason (c) is based on advice of a single clinical specialist, with whom the company disagrees. Furthermore, if there are any additional examples of ways in which the Committee believed that UK management of advanced breast cancer differs from practice in parts of Region 1, we request details of these so that we may provide a considered response before the next meeting of the Appraisal Committee. The comment regarding the 'reimbursement incentive' determining clinical decision making by oncologists in North America seems especially unfair. A similar accusation could be made in the UK where hospital waiting lists and additional resource challenges may be cited as a reason to encourage use of oral therapies but hospital reimbursement is greater for in-patient stays. We believe this is an erroneous point that does little to inform the relevance of the region specific analyses which is based purely on clinical grounds. Finally, NICE's assessment differs from that carried out by the regulatory authority considering whether a marketing authorisation should be granted and reason (d) does not therefore justify reliance on the ITT population, rather than an analysis based on patients from Region 1. While the ITT population may be most appropriate for the regulatory assessment of safety and efficacy, the Region 1 population best meets the requirements for NICE's evaluation which focuses on the magnitude of clinical benefit in a patient population as close as possible to that in the UK. Region 1 best reflects the manner and type of treatments patient in the UK would be expected to receive for MBC. NICE have repeatedly stated that manufacturers should generate data relevant for the UK population. Therefore, Region 1 should be accepted as the most relevant population on which to base recommendations for eribulin in the UK.	

Consultee	Comment	Response
	Applicability of the End of Life advice It appears that the Appraisal Committee has accepted that eribulin meets 2 out of the 3 criteria for end of life, namely that patients eligible for treatment have a life expectancy less than 24 months and that eribulin is indicated for a small patient population. The conclusion that eribulin does not meet the third criterion, a survival benefit of at least three months, is based on an assessment of data from the ITT population from EMBRACE. However, as mentioned above Region 1 best represent clinical practice in the UK rather than Regions 2 or 3 and Eisai firmly believes that the Committee's recommendations should be based on that patient population the overall survival gain in Region 1 (> 3 months) implies that the third criterion for end of life is met. For completeness, the Committee will be aware that the End of Life advice issued by NICE did not impose an absolute requirement for a three month overall survival benefit, but simply stated that this would "normally" be the case. While Eisai believes that the data from Region 1, which demonstrates an overall survival benefit in excess of 3 months, should be relied upon, the Committee is also required to consider whether a lower benefit should qualify in this case. In this context, the Committee should consider the innovative nature of the treatment and the fact that, as recognised at paragraph 4.3 of the ACD, it is unusual for any technology to show an overall survival benefit at this stage of the treatment pathway. Once again, eribulin is the first and only single therapy to provide in a phase III RCT in such a heavily pre-treated population, evidence to extend overall survival versus current standards of care. A pragmatic approach needs to be taken here when assessing end of life and no specific allowance for this has been made. Eisai's view is that NICE has chosen specifically the lowest figure in order not to all the end of life criteria when the evidence is contrary to this. The overall survival benefit of eribulin vs: • Region 1 is 3.1 months (prospective, protocol specified analysis) • Capecitabine is 4.7 months • Vinorelbine is 4.2 months • Gemcitabine is 3.6 months	For the reasons outlined in section 4.4 of the FAD, the Committee was not persuaded that the region 1 population was more applicable to the UK and concluded that it would be most appropriate to base its recommendations on the results from the overall ITT population. The discussion around end of life followed from this conclusion, which has been explained clearly in the FAD. Please note that NICE has not specifically chosen the lowest figure in order not to meet all the end of life criteria. In addition, section 4.19 of the FAD states that given that the most optimistic ICER for the overall ITT group was £68,600 per QALY gained, the Committee concluded that eribulin could not be considered a cost-effective use of resources for NHS use even if all of the criteria for being a life-extending, end-of-life treatment were met.

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<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
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Post capecitabine group is 2.9 months
To provide further context to inform this consideration, the end of life criteria need to recognise the different stages of disease and the nature of the interventions being evaluated. Had Eisai conducted the EMBRACE study against placebo, which was a valid consideration given the lack of registered options, then clearly a magnitude of benefit far greater than 3 months would have been achieved. However, in choosing an active comparator Eisai has sought to satisfy regulators and NICE that eribulin is associated with incremental innovation in this setting and is adding real value to the treatment armamentarium. It is for the committee to consider practically whether evidence of a 3 month gain over an active therapy in an earlier stage of metastatic disease is the same as a 3 month gain in a far advanced setting. The point is further illustrated below where a combination strategy approved by NICE in CG81 in a far earlier stage of advanced disease is presented alongside the data from EMBRACE:
<table>
<tr><th>Disease Stage</th><th>Control</th><th>Investigation</th><th>OS Gain</th><th>p-value</th></tr>
<tr><td>1st and 2nd Line</td><td>Paclitaxel</td><td>Gemcitabine + Paclitaxel</td><td>18.6, vs. 15.8m (+2.8m)</td><td>0.0489</td></tr>
<tr><td>3rd line +</td><td>TPC</td><td>Eribulin</td><td>Region 1
13.1m vs. 10.1 (+3m)

ITT
13.2 vs. 10.5 (+2.5m)</td><td>0.009

0.014 (nominal)</td></tr>
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<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
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<u>Drug administration costs</u>

It appears there are two ways that chemotherapy delivery is coded according to HRG.
• Chemotherapy delivery outpatient (30% of activities)
• Chemotherapy delivery day case and regular day/night. (70% of activities)

The difference is illustrated below and the ACD has not accounted for this in a weighted average manner but assumes only one way of coding chemotherapy delivery which is not the case. In addition eribulin has started to be used as a home delivery service and thus these costs may not apply.

<table>
<tr><td></td><td>Chemo 1st</td><td>Chemo subsequent</td><td>Oral</td></tr>
<tr><td>Day case + regular day/ night</td><td>£207</td><td>£284</td><td>£152</td></tr>
<tr><td>Outpatient</td><td>£248</td><td>£212</td><td>£171</td></tr>
</table>

No account seems to have been taken about the efficiency savings that eribulin can offer:

• No reconstitution is required as eribulin is prepared in a ready-to-use formulation (thereby saving pharmacy preparation time).
• No routine pre-medication is required for hypersensitivity (less drug costs).
• Eribulin is given as a quick 2-5 minute infusion (less time in chemotherapy chair and nursing time).
</td><td>The Committee noted in section 4.16 of the FAD that the efficiency savings to the NHS suggested for eribulin also largely applied to vinorelbine.</td></tr>
<tr><td></td><td>
<u>Quality of life (QoL)</u>

Eisai does not feel that the summary of the effect of Eribulin on health-related quality of life is a reasonable interpretation of the evidence.

Overall survival is recognised as the most definitive cancer outcome and is of most importance to patients and clinicians when making decisions regarding treatment options. In a recent survey, patients with breast cancer rated overall survival as the most important attribute of an advanced breast cancer treatment. Specifically, an overall survival advantage of 3 months versus no advantage was most influential in the perceived value of chemotherapy. (6) This is
</td><td>The Committee noted that none of responders in the Phase II trials reported deterioration in quality of life.
In addition, the Committee did recognise the importance of prolonging survival in this group of patient and also recognised that eribulin did so.
However, the Committee was also concerned, with respect QOL in a population of patients with a short life-</td></tr>
</table>

Consultee	Comment	Response
	consistent with the submissions of the patient groups in this appraisal. As mentioned above, the duration of therapy in EMBRACE was longer in the eribulin arm than the TPC arm, reflecting the promising effect on patient's quality of life. In addition, it is worth noting that a 2009 systematic review of the clinical efficacy of cytotoxic agents in locally advanced or metastatic breast cancer patients pre-treated with an anthracycline and a taxane, found that both capecitabine and vinorelbine had very limited evidence of improvements in QoL. (7) Indeed this is also a conclusion made by NICE in CG81. When the TPC consists of numerous drugs that are given at different dosing regimens it is very difficult to assess difference in QoL between a range of options. In these circumstances we do not believe it would have been appropriate to have measured QoL in EMBRACE. However, the phase II trials showed an improvement in QoL in those patients that responded to eribulin. The Appraisal Committee was clearly concerned regarding the risk of alopecia associated with use of eribulin. While Eisai does not suggest that alopecia is an unimportant consequence of chemotherapy, it is important to take into account that patients eligible for eribulin have advanced metastatic breast cancer and have very few treatment options and no regulatory approved options; eribulin is the only technology with established regulatory benefits in this patient population. The most important consideration for patients at this stage of treatment for their advanced breast cancer is overall survival and, as stated by the patient organisations participating in this appraisal, patients may therefore tolerate the side-effects of treatment if they will gain other critically important clinical benefits. A study assessed psychosocial morbidity in patients with breast cancer and compared the differential rates between patients with early stage (n=303) and advanced disease (n=200). In this study, of the 31% of patients with early breast cancer who experienced hair loss, 77% found this to be distressing. In contrast, this percentage halved in patients with metastatic breast cancer i.e. of the 29.5% who experienced hair loss, 38.6% found it to be distressing (8). The patient organisations also confirmed in their submissions that the side-effects associated with eribulin were "manageable". By way of example, there are various methods that can be used to minimise drug induced alopecia e.g. cold cap.	expectancy as stated in section 4.3 of the FAD that no health-related quality of life data were collected during the EMBRACE trial and that data were presented from two phase II trials in which there was no comparator arm. The Committee considered quality of life to be an important outcome measure in advanced cancer and that this was an important omission from the phase III trial.
	Are the provisional recommendations sound and a suitable basis for guidance to the NHS?	The evaluation of eribulin against individual comparators was not ignored in the ERG report or in the ACD. The

Consultee	Comment	Response
	Overall Eisai does not believe that these provisional recommendations provide sound and suitable guidance to the NHS. The quantity and quality of the available evidence regarding the efficacy of particular chemotherapy regimens in patients with advanced metastatic breast cancer pre-treated with an anthracycline and a taxane is extremely limited. New effective therapies are sorely needed in this patient population. For the first time a single agent has shown an improvement in overall survival in this patient population. None of the currently available cytotoxic agents have shown this and as such the outcome of these patients is poor and there remains a high level of unmet clinical need. When eribulin is evaluated against specific comparators as specified in the NICE scope, the manufacturer has shown that eribulin is cost effective. However this analysis has been ignored by ERG and in the ACD and no demonstration of cost effectiveness against specific comparators agents has been performed. This is irrational as eribulin would be replacing a comparator when used in practice not a pool of treatments. **For overall survival, rather than a surrogate marker of efficacy, to be the primary endpoint in advanced metastatic breast cancer trials is rare. In an exhaustive literature review, only 5 of 76 major phase III clinical studies of systemic therapy in metastatic breast cancer defined overall survival as their primary endpoint, and none met this primary endpoint (9).** **The current recommendation denies patients and their families' access to a proven medicine that prolongs life and the opportunity for the NHS to improve cancer outcomes in advanced metastatic breast cancer.** **Eribulin is a first in class novel agent with robust evidence to extend life, which is being offered to the NHS via the proposed PAS at a price that is LOWER than the price of NICE approved chemotherapy (Taxotere) that was approved over a decade ago. In addition to the weight of clinical evidence and innovation, this lower acquisition cost to the NHS should also be considered alongside the relatively superior profile of eribulin compared to currently available intravenous chemotherapy options including a short 2-5 minute infusion, a lack of requirement of pre-medication to address hypersensitivity reactions, and a ready to use formulation.**	details were not presented in the evidence section of the ACD as Eisai indicated that this analysis was confidential. Section 4.5 of the ACD states that the Committee agreed with the ERG's critique that the results should be treated with caution because the analyses were defined post-hoc, and the results were based on small numbers, had wide confidence intervals and did not include appropriate adjustment for multiple testing thus increasing the risk of chance findings. In addition, the Committee was aware that the trial was not powered to detect differences between individual treatment groups. The Committee concluded that it was not appropriate to consider the results from these individual TPC comparisons. This discussion is also included in section 4.5 of the FAD. The previous guidance refers to a time when the treatment pathway was very different to what it is now and was also in a different place in the pathway (i.e. in an earlier line of therapy), and so the situation is not analogous. Please note that docetaxel was one of the TPC treatments, and so was used as part of the TCP comparator in this appraisal. The Committee also noted (section 4.16) that the efficiency savings to the NHS suggested for eribulin also largely applied to vinorelbine.

Consultee	Comment	Response
	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? None. **Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?** None.	Comments noted.
NHS Camden	We are in agreement with the recommendations in the ACD to not recommend Eribulin for this indication on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective in real life clinical practice.	Comment noted.
	Unit costs: Prior to the release of the ACD, UK cost information for eribulin was not available. The manufacturer reported that a vial of 1.0mg eribulin mesylate costs £313. The manufacturer has agreed a patient access scheme with the Department of Health, but the discount agreed is commercial in confidence information and not available in the ACD. Eribulin is given as a dose of 1.4mg/m2 eribulin mesylate on days 1 and 8 of a 21 day cycle. Based on an average body surface area of 1.74m2, as used in manufacturer's submission, the average undiscounted cost per cycle is estimated to be £1,878 (assuming wastage). In the EMBRACE trial participants received an average of 5 cycles of eribulin, which suggests an average undiscounted cost for eribulin treatment of £9,390 per patient. The patient access scheme would reduce this cost; costs may also vary in different settings because of negotiated procurement discounts.	Comment noted.
	Affordability: The number of patients who would be eligible for treatment with eribulin is uncertain. There are estimated to be 23 cases of advanced breast cancer per 100,000 population each year. Only a small proportion of these will require third-line (or subsequent) therapy (i.e. the indication for which eribulin is approved). In their submission to NICE, the manufacturer of eribulin estimated that about 10% of patients with locally advanced or metastatic breast cancer would receive third or subsequent line chemotherapy; this would equate to about 3 patients per 100,000 population each year being eligible for eribulin. If all of these patients received eribulin, this would equate to a cost of £28,170 per 100,000 population per year (not including patient access discount). However, the clinical specialist advising the Committee noted that due to its toxicity profile, eribulin was unlikely to displace capecitabine or	Comment noted.

Consultee	Comment	Response
	vinorelbine in the existing treatment pathway, and would be given after these therapies. This might reduce the number of people who would receive eribulin.	
	Efficacy: Evidence on efficacy came from the EMBRACE international multicenter phase III RCT, as well as three uncontrolled phase II studies. The RCT compared eribulin with treatment of the physician's choice (TPC). The manufacturer provided subgroup analyses comparing eribulin versus the individual treatments used in the comparator group, and looking at the results for different geographical regions (e.g. region 1 included North America, Western Europe, and Australia). The results of the efficacy analysis by comparator are not available as they were commercial in confidence. The evidence review group felt that the sub-group analyses by comparator should be treated with caution, as they were post-hoc, included small numbers of patients, and did not adjust appropriately for multiple testing.	Comment noted.
	Overall survival: In their primary analysis (after 55% of participants had died) the EMBRACE trial found that eribulin monotherapy improved median overall survival by 2.5 months (13.1 months with eribulin vs. 10.6 months with TPC; HR 0.809, 95% CI 0.660 to 0.991). In an updated analysis (after 77% of participants had died) this difference increased to 2.7 months (median survival: 13.2 months with eribulin vs. 10.5 months with TPC; HR 0.805, 95% CI 0.667 to 0.958). The manufacturer also presented planned subgroup analyses for region 1 participants, as they felt this was more generalisable to UK clinical practice. In region 1, eribulin increased median overall survival by 3.1 months (13.1 months with eribulin vs. 10.0 months with treatment of the physician's choice; HR 0.724, 95% CI 0.568 to 0.924; data as reported by the manufacturer for their primary analysis). However, the Committee did not agree that region 1 data was more appropriate for consideration.	Comment noted.
	Progression free survival (PFS): In EMBRACE, eribulin increased PFS compared to TPC if progression was assessed by investigator review (3.6 months vs. 2.2 months, p=0.002) but not by independent review (3.7 months vs. 2.2 months, p=0.137). The manufacturer reported that this difference arose because more patients were censored in the independent review.	Comment noted.
	Quality of life (QoL): The EMBRACE RCT did not look at QoL, so data was reported from two phase II studies. These studies were uncontrolled, so it was not possible to determine whether QoL with eribulin differs from other treatment options. The Appraisal Committee considered that QoL is an important outcome in advanced cancer, and therefore this was an important omission from the RCT. Data on QoL from the phase II trials was not used to assess utility in the cost-effectiveness analysis.	Comment noted.
	Safety: Treatment-related serious adverse effects were more common in the eribulin group (11.7%) than the TPC group (6.9%), but discontinuations due to adverse events were lower with eribulin (13.3% versus 15.4%). The manufacturer reported that most adverse events were mild or moderate. Adverse events that were more common with eribulin than TPC included:	Comment noted.

Consultee	Comment	Response
	asthenia/fatigue (53.7% vs. 39.7%), alopecia (44.5% vs. 9.7%), peripheral neuropathy (34.6% vs. 16.2%), arthralgia/myalgia (21.7% vs. 11.7%), and febrile neutropenia (4.6% vs. 1.6%). The clinical specialist advising the Committee noted that trial data indicate that eribulin is less well tolerated than capecitabine and vinorelbine, and is associated with peripheral neuropathy and alopecia in particular. Alopecia was highlighted as an important consideration for patients at this stage of treatment as they may already have had hair loss earlier in the treatment pathway.	
	Quality of the research: There was only one RCT available (the EMBRACE trial) which provided the majority of the evidence about clinical effectiveness of eribulin. The treatments included in the comparator arm of this RCT were considered to be a reasonable reflection of UK practice, except for the use of gemcitabine monotherapy, which was thought likely to be less common in the UK than in the trial. The RCT did not report on health related quality of life, which was considered by the Committee to be an important omission. Information on the effects of eribulin on quality of life had to be obtained from weaker sources (small non-comparative phase II trials of eribulin).	Comment noted.
	Cost-effectiveness: The manufacturer used efficacy data from region 1 in its base case analysis along with utility data from published literature on UK societal preferences in metastatic breast cancer. They used a trial duration time horizon, and assumed that all patients still alive at the end of the trial entered a 'terminal' state. They based utilities on disease state and grade 3 or 4 treatment-related toxicities (only those that were present in 10% of participants or more were included). The analysis took into account the patient access scheme agreed with the Department of Health. Their base case yielded an ICER for eribulin of £46,040 per QALY gained compared with treatment of the physician's choice, £27,183 per QALY gained compared with gemcitabine, £35,602 per QALY gained compared with vinorelbine, and £47,631 compared with capecitabine. Using data for the overall population of the trial rather than just region 1 data gave an ICER for eribulin of £50,100 per QALY gained compared to treatment of the physician's choice. • The Evidence Review Group (ERG) made a number of adjustments to the manufacturer's model, including correcting minor errors, adjusting costs and utilities, assuming vinorelbine is given in its generic intravenous formulation rather than its branded oral formulation, incorporating the cost and disutility associated with febrile neutropenia, adjusting source of progression-free survival data, and including projected overall survival to the end of life rather than to the end of the trial period. They also used data for the overall trial population rather than those from region 1 only. These adjustments resulted in an ICER for eribulin of £68,590 compared with treatment of the physician's choice. Eribulin provided 0.1229 additional QALYs for an additional cost of £8,269 in this analysis.	Comment noted.

Consultee	Comment	Response
	• The Appraisal Committee supported the ERG's adjustments to the model, and considered that their estimated ICER (£68,590 per QALY gained) provided the most plausible estimate. They considered that this figure was still likely to be an underestimate of the true cost per QALY gained as it did not incorporate the full toxicity profile of eribulin (e.g. the disutility associated with alopecia), the uncertainty about quality of life effects of eribulin, the fact that the estimate included median cost of available formulations of comparators rather than that of generic formulations where available, and the fact that in practice vinorelbine is often used in a less frequent schedule than that used in the model due to toxicity	
	Additional factors: The Appraisal Committee judged that the technology did not meet criteria for using end-of-life considerations. They considered that eribulin was indicated for patients with a short life expectancy (<24 months), and that it was likely to be licensed for a small patient population, but that it did not extend life in the overall trial population by at least 3 months compared with the comparator (treatment of the physician's choice). The manufacturer had shown that the median extension in survival in region 1 (North America, Western Europe, and Australia) was 3.1 months, but the Committee judged that it was more appropriate to consider the results of the trial as a whole. This was due to the small numbers of individuals in the region 1 group, the lack of a significant difference in overall survival between region 1 and the other regions, the fact that clinical practice in some of the region 1 areas differs considerably from that of the UK (e.g. that vinorelbine is used more than capecitabine in North America, which is not the case in the UK), and that European marketing authorisation was awarded based on overall data (rather than region 1 data). It also noted that even if the technology had met the end of life criteria, the high ICER meant that it would still not be considered a cost-effective use of NHS resources. No equality issues were raised.	Comment noted.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Breakthrough Breast Cancer	**Has all of the relevant evidence been taken into account?** There is no cure for metastatic breast cancer and treatment options are used to alleviate symptoms, delay progression or improve survival. It is therefore essential more treatment options are made available to this patient group. If treatments can prolong survival this may give patients extra time to spend with their family and loved ones. For patients with metastatic breast	Comment noted.

Nominating organisation	Comment	Response
	cancer the importance of this should not be underestimated. The EMBRACE trial, which assessed eribulin versus treatment of physician's choice for metastatic breast cancer, demonstrated a statistically significant median overall survival benefit of 2.5 months (updated to 2.7 months after later analysis) for patients treated with eribulin. This is noteworthy as an extra few months of survival for metastatic patients is important to these patients and their families. Indeed, as stated in the Appraisal Consultation Document (ACD) both clinical specialist and patient expert stated to the Committee that an overall survival benefit in advanced breast cancer at this stage in the clinical pathway was unusual and stressed the importance of having additional treatment options when previous chemotherapy regimens had failed. However, Breakthrough does accept that the manufacturers had not collected health-related quality of life data during the EMBRACE trial and that this omission leaves questions around how potential side effects of eribulin may impact patients. This is important as it has been suggested that eribulin is less well tolerated than capecitabine and vinorelbine, comparators to eribulin, and can lead to side effects including peripheral neuropathy and alopecia. These side effects have the potential to impact a patients quality of life since the patient may have already experienced them earlier in the treatment pathway and not wish to experience them again. However, it is worth considering that due to its toxicity profile eribulin would only be given as a third- or fourth-line treatment for metastatic breast cancer and so would be unlikely to replace capecitabine and vinorelbine in the established treatment profile. Patients with advanced breast cancer have limited treatment options so they may wish to have access to more therapies regardless of certain side effects. Additionally, it should not be overlooked that the manufacturer did submit data on quality of life although we appreciate this was from Phase II trial data and did not include a comparator arm. Nevertheless, the manufacturer reported that patients whose disease had responded to eribulin did not report deterioration in quality of life.	
	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? We are disappointed the Appraisal Committee is unable to recommend eribulin for the treatment of locally advanced or metastatic breast cancer.	Comment noted.

Nominating organisation	Comment	Response
	However, we acknowledge there are concerns regarding the quality of life data included by the manufacturer. No health-related quality of life data were collected during the EMBRACE trail and instead data were presented from two phase II trials. Unfortunately, these trials were not without limitations and as stated by the Committee did not include a comparator arm and may have excluded some potentially important adverse events. Although the toxicity profile of eribulin is reported to be higher than comparators capecitabine and vinorelbine it is worth noting that because of limited treatment options available to metastatic breast cancer patients, especially third- or fourth-line treatment options, they may be more willing to accept adverse side effects of chemotherapy, especially if it means they may see benefits such as longer survival. Providing accurate information about possible side effects can assist patients in making decisions relating to their treatment. Breakthrough accepts there are uncertainties regarding the exact cost per QALY and what evidence should be included in this calculation. We therefore accept this makes eribulin difficult to approve at this time.	

Nominating organisation	Comment	Response
	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? It is disappointing that the committee is unable to recommend eribulin for the treatment of locally advanced or metastatic breast cancer. As a patient organisation, Breakthrough Breast Cancer would like to emphasise how crucial it is for this patient group to have a variety of treatment options. However, we accept that no health-related quality of life data was collected during the EMBRACE trial and this has led to uncertainties around how well eribulin is tolerated in the patient population. We therefore support the recommendation that further research be conducted on health-related quality of life to compare eribulin treatment with that of vinorelbine and capecitabine. We appreciate the advice from NICE on assessing end-of-life treatments state these treatments should offer an extension of life 'of normally at least three additional months compared to current NHS treatments'. However, upon updated analysis the median overall survival benefit of patients receiving eribulin was 2.7 months. The use of the word 'normally' here is significant and we would argue 2.7 months is very close to 3 months. Since the other two end-of-life criteria were met – that is the patients' life expectancy is short and the treatment is indicated for a small patient population – we would suggest eribulin does fulfil all the criteria for a life-extending, end-of-life treatment.	Comment noted. Section 4.19 of the FAD states that given that the most optimistic ICER for the overall ITT group was £68,600 per QALY gained, the Committee concluded that eribulin could not be considered a cost-effective use of resources for NHS use even if all of the criteria for being a life-extending, end-of-life treatment were met.
	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? None of which we are aware. **Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?** None of which we are aware.	Comment noted.

Nominating organisation	Comment	Response
The Royal College of Physicians (NCRI/RCP/RCR/ACP/JCCO)	**Has all of the relevant evidence been taken into account?** Yes, the EMBRACE study forms the major part of the submission and relevant data.	Comment noted.
	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes. There were concerns at the appraisal meeting regarding the lack of quality of life data in the main study and also regarding inaccuracies of supportive care costs. The post-hoc analysis of splitting by treatment of physicians choice was appropriately disregarded. There was much discussion regarding whether it was appropriate to take geographical Region 1 data or overall ITT data for overall survival analysis. This point is critical when the end-of-life criteria are considered as by taking Region 1 data alone, the OS benefit rises above the cut-off value of 3 months. However, it was felt that using overall ITT population was more appropriate for applying to UK practice (which does not necessarily mirror North American practice).	Comment noted.
	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Yes	Comment noted.
	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? No. **Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?** No.	Comment noted.

Nominating organisation	Comment	Response

Comments received from commentators

Commentator	Comment	Response
Commissioning Support, Appraisals Service (CSAS)	We are in agreement with the recommendations in the ACD to not recommend Eribulin for this indication on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective in real life clinical practice.	Comment noted.
	Unit costs: Prior to the release of the ACD, UK cost information for eribulin was not available. The manufacturer reported that a vial of 1.0mg eribulin mesylate costs £313. The manufacturer has agreed a patient access scheme with the Department of Health, but the discount agreed is commercial in confidence information and not available in the ACD. Eribulin is given as a dose of 1.4mg/m2 eribulin mesylate on days 1 and 8 of a 21 day cycle. Based on an average body surface area of 1.74m2, as used in manufacturer's submission, the average undiscounted cost per cycle is estimated to be £1,878 (assuming wastage). In the EMBRACE trial participants received an average of 5 cycles of eribulin, which suggests an average undiscounted cost for eribulin treatment of £9,390 per patient. The patient access scheme would reduce this cost; costs may also vary in different settings because of negotiated procurement discounts.	Comment noted.
	Affordability: The number of patients who would be eligible for treatment with eribulin is uncertain. There are estimated to be 23 cases of advanced breast cancer per 100,000 population each year. Only a small proportion of these will require third-line (or subsequent) therapy (i.e. the indication for which eribulin is approved). In their submission to NICE, the manufacturer of eribulin estimated that about 10% of patients with locally advanced or metastatic breast cancer would receive third or subsequent line chemotherapy; this would equate to about 3 patients per 100,000 population each year being eligible for eribulin. If all of these patients received eribulin, this would equate to a cost of £28,170 per 100,000 population per year (not including patient access discount). However, the clinical specialist advising the Committee noted that due to its toxicity profile, eribulin was unlikely to displace capecitabine or vinorelbine in the existing treatment pathway, and would be given after these therapies. This might reduce the number of people who would receive eribulin.	Comment noted.
	Efficacy: Evidence on efficacy came from the EMBRACE international multicenter	Comment noted.

Commentator	Comment	Response
	phase III RCT, as well as three uncontrolled phase II studies. The RCT compared eribulin with treatment of the physician's choice (TPC). The manufacturer provided subgroup analyses comparing eribulin versus the individual treatments used in the comparator group, and looking at the results for different geographical regions (e.g. region 1 included North America, Western Europe, and Australia). The results of the efficacy analysis by comparator are not available as they were commercial in confidence. The evidence review group felt that the sub-group analyses by comparator should be treated with caution, as they were post-hoc, included small numbers of patients, and did not adjust appropriately for multiple testing.	
	Overall survival: In their primary analysis (after 55% of participants had died) the EMBRACE trial found that eribulin monotherapy improved median overall survival by 2.5 months (13.1 months with eribulin vs. 10.6 months with TPC; HR 0.809, 95% CI 0.660 to 0.991). In an updated analysis (after 77% of participants had died) this difference increased to 2.7 months (median survival: 13.2 months with eribulin vs. 10.5 months with TPC; HR 0.805, 95% CI 0.667 to 0.958). The manufacturer also presented planned subgroup analyses for region 1 participants, as they felt this was more generalisable to UK clinical practice. In region 1, eribulin increased median overall survival by 3.1 months (13.1 months with eribulin vs. 10.0 months with treatment of the physician's choice; HR 0.724, 95% CI 0.568 to 0.924; data as reported by the manufacturer for their primary analysis). However, the Committee did not agree that region 1 data was more appropriate for consideration.	Comment noted.
	Progression free survival (PFS): In EMBRACE, eribulin increased PFS compared to TPC if progression was assessed by investigator review (3.6 months vs. 2.2 months, p=0.002) but not by independent review (3.7 months vs. 2.2 months, p=0.137). The manufacturer reported that this difference arose because more patients were censored in the independent review.	Comment noted.
	Quality of life (QoL): The EMBRACE RCT did not look at QoL, so data was reported from two phase II studies. These studies were uncontrolled, so it was not possible to determine whether QoL with eribulin differs from other treatment options. The Appraisal Committee considered that QoL is an important outcome in advanced cancer, and therefore this was an important omission from the RCT. Data on QoL from the phase II trials was not used to assess utility in the cost-effectiveness analysis.	Comment noted.
	Safety: Treatment-related serious adverse effects were more common in the eribulin group (11.7%) than the TPC group (6.9%), but discontinuations due to adverse events were lower with eribulin (13.3% versus 15.4%). The manufacturer reported that most adverse events were mild or moderate. Adverse events that were more	Comment noted.

Commentator	Comment	Response
	common with eribulin than TPC included: asthenia/fatigue (53.7% vs. 39.7%), alopecia (44.5% vs. 9.7%), peripheral neuropathy (34.6% vs. 16.2%), arthralgia/myalgia (21.7% vs. 11.7%), and febrile neutropenia (4.6% vs. 1.6%). The clinical specialist advising the Committee noted that trial data indicate that eribulin is less well tolerated than capecitabine and vinorelbine, and is associated with peripheral neuropathy and alopecia in particular. Alopecia was highlighted as an important consideration for patients at this stage of treatment as they may already have had hair loss earlier in the treatment pathway.	
	Quality of the research: There was only one RCT available (the EMBRACE trial) which provided the majority of the evidence about clinical effectiveness of eribulin. The treatments included in the comparator arm of this RCT were considered to be a reasonable reflection of UK practice, except for the use of gemcitabine monotherapy, which was thought likely to be less common in the UK than in the trial. The RCT did not report on health related quality of life, which was considered by the Committee to be an important omission. Information on the effects of eribulin on quality of life had to be obtained from weaker sources (small non-comparative phase II trials of eribulin).	Comment noted.
	Cost-effectiveness: The manufacturer used efficacy data from region 1 in its base case analysis along with utility data from published literature on UK societal preferences in metastatic breast cancer. They used a trial duration time horizon, and assumed that all patients still alive at the end of the trial entered a 'terminal' state. They based utilities on disease state and grade 3 or 4 treatment-related toxicities (only those that were present in 10% of participants or more were included). The analysis took into account the patient access scheme agreed with the Department of Health. Their base case yielded an ICER for eribulin of £46,040 per QALY gained compared with treatment of the physician's choice, £27,183 per QALY gained compared with gemcitabine, £35,602 per QALY gained compared with vinorelbine, and £47,631 compared with capecitabine. Using data for the overall population of the trial rather than just region 1 data gave an ICER for eribulin of £50,100 per QALY gained compared to treatment of the physician's choice. • The Evidence Review Group (ERG) made a number of adjustments to the manufacturer's model, including correcting minor errors, adjusting costs and utilities, assuming vinorelbine is given in its generic intravenous formulation rather than its branded oral formulation, incorporating the cost and disutility associated with febrile neutropenia, adjusting source of progression-free survival data, and including projected overall survival to the end of life rather	Comment noted.

Commentator	Comment	Response
	than to the end of the trial period. They also used data for the overall trial population rather than those from region 1 only. These adjustments resulted in an ICER for eribulin of £68,590 compared with treatment of the physician's choice. Eribulin provided 0.1229 additional QALYs for an additional cost of £8,269 in this analysis. • The Appraisal Committee supported the ERG's adjustments to the model, and considered that their estimated ICER (£68,590 per QALY gained) provided the most plausible estimate. They considered that this figure was still likely to be an underestimate of the true cost per QALY gained as it did not incorporate the full toxicity profile of eribulin (e.g. the disutility associated with alopecia), the uncertainty about quality of life effects of eribulin, the fact that the estimate included median cost of available formulations of comparators rather than that of generic formulations where available, and the fact that in practice vinorelbine is often used in a less frequent schedule than that used in the model due to toxicity	
	Additional factors: The Appraisal Committee judged that the technology did not meet criteria for using end-of-life considerations. They considered that eribulin was indicated for patients with a short life expectancy (<24 months), and that it was likely to be licensed for a small patient population, but that it did not extend life in the overall trial population by at least 3 months compared with the comparator (treatment of the physician's choice). The manufacturer had shown that the median extension in survival in region 1 (North America, Western Europe, and Australia) was 3.1 months, but the Committee judged that it was more appropriate to consider the results of the trial as a whole. This was due to the small numbers of individuals in the region 1 group, the lack of a significant difference in overall survival between region 1 and the other regions, the fact that clinical practice in some of the region 1 areas differs considerably from that of the UK (e.g. that vinorelbine is used more than capecitabine in North America, which is not the case in the UK), and that European marketing authorisation was awarded based on overall data (rather than region 1 data). It also noted that even if the technology had met the end of life criteria, the high ICER meant that it would still not be considered a cost-effective use of NHS resources. No equality issues were raised.	Comment noted.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	1	The guidance has been reviewed by the Pharmaceutical Advisor for NHS Tameside and Glossop and is consistent with the evidence reviewed. This treatment is currently funded via the Cancer Drugs Fund within NHSNW, so if this guidance is not approved there will not be an immediate funding pressure for the PCT. However, in the longer term there could be consequences for funding of more cost effective interventions if the PCT is required to fund this treatment.	Comment noted.
NHS Professional	2	The Appraisal Committee needs to note that commissioners will be charged the discounted price plus VAT at 20%. Our experience with drugs approved by the NICE demonstrates that there are no local discounts obtained. The VAT of 20% is a significant burden for the NHS and should be considered by the Committee.	Comment noted. The Method's Guide states that Value added tax (VAT) should be excluded from all economic evaluations but included in budget impact calculations at the appropriate rate when the resources in question are liable for this tax.
	3	We have similar concerns to those highlighted by the ERG regarding the manufacturer's submission. We agree with the comments of the ERG and adjustments made to calculate the cost/ QALY. We have concerns about projecting overall and progression free survival from the number of patients alive at the end of the study as this would over-estimate these outcomes.	Comment noted.
	4	We agree that Eribulin is not a cost-effective use of NHS resources. Whilst the treatment improves median survival by 2.5 months compared to other treatments, the quality of this survival is not known but is increasingly important to patients. We note the less favourable toxicity profile of eribulin, especially alopecia, peripheral neuropathy and fatigue - these are important considerations for patients at end-of-life. We have real concerns about the quality of the research available and lack of health related quality of life measures. We understand from our local oncologists and palliative care consultants that patients, at the end-of-life would value being given the benefits and harms to make decisions on whether to continue being treated.	Comment noted.
	5	The exact number of patients who would be eligible to receive eribulin in	Comment noted.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
		preference to alternatives is uncertain. Applying the manufacturers estimate to NHS Hertfordshires population, it would cost £290k for drug plus about £160k for activity plus cost of associated drugs. With this level of investment, NHS Hertfordshire would be unable to develop pulmonary rehabilitation services for its population and would not be able to increase the number of hospice beds (8 beds planned). We would like to bring to the NICE our experience that the Costing template does not accurately reflect all the costs charged by providers and usually underestimates cost pressures.	
NHS Professional	1	Agree with these recommendations	Comment noted.
	4	In this indication this technology is not a cost effective use of NHS resources. The Appraisal Committee concluded that the most plausible ICER for eribulin monotherapy was in excess of £68,600 per QALY gained compared with treatment of physician's choice. This ICER took into account a patient access scheme agreed by the Department of Health and the manufacturer of Eribulin. Eribulin monotherapy improves median overall survival by only 2.5 months compared with alternative treatments. Eribulin has a less favourable toxicity profile than alternative treatments. Treatment-related serious adverse effects were more common in the Eribulin group than the treatment of the physician's choice. There were limitations to quality of the research available. There was only one RCT available (the EMBRACE trial) which provided the majority of the evidence about clinical effectiveness. The RCT did not report on health related quality of life, and this information had to be obtained from weaker sources (small non-comparative phase II trials of eribulin). Eribulin does not fulfil the end-of-life criteria, as it did not extend life by at least 3 additional months in the overall trial population.	Comment noted.
	5	The exact number of people who would be eligible to receive Eribulin (if approved) in preference to alternatives is uncertain. There are estimated to be 23 cases of advanced breast cancer per 100,000 population each year. Only a small proportion of these will require third line (or subsequent) therapy (i.e. the indication for which Eribulin is approved). Based on manufacturer's estimates of the proportion of individuals with advanced breast cancer who receive third or subsequent line chemotherapy, about 3	Comment noted.

Role*	Section	Comment	Response
		people per 100,000 population each year might be eligible for Eribulin. The clinical specialist advising the Committee noted that due to its toxicity profile, Eribulin was unlikely to displace capecitabine or vinorelbine in the existing treatment pathway, and would be given after these therapies.	
NHS Professional	1	Agree	Comment noted.
	2	End of life criteria (as laid down by NICE) not fulfilled, and the ICER is in excess of £68k even when patient access scheme is taken into account. It has little to recommend it over existing treatments as an infusion requiring hospital treatment Of the patient access schemes in place, most are not returning the money to the NHS that was predicted through NICE gudiance, and most are complicated to administer and audit. It requires a lot of NHS professional time - clinical and non clinical, and this is not taken into account by NICE.	Comment noted.
	3	Only one RCT - no quality of life data - which is what you're looking for in a treatment at this stage, especially with the toxicity associated with this treatment	Comment noted.
	4	Agree - but also to emphasise that toxicity can adversely affect end of life and other treatments are available	Comment noted.
	6	Agree	Comment noted.
NHS Professional	5	Network perspective from Avon Somerset and Wiltshire Cancer Services: If used, this drug would be used between 3rd and 5th line. Increasing numbers of patients are fit enough for chemotherapy at that time and many would currently be offered an alternative chemotherapy schedule (as in the published trial). A guesstimate for the network would be around 30 - 50/year. (But this would probably increase with time as clinicians became more familiar with use). Currently patients who might be eligible for eribulin are offered other chemotherapy drugs so this would have potentially little additional service impact in terms of capacity. The drug is administered as a short IV infusion on days 1 and 8 so may free up a bit of time on the chemo day unit (assuming it was replacing an IV treatment as opposed to oral e.g	Comment noted.

Role*	Section	Comment	Response
		capecitabine or oral vinorelbine).	
NHS Professional	1	I am in agreement with committees recommendations	Comment noted.
	2	From local anecdotal experience, reimbursement under patient access schemes are not well implemented by local hospitals as it constitutes significant extra administrative burden for no obvious benefit for those undertaking the extra burden (usually hospital pharmacists). If this technology will be agreed this will have significant impact and opportunity costs in our local health economy as it will reduce the funding available for the development of a hospice centre that aims to provide care for the same group of patients that could benefit from this technology.	Comment noted.
	3	Eribulin does not fulfil the end-of-life criteria, as it did not extend life by at least 3 additional months in the overall trial population. The manufacturer has reported that the median extension in survival in region 1 (North America, Western Europe, and Australia) was 3.1 months, but the Committee judged that it was more appropriate to consider the results of the trial as a whole. Eribulin meets the other end-of-life criteria, as it is indicated in patients with a short life expectancy (less than 24 months), and is likely to be indicated for a small population. However, the Committee noted that even if the technology had met all of the end-of-life criteria, the high ICER meant that it would still not be considered a cost-effective use of NHS resources.	Comment noted.
	4	This technology is not a cost effective use of NHS resources. The Committee concluded that the most plausible ICER for eribulin monotherapy was in excess of £68,600 per QALY gained compared with treatment of physician's choice. This took into account a patient access scheme agreed by DH and the manufacturer. Eribulin monotherapy improves median overall survival by 2.5 months compared with alternative treatments. One international multicenter phase III RCT in 762 patients found that eribulin monotherapy improved median overall survival to 13.1 months, from 10.6 months with treatment of the physician's choice. The treatment of the physician's choice in the comparator group was vinorelbine in 24.0%, gemcitabine in 18.1%,	Comment noted.

Role*	Section	Comment	Response
		capecitabine in 17.3%, taxanes in 15.0%, anthracyclines in 9.4%, other chemotherapy in 9.8%, and hormone therapy in 3.5%. Eribulin has a less favourable toxicity profile than alternative treatments. Treatment-related serious adverse effects were more common in the eribulin group than physician's choice (TPC) group (11.7% vs. 6.9%), but discontinuations due to adverse events were lower with eribulin (13.3% versus 15.4%).	
	5	The exact number of people who would be eligible to receive eribulin (if approved) in preference to alternatives is uncertain. There are estimated to be 23 cases of advanced breast cancer per 100,000 population each year. Only a small proportion of these will require third line (or subsequent) therapy (i.e. the indication for which eribulin is approved). Based on manufacturer's estimates of the proportion of individuals with advanced breast cancer who receive third or subsequent line chemotherapy, about 3 people per 100,000 population each year might be eligible for eribulin. The clinical specialist advising the Committee noted that due to its toxicity profile, eribulin was unlikely to displace capecitabine or vinorelbine in the existing treatment pathway, and would be given after these therapies.	Comment noted.
	6	There were limitations to quality of the research available. There was only one RCT available (the EMBRACE trial) which provided the majority of the evidence about clinical effectiveness. The RCT did not report on health related quality of life, and this information had to be obtained from weaker sources (small non-comparative phase II trials of eribulin).	Comment noted.
	8	This (proposed review date) is acceptable.	Comment noted.
NHS Professional	1	Recommendation 1.2 does not mean that PCTs can or will be able to fund this treatment in current patients if it is not recommended by NICE. To do so would disadvantage new patients.	Comment noted.
	2	The DH may not consider that PAS constitute an excessive administrative burden on the NHS but that is not consistent with evidence in practice. From local anecdotal experience, reimbursement under patient access schemes are not well implemented by local hospitals as it constitutes significant extra administrative burden for no obvious benefit for those undertaking the extra burden (usually hospital pharmacists).	Comment noted.
	3	If this technology were to be agreed this will have significant impact and	Comment noted.

Role*	Section	Comment	Response
		opportunity costs in our local health economy as it would reduce the funding available for the development of hospice care that aims to provide for the same group of patients that could benefit from this technology.	
	4	Haemotological toxicity was common with eribulin, with grade 3 neutropenia occurring in 21.1% of participants, and grade 4 neutropenia in 24.1%. The full costs of managing this are not fully reflected in the costs considered by NICE. They do however represent a substantial cost for PCTs, over and above the costs shown. Adverse events that were more common with eribulin than with TPC included alopecia (44.5% vs. 9.7%), peripheral neuropathy (34.6% vs. 16.2%), and febrile neutropenia (4.6% vs. 1.6%). Alopecia was highlighted as an important consideration for patients at this stage of treatment as they may already have had hair loss earlier in the treatment pathway	Comment noted.
	5	For my PCT adding yet another, barely effective, line of therapy would mean paying for around 18 patients. Local experience suggests that this would be used after existing third-line alternatives. This could mean £500,000 a year taken away from care of people with dementia, and from patients with conditions where treatment could substantially affect quality and length of life. This is not an appropriate use of resources.	Comment noted.
	6	There was only one RCT available (the EMBRACE trial) which provided the majority of the evidence about clinical effectiveness. The RCT did not report on health related quality of life, and this information had to be obtained from weaker sources (small non-comparative phase II trials of eribulin). QoL studies for patients with late-stage breast cancer are needed in order to understand how quality of life is affected by these many extra lines of therapy	Comment noted.
	7	Related NICE Guidance: lapatinib guidance?	Comment noted.
	8	This review date is after the planned end-date for the Cancer Drugs Fund	Comment noted. The review date has been decided in line with the standard NICE practice of considering topics for review 3 years after publication of Guidance.
NHS	1	I agree with the appraisal committee's preliminary recommendations on the basis that the drug fails to meet end of life criteria and would not be a	Comment noted.

Role*	Section	Comment	Response
Professional		cost-effective use of NHS resources.	
NHS Professional	1	We would support these preliminary recommendations. Eribulin does not fulfil the end-of-life criteria, as it did not extend life by at least 3 additional months in the overall trial population. Please clarify 1.2 to say that patients already receiving eribulin "WITH NHS FUNDING" should have the option to continue therapy...etc. Privately funded patients should NOT have the option to continue treatment with NHS funding.	Comment noted.
	4	There were limitations to quality of the research available. There was only one RCT available (the EMBRACE trial). Eribulin monotherapy improves median overall survival by 2.5 months compared with alternative treatments. One international multicenter phase III RCT (the EMBRACE trial) in 762 patients found that eribulin monotherapy improved median overall survival to 13.1 months, from 10.6 months with treatment of the physician's choice (HR 0.809, 95% CI 0.660 to 0.991). The treatment of the physician's choice in the comparator group was vinorelbine in 24.0% of participants, gemcitabine in 18.1%, capecitabine in 17.3%, taxanes in 15.0%, anthracyclines in 9.4%, other chemotherapy in 9.8%, and hormone therapy in 3.5%. Eribulin has a less favourable toxicity profile than alternative treatments. Treatment-related serious adverse effects were more common in the eribulin group than the treatment of the physician's choice (TPC) group (11.7% vs. 6.9%), but discontinuations due to adverse events were lower with eribulin (13.3% versus 15.4%).	Comment noted.
	5	The exact number of people who would be eligible to receive eribulin (if approved) in preference to alternatives is uncertain. We have not received any individual funding requests and therefore there appears to be no local demand for this treatment.	Comment noted.
NHS Professional	1	We agree with the Appraisal Committee's preliminary recommendation that Eribulin should not be recommended for treatment of locally advanced or metastatic breast cancer in people whose disease has progressed after at least two chemotherapeutic regimens for advanced disease as it is not a cost effective use of NHS resources for this indication.	Comment noted.
	4	In this indication we do not consider eribulin to be a cost-effective use of NHS resources for the following reasons Clinical Effectiveness - there were limitations to quality of the research available. There was only one	Comment noted.

Role*	Section	Comment	Response
		RCT available (the EMBRACE trial) which provided the majority of the evidence about clinical effectiveness. This RCT did not report on health related quality of life, and this information had to be obtained from weaker sources (small non-comparative phase II trials of eribulin). Health related quality of life is an important outcome measure in advanced cancer and failure to assess this is a serious omission. Eribulin monotherapy improves median overall survival by 2.5 months compared with treatment of physician choice but does not fulfil the criteria for being a life extending, end of life treatment, as it did not extend life by at least 3 additional months in the overall trial population. Eribulin has a less favourable toxicity profile than alternative treatments. Cost effectiveness - the ICER for eribulin is likely to exceed £68,000 per QALY gained compared with physician's choice even when the patient access scheme is taken into account. Even if eribulin met the criteria for end of life treatment it would not be cost effective for this indication.	
	5	If eribulin were to be approved for this indication by NICE we have significant concerns regarding affordability for our PCT. The exact number of people who would be eligible to receive eribulin if it were to be approved in preference to alternatives is uncertain. There are estimated to be 23 cases of advanced breast cancer per 100,000 population each year. Only a small proportion of these will require third line (or subsequent) therapy (i.e. the indication for which eribulin is approved). Based on manufacturer's estimates of the proportion of individuals with advanced breast cancer who receive third or subsequent line chemotherapy, about 3 people per 100,000 population each year might be eligible for eribulin. For our PCT we estimate that the cost of treating the eligible population would be £364,000 per annum which may be reduced to £300,000 with discount. With discounting this is still a very significant cost and would inevitably impact on other cancer services that the PCT commissions. As an example £ 300,000 equates to 2,300 radiotherapy fractions, just under 4.5% of the radiotherapy fractions that our PCT commissions each year.	Comment noted.
NHS Professional	1	This is reasonable as eribulin is an expensive option but patients already on it should be allowed to continue.	Comment noted.
	2	This is a new agent and quite well tolerated. Toxicity is comparable with other agents.	Comment noted.
	3	The manufacturer's submission is appropriate. Trial was company-	Comment noted.

Role*	Section	Comment	Response
		sponsored.	
	4	This appropriate. The data are not strong but a very select group of patients may benefit from this treatment. It should not be used in patients who progress.	Comment noted. The manufacturer submitted additional evidence in response to consultation for patients who had previously been treated with capecitabine. However, for reason presented in the FAD (section 4.10 onwards), the Committee concluded that eribulin could not be recommended as a cost-effective use of NHS resources for the treatment of locally advanced or metastatic breast cancer in people whose disease has progressed after at least two chemotherapeutic regimens for advanced disease, for the whole population as well as for the people previously treated with capecitabine.
	5	Eribulin is not currently funded in the North West. It has been considered and prioritised against other drugs and will be funded through the North West Cancer Drugs Fund for a highly selected group of patients.	Comment noted.
	6	This is appropriate.	Comment noted.
	7	Related NICE Guidance - Fulvestrant guidance will be welcome	Comment noted. Fulvestrant for the treatment of locally advanced or metastatic breast cancer is being appraised by NICE and publication is expected in December 2011.
	8	Review date - This is appropriate	Comment noted.
NHS Professional	1	Acceptable.	Comment noted.
	2	Acceptable.	Comment noted.
	3	Acceptable.	Comment noted.
	4	**In this indication this technology is not a cost effective use of NHS resources.** The Appraisal Committee concluded that the most plausible ICER for eribulin monotherapy was in excess of £68,600 per QALY gained compared with treatment of physician's choice. This ICER took into account a patient access scheme agreed by the Department of Health and the manufacturer of eribulin.	Comment noted.

Role*	Section	Comment	Response
		Eribulin monotherapy improves median overall survival by 2.5 months compared with alternative treatments. One international multicenter phase III RCT (the EMBRACE trial) in 762 patients found that eribulin monotherapy improved median overall survival to 13.1 months, from 10.6 months with treatment of the physician's choice (HR 0.809, 95% CI 0.660 to 0.991). The treatment of the physician's choice in the comparator group was vinorelbine in 24.0% of participants, gemcitabine in 18.1%, capecitabine in 17.3%, taxanes in 15.0%, anthracyclines in 9.4%, other chemotherapy in 9.8%, and hormone therapy in 3.5%. **Eribulin has a less favourable toxicity profile than alternative treatments.** Treatment-related serious adverse effects were more common in the eribulin group than the treatment of the physician's choice (TPC) group (11.7% vs. 6.9%), but discontinuations due to adverse events were lower with eribulin (13.3% versus 15.4%). Haematological toxicity was common with eribulin, with grade 3 neutropenia occurring in 21.1% of participants, and grade 4 neutropenia in 24.1%. Adverse events that were more common with eribulin than with TPC included alopecia (44.5% vs. 9.7%), peripheral neuropathy (34.6% vs. 16.2%), and febrile neutropenia (4.6% vs. 1.6%). Alopecia was highlighted as an important consideration for patients at this stage of treatment as they may already have had hair loss earlier in the treatment pathway. **There were limitations to quality of the research available.** There was only one RCT available (the EMBRACE trial) which provided the majority of the evidence about clinical effectiveness. The RCT did not report on health related quality of life, and this information had to be obtained from weaker sources (small non-comparative phase II trials of eribulin). **Eribulin does not fulfil the end-of-life criteria, as it did not extend life by at least 3 additional months in the overall trial population.** The manufacturer has reported that the median extension in survival in region 1 (North America, Western Europe, and Australia) was 3.1 months, but the Committee judged that it was more appropriate to consider the results of the trial as a whole. Eribulin meets the other end-of-life criteria, as it is indicated in patients with a short life expectancy (less than 24 months), and is likely to be indicated for a small population. However, the Committee noted that even if the technology had met all of the end-of-life criteria, the high ICER meant that it would still not be considered a cost-effective use of NHS resources.	

Role*	Section	Comment	Response
	5	**The exact number of people who would be eligible to receive eribulin (if approved) in preference to alternatives is uncertain.** There are estimated to be 23 cases of advanced breast cancer per 100,000 population each year. Only a small proportion of these will require third line (or subsequent) therapy (i.e. the indication for which eribulin is approved). Based on manufacturer's estimates of the proportion of individuals with advanced breast cancer who receive third or subsequent line chemotherapy, about 3 people per 100,000 population each year might be eligible for eribulin. The clinical specialist advising the Committee noted that due to its toxicity profile, eribulin was unlikely to displace capecitabine or vinorelbine in the existing treatment pathway, and would be given after these therapies. The NHS is currently making prioritisation decision restricting the use of evidence based treatments at a lower acquisition or cost per QALY.	Comment noted.
	6	Acceptable.	Comment noted.
	7	Related NICE Guidance - Acceptable.	Comment noted.
	8	Review date - Acceptable.	Comment noted.
NHS Professional	1	We are aware of the draft NICE guidance for this product with which we agree. Following assessment by the above process, it is now available via the cancer drug fund in the North West so is accessible to patients via this route.	Comment noted.
NHS Professional		We agree with NICE in that this technology is not recommended for the following reasons 1. It does not fulfil end-of-life criteria in that it did not extend life by 3 months or more in the overall trial population 2. The trial evidence for health related quality of life was derived from low grade evidence i.e. small non-comparative phase II trials 3. Eribulin is associated with more serious adverse effects than other standard therapy. 4. Eribulin is not a cost effective use of NHS resources at £68,000 per QALY	Comment noted.

Eribulin for the treatment of locally advanced or metastatic breast cancer

Eisai Response to the Appraisal Consultation Document (ACD)

July 2011

Eisai provides the following comments on the Appraisal Consultation Document (ACD). In addition Eisai will be submitting new evidence and a revised model to NICE for evaluation at the next appraisal meeting that addresses these issues.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

1. Adverse Events

Eisai does not believe that the Committee's assessment of the toxicity profile of eribulin is either a reasonable interpretation of the available evidence or appropriately represents the overall safety profile of the medicinal product.

At paragraph 4.3 the Committee states that it "concluded that eribulin was associated with a greater overall survival benefit compared with TPC but with a less favourable toxicity profile". The basis for this conclusion appears to be that "it heard from the clinical specialist that the trial data indicated that eribulin is less well tolerated than capecitabine and vinorelbine, and in particular is associated with peripheral neuropathy and alopecia (hair loss)".

As stated in our submission, the pivotal Phase III RCT (EMBRACE) has demonstrated that eribulin is associated with a predictable and well-characterised safety profile and is generally well-tolerated, for a chemotherapeutic agent being used in heavily pre-treated metastatic breast cancer (MBC) (1-3). This is the first and only study to achieve Marketing Authorisation in this setting therefore NICE have not seen a phase III RCT in such a severe breast cancer patient population before.

When assessing the overall safety profile in EMBRACE eribulin is associated with less fatal AEs and fewer discontinuations and dose interruptions due to AEs than TPC in the EMBRACE study:

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

Importantly the duration of therapy in EMBRACE was longer in the eribulin arm (median: 118 days) than the TPC arm (median: 64 days for chemotherapy agents and 30 days for hormonal agents), again reflecting the acceptability of the safety profile and tolerability of this agent for the treatment of heavily pre-treated MBC.

In addition as patients continue to benefit from eribulin for a longer duration than other currently available therapies, as defined by TPC, it is unsurprising that patients on eribulin would experience a higher frequency of AEs than patients who stayed on TPC for half the duration. This is a function of unit time exposure for a chemotherapeutic agent. Despite these favourable results, the extended duration of therapy in patients receiving eribulin as compared with TPC resulted in a longer period for adverse events to be experienced/ reported and it is therefore likely that eribulin is even better tolerated, relative to TPC, than is suggested by these data.

Again, it is important to reiterate that NICE consider the specific and unique profile of these patients for whom all other registered options have been exhausted and no evidence-based option proven to extend overall survival is available. To be able to positively impact overall survival for these patients without introducing new or severe toxicities that are not commonly addressed is an important consideration.

Limited inference can be drawn from direct comparison of safety between patients treated with eribulin and those treated with TPC, as the TPC group comprises patients treated with a wide range of therapies and dosing regimens. Further, as each of the therapies in the TPC group has a distinct safety profile, and the number of patients receiving each TPC was relatively small, conclusions cannot be drawn from the comparison of incidences of specific AEs between each TPC and eribulin. Thus the view of the clinical specialist suggesting that eribulin is less well tolerated than either capecitabine or vinorelbine is not evidence-based. From clinicians who have used eribulin in their practice in the UK, we have heard quite different feedback and we would urge NICE to review such comments where available.

Therefore, as direct safety comparisons using data from EMBRACE are likely to be unreliable and to underestimate adverse events associated with TPC therapies, it is important to take into account the safety data quoted in the each TPC agent's Summary of Product Characteristics (SPC), as below, when developing hypotheses as to the incidence of adverse events associated with the individual products:

- Neutropenia (All grades) occurred in 49% of patients on vinorelbine in the EMBRACE trial, whereas the incidence is 71.5% in the vinorelbine SPC (4).

- Peripheral neuropathy (Grades 3 & 4) occurred in less than 10% of patients in the EMBRACE trial for both eribulin and vinorelbine. This is consistent with the incidence reported in the vinorelbine SPC (4). (Please note as described in our submission that patients with pre-existing neuropathies of grade 2 or below were allowed entry to the EMBRACE study. This is in direct reflection of the reality facing patients at this late stage of disease. Critically, eribulin was not associated with an exacerbation of this toxicity in those patients who had already been compromised by neuropathies).

- The incidence of hand-foot syndrome commonly seen with certain chemotherapies, e.g. capecitabine [53%-60%] across monotherapy trials (5), occurred in only 1.4% of patients at any severity grade with eribulin.

- 91% of the intended dose intensity for eribulin was achieved demonstrating the well tolerated profile of the drug.

Finally the Appraisal Committee does not appear to have taken into account the submissions from patient groups in relation to the significance of the adverse event profile for eribulin. Breast Cancer Care, Breakthrough Breast Cancer and Breast Cancer Campaign described the side-effects associated with eribulin as “acceptable for a standard regime” and “likely to be manageable for patients in this setting”.

Side effects and their severity are clearly vital considerations. However, these must be balanced against the potential benefit to be derived from treatment. This is the realistic decision facing patients facing a new treatment option. For a patient who has exhausted all other available options and is desperate to extend her life, the opportunity to decide on the balance of known side-effects against the opportunity for extended life should be available. The current negative ACD would result in the patient in consultation with their oncologist not even having the option to make this decision.

It is relevant to highlight that in their role as the authority of determining the safety and efficacy of medicines, the CHMP have stated in the European Public Assessment Report that ‘Halaven’s (eribulin) benefits are greater than its risks and recommend that it be given a marketing authorisation’. NICE are clearly within their right to evaluate the clinical and cost-effectiveness however drawing a different conclusion from the CHMP on the benefit/risk profile for clinical effectiveness is highly questionable.

The ACD has not adequately considered the overall safety profile of eribulin in circumstances where, despite the fact that EMBRACE was likely to underestimate adverse events in the TPC arm, the incidence of serious adverse events and adverse events leading to treatment delays or modifications and fatal adverse events were almost identical in both groups. The side effects are manageable for such a heavily pre-treated MBC population and have minimal impact on the ICER.

2. Reliance on the analysis of data from Region 1 of EMBRACE

Eisai does not agree that the results from the overall ITT population are more applicable to the UK than the Region 1 population.

There is extensive research proving that regional differences play an important role in impacting patient outcomes. Differences occur for various reasons including availability of treatments, national screening policies, social and economic conditions.

When conducting a global study treatment differences can exist particularly when using TPC and for this reason the geographical regions were included as a pre-planned stratification factor in EMBRACE. Region 1 (the EU, North America and Australia) was identified as being most likely to reflect the UK population and an analysis of the data from these participants specified in the trial protocol was used to inform a comparison of the relative benefits of eribulin against standard therapies in this region. NICE has regularly requested manufacturers to present data for the local population where available for understandable reasons. Eisai, in discussion with Global regulatory authorities, therefore ensured that such an analysis was pre-planned to avoid bias and demonstrate any differences in how therapy takes effects in different regions given this is not uncommon.

The ERG has only looked at the mean survival between the three regions. Means are misleading when reporting survival data. In addition a non-significant p value does

not mean that there is not a meaningful difference between the groups. This draft guidance failed to acknowledge how patients were managed within the regions and this is what determines outcomes.

When considering the generalisability of the ITT population from EMBRACE versus the population from Region 1, the ERG states that the results from Region 1 should not be preferred to the ITT population as a result of (a) its conclusion that the patient characteristics in Region 1 do not differ from those in the remainder of the trial population; and (b) the fact that the EU marketing authorisation for eribulin was based on the results of the overall EMBRACE population (pages 36-37 ERG report).

The Appraisal Committee's reasons for preferring the analysis based on the ITT population are: (a) the differences in survival between Region 1 and the overall ITT population are evident only for the comparator arm; (b) patients in Region 1 did not differ in terms of overall prognosis from the remainder of the trial population; (c) the advice of the clinical specialist "that UK practice in the management of advanced breast cancer differs considerably from some areas of Region 1" (e.g. in North America there is a greater reimbursement incentive for drugs that are administered intravenously, resulting in greater use of vinorelbine relative to capecitabine than in the UK); and (d) the EU marketing authorisation for eribulin was based on the results of the overall EMBRACE population.

Eisai believes these explanations are either invalid or do not provide a proper basis for reliance on the ITT population rather than the analysis based on patients from Region 1.

The reason for the pre-specified geographical stratification in EMBRACE was Eisai's concern that the particular therapies included in the TPC arm of the study would not be consistent across all regions, as was subsequently demonstrated by the trial data. Reasons (a) and (b) above are accordingly consistent with differences in overall survival between the Region 1 and the ITT populations being attributable to the particular TPC used in the different regions and the associated effect on outcomes. Furthermore, there were differences in baseline characteristics between patients in Region 1 and the other two regions, which do not appear to have been taken into account by the ERG in reaching its conclusions:

- Region 2 and 3 contained higher proportion of patients with less than 3 prior chemotherapy regimens. This implies that patients in these regions had received less intensive treatment and any new anti-cancer therapy would result in improvement (as the patients' baseline condition represents a condition that had received minimal intervention).

- In all geographic regions Her2 negative patients comprised the bulk of the patient population. However Her2 unknown patients comprised a larger percentage of the Eastern Europe (~20%) and Latin America (~20%) regions as compared with North America/Western Europe (~4%). [~75% of all Her2 unknown patients were from region 2 and 3].

Across all regions the most commonly prescribed TPC treatments were: vinorelbine, gemcitabine and capecitabine. However hormonal medications were predominantly prescribed in Eastern Europe (71% of total hormonal anti-cancer use for the study) whereas in Region 1, it was 19%. Vinorelbine use in Region1 accounted for 74% of

total anti-cancer use for the study and only 14% in Region 2. Capecitabine use was more balanced with Region 1 accounting for 44% and Region 2 for 45% of total use but gemcitabine was 53% in Region 1 and 30% in Region 2.

Thus one can see that the mix of therapies used as TPC in Region 2 is not therefore in keeping with UK practice. The current NICE guidelines on advanced breast cancer recommend vinorelbine or capecitabine in patients with advanced metastatic breast cancer that have been treated with previous lines of treatment and thus Region 1 best reflects the current management and therapies of those patients with advanced metastatic breast cancer in England and Wales.

In addition, the results in Region 1 are most impressive as this is the region that had the greatest choice in treatment and consisted of patients who were more heavily pre-treated. Actually it is more difficult to demonstrate a benefit in such a late stage heavily pre-treated patient population.

Reason (c) is based on advice of a single clinical specialist, with whom the company disagrees. Furthermore, if there are any additional examples of ways in which the Committee believed that UK management of advanced breast cancer differs from practice in parts of Region 1, we request details of these so that we may provide a considered response before the next meeting of the Appraisal Committee. The comment regarding the 'reimbursement incentive' determining clinical decision making by oncologists in North America seems especially unfair. A similar accusation could be made in the UK where hospital waiting lists and additional resource challenges may be cited as a reason to encourage use of oral therapies but hospital reimbursement is greater for in-patient stays. We believe this is an erroneous point that does little to inform the relevance of the region specific analyses which is based purely on clinical grounds.

Finally, NICE's assessment differs from that carried out by the regulatory authority considering whether a marketing authorisation should be granted and reason (d) does not therefore justify reliance on the ITT population, rather than an analysis based on patients from Region 1. While the ITT population may be most appropriate for the regulatory assessment of safety and efficacy, the Region 1 population best meets the requirements for NICE's evaluation which focuses on the magnitude of clinical benefit in a patient population as close as possible to that in the UK.

Region 1 best reflects the manner and type of treatments patient in the UK would be expected to receive for MBC. NICE have repeatedly stated that manufacturers should generate data relevant for the UK population. Therefore, Region 1 should be accepted as the most relevant population on which to base recommendations for eribulin in the UK.

3. Applicability of the End of Life advice

It appears that the Appraisal Committee has accepted that eribulin meets 2 out of the 3 criteria for end of life, namely that patients eligible for treatment have a life expectancy less than 24 months and that eribulin is indicated for a small patient population.

The conclusion that eribulin does not meet the third criterion, a survival benefit of at least three months, is based on an assessment of data from the ITT population from EMBRACE. However, as mentioned above Region 1 best represent clinical practice in the UK rather than Regions 2 or 3 and Eisai firmly believes that the Committee's recommendations should be based on that patient population the overall survival gain in Region 1 (> 3 months) implies that the third criterion for end of life is met.

For completeness, the Committee will be aware that the End of Life advice issued by NICE did not impose an absolute requirement for a three month overall survival benefit, but simply stated that this would "normally" be the case. While Eisai believes that the data from Region 1, which demonstrates an overall survival benefit in excess of 3 months, should be relied upon, the Committee is also required to consider whether a lower benefit should qualify in this case. In this context, the Committee should consider the innovative nature of the treatment and the fact that, as recognised at paragraph 4.3 of the ACD, it is unusual for any technology to show an overall survival benefit at this stage of the treatment pathway. Once again, eribulin is the first and only single therapy to provide in a phase III RCT in such a heavily pre-treated population, evidence to extend overall survival versus current standards of care.

A pragmatic approach needs to be taken here when assessing end of life and no specific allowance for this has been made. Eisai's view is that NICE has chosen specifically the lowest figure in order not to all the end of life criteria when the evidence is contrary to this.

The overall survival benefit of eribulin vs:

- Region 1 is 3.1 months (prospective, protocol specified analysis)
- Capecitabine is 4.7 months
- Vinorelbine is 4.2 months
- Gemcitabine is 3.6 months
- Post capecitabine group is 2.9 months

To provide further context to inform this consideration, the end of life criteria need to recognise the different stages of disease and the nature of the interventions being evaluated. Had Eisai conducted the EMBRACE study against placebo, which was a valid consideration given the lack of registered options, then clearly a magnitude of benefit far greater than 3 months would have been achieved. However, in choosing an active comparator Eisai has sought to satisfy regulators and NICE that eribulin is associated with incremental innovation in this setting and is adding real value to the treatment armamentarium. It is for the committee to consider practically whether evidence of a 3 month gain over an active therapy in an earlier stage of metastatic disease is the same as a 3 month gain in a far advanced setting. The point is further illustrated below where a combination strategy approved by NICE in CG81 in a far earlier stage of advanced disease is presented alongside the data from EMBRACE:

Disease Stage	Control	Investigation	OS Gain	p-value
1st and 2nd Line	Paclitaxel	Gemcitabine + Paclitaxel	18.6, vs. 15.8m (+2.8m)	0.0489
3rd line +	TPC	Eribulin	Region 1 13.1m vs. 10.1 (+3m) ITT 13.2 vs. 10.5 (+2.5m)	0.009 0.014 (nominal)

4. Drug administration costs

It appears there are two ways that chemotherapy delivery is coded according to HRG.

- Chemotherapy delivery outpatient (30% of activities)
- Chemotherapy delivery day case and regular day/night. (70% of activities)

The difference is illustrated below and the ACD has not accounted for this in a weighted average manner but assumes only one way of coding chemotherapy delivery which is not the case. In addition eribulin has started to be used as a home delivery service and thus these costs may not apply.

	Chemo 1st	Chemo subsequent	Oral
Day case + regular day/ night	£207	£284	£152
Outpatient	£248	£212	£171

No account seems to have been taken about the efficiency savings that eribulin can offer:

- No reconstitution is required as eribulin is prepared in a ready-to-use formulation (thereby saving pharmacy preparation time).
- No routine pre-medication is required for hypersensitivity (less drug costs).
- Eribulin is given as a quick 2-5 minute infusion (less time in chemotherapy chair and nursing time).

5. Quality of life (QoL)

Eisai does not feel that the summary of the effect of Eribulin on health-related quality of life is a reasonable interpretation of the evidence.

Overall survival is recognised as the most definitive cancer outcome and is of most importance to patients and clinicians when making decisions regarding treatment options. In a recent survey, patients with breast cancer rated overall survival as the most important attribute of an advanced breast cancer treatment. Specifically, an overall survival advantage of 3 months versus no advantage was most influential in

the perceived value of chemotherapy. (6) This is consistent with the submissions of the patient groups in this appraisal.

As mentioned above, the duration of therapy in EMBRACE was longer in the eribulin arm than the TPC arm, reflecting the promising effect on patient's quality of life. In addition, it is worth noting that a 2009 systematic review of the clinical efficacy of cytotoxic agents in locally advanced or metastatic breast cancer patients pre-treated with an anthracycline and a taxane, found that both capecitabine and vinorelbine had very limited evidence of improvements in QoL. (7) Indeed this is also a conclusion made by NICE in CG81.

When the TPC consists of numerous drugs that are given at different dosing regimens it is very difficult to assess difference in QoL between a range of options. In these circumstances we do not believe it would have been appropriate to have measured QoL in EMBRACE. However, the phase II trials showed an improvement in QoL in those patients that responded to eribulin.

The Appraisal Committee was clearly concerned regarding the risk of alopecia associated with use of eribulin. While Eisai does not suggest that alopecia is an unimportant consequence of chemotherapy, it is important to take into account that patients eligible for eribulin have advanced metastatic breast cancer and have very few treatment options and no regulatory approved options; eribulin is the only technology with established regulatory benefits in this patient population. The most important consideration for patients at this stage of treatment for their advanced breast cancer is overall survival and, as stated by the patient organisations participating in this appraisal, patients may therefore tolerate the side-effects of treatment if they will gain other critically important clinical benefits.

A study assessed psychosocial morbidity in patients with breast cancer and compared the differential rates between patients with early stage (n=303) and advanced disease (n=200). In this study, of the 31% of patients with early breast cancer who experienced hair loss, 77% found this to be distressing. In contrast, this percentage halved in patients with metastatic breast cancer i.e. of the 29.5% who experienced hair loss, 38.6% found it to be distressing (8).

The patient organisations also confirmed in their submissions that the side-effects associated with eribulin were "manageable". By way of example, there are various methods that can be used to minimise drug induced alopecia e.g. cold cap.

- **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

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

The quantity and quality of the available evidence regarding the efficacy of particular chemotherapy regimens in patients with advanced metastatic breast cancer pre-treated with an anthracycline and a taxane is extremely limited. New effective therapies are sorely needed in this patient population. For the first time a single agent has shown an improvement in overall survival in this patient population. None of the

currently available cytotoxic agents have shown this and as such the outcome of these patients is poor and there remains a high level of unmet clinical need.

When eribulin is evaluated against specific comparators as specified in the NICE scope, the manufacturer has shown that eribulin is cost effective. However this analysis has been ignored by ERG and in the ACD and no demonstration of cost effectiveness against specific comparators agents has been performed. This is irrational as eribulin would be replacing a comparator when used in practice not a pool of treatments.

For overall survival, rather than a surrogate marker of efficacy, to be the primary endpoint in advanced metastatic breast cancer trials is rare. In an exhaustive literature review, only 5 of 76 major phase III clinical studies of systemic therapy in metastatic breast cancer defined overall survival as their primary endpoint, and <u>none</u> met this primary endpoint (9).

The current recommendation denies patients and their families' access to a proven medicine that prolongs life and the opportunity for the NHS to improve cancer outcomes in advanced metastatic breast cancer.

Eribulin is a first in class novel agent with robust evidence to extend life, which is being offered to the NHS via the proposed PAS at a price that is LOWER than the price of NICE approved chemotherapy (Taxotere) that was approved over a decade ago. In addition to the weight of clinical evidence and innovation, this lower acquisition cost to the NHS should also be considered alongside the relatively superior profile of eribulin compared to currently available intravenous chemotherapy options including a short 2-5 minute infusion, a lack of requirement of pre-medication to address hypersensitivity reactions, and a ready to use formulation.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?**

None.

- **Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?**

None.

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Kate Moore
Technology Appraisal Project Manager
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8 August 2011

Dear Ms Moore,

Eribulin for the treatment of locally advanced or metastatic breast cancer

Breakthrough Breast Cancer is a pioneering charity committed to the prevention, treatment and ultimate eradication of breast cancer. We fight on three fronts: research, campaigning and education. Our aim is to bring together the best minds and rally the support of all those whose lives have been, or may one day be, affected by the disease. The result will save lives and change futures – by removing the fear of breast cancer for good.

This submission reflects the views of Breakthrough, based on our experience of working with people with personal experience of, or who are concerned about, breast cancer. We regularly consult with members of our Campaigns and Advocacy Network (Breakthrough CAN) for their views on a range of breast cancer issues. Originally founded by women with personal experience of breast cancer, Breakthrough CAN brings together over 1,700 individuals, regional groups and national organisations to campaign for improvements in breast cancer research, treatments and services. Through supporting and training members to become patient advocates in their own right, Breakthrough CAN aims to increase the influence of patients in decisions regarding breast cancer issues.

Breakthrough welcomes the opportunity to comment on the appraisal consultation document regarding the use of eribulin for the treatment of locally advanced or metastatic breast cancer in people whose disease has progressed after at least two chemotherapeutic regimens for advanced disease.

Has all of the relevant evidence been taken into account?

There is no cure for metastatic breast cancer and treatment options are used to alleviate symptoms, delay progression or improve survival. It is therefore essential more treatment options are made available to this patient group. If treatments can prolong survival this may give patients extra time to spend with their family and loved ones. For patients with metastatic breast cancer the importance of this should not be underestimated.

The EMBRACE trial, which assessed eribulin versus treatment of physician's choice for metastatic breast cancer, demonstrated a statistically significant median overall survival benefit of 2.5 months (updated to 2.7 months after later analysis) for patients treated with eribulin. This is noteworthy as an extra few months of survival for metastatic patients is important to these patients and their families. Indeed, as stated in the Appraisal Consultation Document (ACD) both clinical specialist and patient expert stated to the Committee that an overall survival benefit in advanced breast cancer at this stage in the clinical pathway was unusual and stressed the importance of having additional treatment options when previous chemotherapy regimens had failed.

However, Breakthrough does accept that the manufacturers had not collected health-related quality of life data during the EMBRACE trial and that this omission leaves questions around how potential side effects of eribulin may impact patients. This is important as it has been suggested that eribulin is less well tolerated than capecitabine and vinorelbine, comparators to eribulin, and can lead to side effects including peripheral neuropathy and alopecia. These side effects have the potential to impact a patients quality of life since the patient may have already experienced them earlier in the treatment pathway and not wish to experience them again. However, it is worth considering that due to its toxicity profile eribulin would only be given as a third- or fourth-line treatment for metastatic breast cancer and so would be unlikely to replace capecitabine and vinorelbine in the established treatment profile. Patients with advanced breast cancer have limited treatment options so they may wish to have access to more therapies regardless of certain side effects. Additionally, it should not be overlooked that the manufacturer did submit data on quality of life although we appreciate this was from Phase II trial data and did not include a comparator arm. Nevertheless, the manufacturer reported that patients whose disease had responded to eribulin did not report deterioration in quality of life.

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Patron HRH The Prince of Wales

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

We are disappointed the Appraisal Committee is unable to recommend eribulin for the treatment of locally advanced or metastatic breast cancer. However, we acknowledge there are concerns regarding the quality of life data included by the manufacturer. No health-related quality of life data were collected during the EMBRACE trail and instead data were presented from two phase II trials. Unfortunately, these trials were not without limitations and as stated by the Committee did not include a comparator arm and may have excluded some potentially important adverse events.

Although the toxicity profile of eribulin is reported to be higher than comparators capecitabine and vinorelbine it is worth noting that because of limited treatment options available to metastatic breast cancer patients, especially third- or fourth-line treatment options, they may be more willing to accept adverse side effects of chemotherapy, especially if it means they may see benefits such as longer survival. Providing accurate information about possible side effects can assist patients in making decisions relating to their treatment.

Breakthrough accepts there are uncertainties regarding the exact cost per QALY and what evidence should be included in this calculation. We therefore accept this makes eribulin difficult to approve at this time.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

It is disappointing that the committee is unable to recommend eribulin for the treatment of locally advanced or metastatic breast cancer. As a patient organisation, Breakthrough Breast Cancer would like to emphasise how crucial it is for this patient group to have a variety of treatment options.

However, we accept that no health-related quality of life data was collected during the EMBRACE trial and this has led to uncertainties around how well eribulin is tolerated in the patient population. We therefore support the recommendation that further research be conducted on health-related quality of life to compare eribulin treatment with that of vinorelbine and capecitabine.

We appreciate the advice from NICE on assessing end-of-life treatments state these treatments should offer an extension of life ‘of normally at least three additional

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months compared to current NHS treatments'. However, upon updated analysis the median overall survival benefit of patients receiving eribulin was 2.7 months. The use of the word 'normally' here is significant and we would argue 2.7 months is very close to 3 months. Since the other two end-of-life criteria were met – that is the patients' life expectancy is short and the treatment is indicated for a small patient population – we would suggest eribulin does fulfil all the criteria for a life-extending, end-of-life treatment.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

None of which we are aware.

Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?

None of which we are aware.

If you require any further information please contact [redacted] on [redacted] or [redacted]

Yours sincerely,

[redacted]

[redacted]

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Professor Carole Longson
Director, Centre for Health Technology Evaluation
By email

From [redacted]

5 August 2011

Dear Professor Longson

Re: Eribulin for the treatment of locally advanced or metastatic breast cancer - ACD

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 25,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

I write on behalf of the NCRI/RCP/RCR/ACP/JCCO who jointly submit responses to NICE oncological consultations. We are grateful for the opportunity to respond to the above ACD and would like to make the following comments.

Has all of the relevant evidence been taken into account?

Yes, the EMBRACE study forms the major part of the submission and relevant data.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes. There were concerns at the appraisal meeting regarding the lack of quality of life data in the main study and also regarding inaccuracies of supportive care costs. The post-hoc analysis of splitting by treatment of physicians choice was appropriately disregarded.

There was much discussion regarding whether it was appropriate to take geographical Region 1 data or overall ITT data for overall survival analysis. This point is critical when the end-of-life criteria are considered as by taking Region 1 data alone, the OS benefit rises above the cut-off value of 3 months. However, it was felt that using overall ITT population was more appropriate for applying to UK practice (which does not necessarily mirror North American practice).

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Yes

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

No.

Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?

No.

Yours sincerely

[redacted]

[redacted]

NHS North Central London
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8th August 2011

FAO: Kate Moore
National Institute for Health and Clinical Excellence

Dear Kate,

RE: Eribulin - metastatic breast cancer

On behalf of NHS North Central London Camden borough presence, I would like to submit our comments on the appraisal consultation document for **Eribulin - metastatic breast cancer**. We are in agreement with the recommendations in the ACD to not recommend **Eribulin** for this indication on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective in real life clinical practice.

- Unit costs: Prior to the release of the ACD, UK cost information for eribulin was not available. The manufacturer reported that a vial of 1.0mg eribulin mesylate costs £313. The manufacturer has agreed a patient access scheme with the Department of Health, but the discount agreed is commercial in confidence information and not available in the ACD. Eribulin is given as a dose of 1.4mg/m2 eribulin mesylate on days 1 and 8 of a 21 day cycle. Based on an average body surface area of 1.74m2, as used in manufacturer's submission, the average undiscounted cost per cycle is estimated to be £1,878 (assuming wastage). In the EMBRACE trial participants received an average of 5 cycles of eribulin, which suggests an average undiscounted cost for eribulin treatment of £9,390 per patient. The patient access scheme would reduce this cost; costs may also vary in different settings because of negotiated procurement discounts.

- Affordability: The number of patients who would be eligible for treatment with eribulin is uncertain. There are estimated to be 23 cases of advanced breast cancer per 100,000 population each year. Only a small proportion of these will require third-line (or subsequent) therapy (i.e. the indication for which eribulin is approved). In their submission to NICE, the manufacturer of eribulin estimated that about 10% of patients with locally advanced or metastatic breast cancer would receive third or subsequent line chemotherapy; this would equate to about 3 patients per 100,000 population each year being eligible for eribulin. If all of these patients received eribulin, this would equate to a cost of £28,170 per 100,000 population per year (not including patient access discount). However, the clinical specialist advising the Committee noted that due to its toxicity profile, eribulin was unlikely to displace capecitabine or vinorelbine in the existing treatment pathway, and would be given after these therapies. This might reduce the number of people who would receive eribulin.

- Efficacy: Evidence on efficacy came from the EMBRACE international multicenter phase III RCT, as well as three uncontrolled phase II studies. The RCT compared eribulin with treatment of the physician's choice (TPC). The manufacturer provided subgroup analyses comparing eribulin versus the individual treatments used in the comparator group, and looking at the results for different geographical regions (e.g. region 1 included North America, Western Europe, and Australia). The results of the efficacy analysis by comparator are not available as

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they were commercial in confidence. The evidence review group felt that the sub-group analyses by comparator should be treated with caution, as they were post-hoc, included small numbers of patients, and did not adjust appropriately for multiple testing.

- Overall survival: In their primary analysis (after 55% of participants had died) the EMBRACE trial found that eribulin monotherapy improved median overall survival by 2.5 months (13.1 months with eribulin vs. 10.6 months with TPC; HR 0.809, 95% CI 0.660 to 0.991). In an updated analysis (after 77% of participants had died) this difference increased to 2.7 months (median survival: 13.2 months with eribulin vs. 10.5 months with TPC; HR 0.805, 95% CI 0.667 to 0.958). The manufacturer also presented planned subgroup analyses for region 1 participants, as they felt this was more generalisable to UK clinical practice. In region 1, eribulin increased median overall survival by 3.1 months (13.1 months with eribulin vs. 10.0 months with treatment of the physician's choice; HR 0.724, 95% CI 0.568 to 0.924; data as reported by the manufacturer for their primary analysis). However, the Committee did not agree that region 1 data was more appropriate for consideration.

- Progression free survival (PFS): In EMBRACE, eribulin increased PFS compared to TPC if progression was assessed by investigator review (3.6 months vs. 2.2 months, p=0.002) but not by independent review (3.7 months vs. 2.2 months, p=0.137). The manufacturer reported that this difference arose because more patients were censored in the independent review.

- Quality of life (QoL): The EMBRACE RCT did not look at QoL, so data was reported from two phase II studies. These studies were uncontrolled, so it was not possible to determine whether QoL with eribulin differs from other treatment options. The Appraisal Committee considered that QoL is an important outcome in advanced cancer, and therefore this was an important omission from the RCT. Data on QoL from the phase II trials was not used to assess utility in the cost-effectiveness analysis.

- Safety: Treatment-related serious adverse effects were more common in the eribulin group (11.7%) than the TPC group (6.9%), but discontinuations due to adverse events were lower with eribulin (13.3% versus 15.4%). The manufacturer reported that most adverse events were mild or moderate. Adverse events that were more common with eribulin than TPC included: asthenia/fatigue (53.7% vs. 39.7%), alopecia (44.5% vs. 9.7%), peripheral neuropathy (34.6% vs. 16.2%), arthralgia/myalgia (21.7% vs. 11.7%), and febrile neutropenia (4.6% vs. 1.6%). The clinical specialist advising the Committee noted that trial data indicate that eribulin is less well tolerated than capecitabine and vinorelbine, and is associated with peripheral neuropathy and alopecia in particular. Alopecia was highlighted as an important consideration for patients at this stage of treatment as they may already have had hair loss earlier in the treatment pathway.

- Quality of the research: There was only one RCT available (the EMBRACE trial) which provided the majority of the evidence about clinical effectiveness of eribulin. The treatments included in the comparator arm of this RCT were considered to be a reasonable reflection of UK practice, except for the use of gemcitabine monotherapy, which was thought likely to be less common in the UK than in the trial. The RCT did not report on health related quality of life, which was considered by the Committee to be an important omission. Information on the effects of eribulin on quality of life had to be obtained from weaker sources (small non-comparative phase II trials of eribulin).

- Cost-effectiveness: The manufacturer used efficacy data from region 1 in its base case analysis along with utility data from published literature on UK societal preferences in metastatic breast cancer. They used a trial duration time horizon, and assumed that all patients still alive at the end of the trial entered a 'terminal' state. They based utilities on disease state and grade 3 or 4 treatment-related toxicities (only those that were present in 10% of participants or more were included). The analysis took into account the patient access scheme agreed with the Department of Health. Their base case yielded an ICER for eribulin of £46,040 per QALY

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gained compared with treatment of the physician's choice, £27,183 per QALY gained compared with gemcitabine, £35,602 per QALY gained compared with vinorelbine, and £47,631 compared with capecitabine. Using data for the overall population of the trial rather than just region 1 data gave an ICER for eribulin of £50,100 per QALY gained compared to treatment of the physician's choice.

- The Evidence Review Group (ERG) made a number of adjustments to the manufacturer's model, including correcting minor errors, adjusting costs and utilities, assuming vinorelbine is given in its generic intravenous formulation rather than its branded oral formulation, incorporating the cost and disutility associated with febrile neutropenia, adjusting source of progression-free survival data, and including projected overall survival to the end of life rather than to the end of the trial period. They also used data for the overall trial population rather than those from region 1 only. These adjustments resulted in an ICER for eribulin of £68,590 compared with treatment of the physician's choice. Eribulin provided 0.1229 additional QALYs for an additional cost of £8,269 in this analysis.

- The Appraisal Committee supported the ERG's adjustments to the model, and considered that their estimated ICER (£68,590 per QALY gained) provided the most plausible estimate. They considered that this figure was still likely to be an underestimate of the true cost per QALY gained as it did not incorporate the full toxicity profile of eribulin (e.g. the disutility associated with alopecia), the uncertainty about quality of life effects of eribulin, the fact that the estimate included median cost of available formulations of comparators rather than that of generic formulations where available, and the fact that in practice vinorelbine is often used in a less frequent schedule than that used in the model due to toxicity.

- Additional factors: The Appraisal Committee judged that the technology did not meet criteria for using end-of-life considerations. They considered that eribulin was indicated for patients with a short life expectancy (<24 months), and that it was likely to be licensed for a small patient population, but that it did not extend life in the overall trial population by at least 3 months compared with the comparator (treatment of the physician's choice). The manufacturer had shown that the median extension in survival in region 1 (North America, Western Europe, and Australia) was 3.1 months, but the Committee judged that it was more appropriate to consider the results of the trial as a whole. This was due to the small numbers of individuals in the region 1 group, the lack of a significant difference in overall survival between region 1 and the other regions, the fact that clinical practice in some of the region 1 areas differs considerably from that of the UK (e.g. that vinorelbine is used more than capecitabine in North America, which is not the case in the UK), and that European marketing authorisation was awarded based on overall data (rather than region 1 data). It also noted that even if the technology had met the end of life criteria, the high ICER meant that it would still not be considered a cost-effective use of NHS resources. No equality issues were raised.

Yours sincerely

[redacted]

[redacted]

[redacted] [redacted]

csas
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8th August 2011

FAO: Kate Moore
National Institute for Health and Clinical Excellence

Dear Kate,

RE: Eribulin - metastatic breast cancer

On behalf of Commissioning Support, Appraisals Service (CSAS), Solutions for Public Health, I would like to submit our comments on the appraisal consultation document for **Eribulin - metastatic breast cancer**. We are in agreement with the recommendations in the ACD to not recommend **Eribulin** for this indication on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective in real life clinical practice.

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Australia). The results of the efficacy analysis by comparator are not available as they were commercial in confidence. The evidence review group felt that the sub-group analyses by comparator should be treated with caution, as they were post-hoc, included small numbers of patients, and did not adjust appropriately for multiple testing.

- Overall survival: In their primary analysis (after 55% of participants had died) the EMBRACE trial found that eribulin monotherapy improved median overall survival by 2.5 months (13.1 months with eribulin vs. 10.6 months with TPC; HR 0.809, 95% CI 0.660 to 0.991). In an updated analysis (after 77% of participants had died) this difference increased to 2.7 months (median survival: 13.2 months with eribulin vs. 10.5 months with TPC; HR 0.805, 95% CI 0.667 to 0.958). The manufacturer also presented planned subgroup analyses for region 1 participants, as they felt this was more generalisable to UK clinical practice. In region 1, eribulin increased median overall survival by 3.1 months (13.1 months with eribulin vs. 10.0 months with treatment of the physician's choice; HR 0.724, 95% CI 0.568 to 0.924; data as reported by the manufacturer for their primary analysis). However, the Committee did not agree that region 1 data was more appropriate for consideration.

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- Quality of the research: There was only one RCT available (the EMBRACE trial) which provided the majority of the evidence about clinical effectiveness of eribulin. The treatments included in the comparator arm of this RCT were considered to be a reasonable reflection of UK practice, except for the use of gemcitabine monotherapy, which was thought likely to be less common in the UK than in the trial. The RCT did not report on health related quality of life, which was considered by

the Committee to be an important omission. Information on the effects of eribulin on quality of life had to be obtained from weaker sources (small non-comparative phase II trials of eribulin).

- Cost-effectiveness: The manufacturer used efficacy data from region 1 in its base case analysis along with utility data from published literature on UK societal preferences in metastatic breast cancer. They used a trial duration time horizon, and assumed that all patients still alive at the end of the trial entered a 'terminal' state. They based utilities on disease state and grade 3 or 4 treatment-related toxicities (only those that were present in 10% of participants or more were included). The analysis took into account the patient access scheme agreed with the Department of Health. Their base case yielded an ICER for eribulin of £46,040 per QALY gained compared with treatment of the physician's choice, £27,183 per QALY gained compared with gemcitabine, £35,602 per QALY gained compared with vinorelbine, and £47,631 compared with capecitabine. Using data for the overall population of the trial rather than just region 1 data gave an ICER for eribulin of £50,100 per QALY gained compared to treatment of the physician's choice.

- The Evidence Review Group (ERG) made a number of adjustments to the manufacturer's model, including correcting minor errors, adjusting costs and utilities, assuming vinorelbine is given in its generic intravenous formulation rather than its branded oral formulation, incorporating the cost and disutility associated with febrile neutropenia, adjusting source of progression-free survival data, and including projected overall survival to the end of life rather than to the end of the trial period. They also used data for the overall trial population rather than those from region 1 only. These adjustments resulted in an ICER for eribulin of £68,590 compared with treatment of the physician's choice. Eribulin provided 0.1229 additional QALYs for an additional cost of £8,269 in this analysis.

- The Appraisal Committee supported the ERG's adjustments to the model, and considered that their estimated ICER (£68,590 per QALY gained) provided the most plausible estimate. They considered that this figure was still likely to be an underestimate of the true cost per QALY gained as it did not incorporate the full toxicity profile of eribulin (e.g. the disutility associated with alopecia), the uncertainty about quality of life effects of eribulin, the fact that the estimate included median cost of available formulations of comparators rather than that of generic formulations where available, and the fact that in practice vinorelbine is often used in a less frequent schedule than that used in the model due to toxicity.

- Additional factors: The Appraisal Committee judged that the technology did not meet criteria for using end-of-life considerations. They considered that eribulin was indicated for patients with a short life expectancy (<24 months), and that it was likely to be licensed for a small patient population, but that it did not extend life in the overall trial population by at least 3 months compared with the comparator (treatment of the physician's choice). The manufacturer had shown that the median extension in survival in region 1 (North America, Western Europe, and Australia) was 3.1 months, but the Committee judged that it was more appropriate to consider the results of the trial as a whole. This was due to the small numbers of individuals in the region 1 group, the lack of a significant difference in overall survival between region 1 and the other regions, the fact that clinical practice in some of the region 1 areas differs considerably from that of the UK (e.g. that vinorelbine is used more than capecitabine in North America, which is not the case in the UK), and that European marketing authorisation was awarded based on overall data

www.sph.nhs.uk/appraisals
Tel: [redacted]
Email: [redacted]

(rather than region 1 data). It also noted that even if the technology had met the end of life criteria, the high ICER meant that it would still not be considered a cost-effective use of NHS resources. No equality issues were raised.

If you require any further information please contact me directly: Phone: [redacted], email [redacted]

Yours sincerely

[redacted]

[redacted]

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The guidance has been reviewed by the [redacted] for NHS Tameside and Glossop and is consistent with the evidence reviewed. This treatment is currently funded via the Cancer Drugs Fund within NHSNW, so if this guidance is not approved there will not be an immediate funding pressure for the PCT. However, in the longer term there could be consequences for funding of more cost effective interventions if the PCT is required to fund this treatment.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	8/9/2011 2:00:00 PM

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Location	England
Conflict	no
Notes	No
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	The Appraisal Committee needs to note that commissioners will be charged the discounted price plus VAT at 20%. Â Our experience with drugs approved by the NICE demonstrates that there are no local discounts obtained. The VAT of 20% is a significant burden for the NHS and should be considered by the Committee.
Section 3 (The manufacturer's submission)	We have similar concerns to those highlighted by the ERG Group regarding the manufacturers submission. We agree with the comments of the ERG group and adjustments made to calcualte the cost/ QALY. Â We have concerns about projecting overall and progression free survival from the number of patients alive at the end of the study as this would over-estimate these outcomes.
Section 4 (Consideration of the evidence)	We agree that Eribulin is not a cost-effective use of NHS resources. Â Whilst the treatment improves median survivial by 2.5 months compared to other treatments, the quality of this survival is not known but is increasingly important to patients. Â We note the less favourable toxicity profile of eribulin, especially alopecia, peripheral neuropathy and fatigue - these are important considerations for patients at end-of-life. We have real concerns about the quality of the research available and lack of health related quality of life measures. Â We understand from our local oncologists and palliative care consultants that patients, at the end-of-life would value being given the benefits and harms to make decisions on whether to continue being treated.
Section 5 (Implementation)	The exact number of patients who would be eligible to receive eribulin in preference to alternatives is uncertain. Â Applying the manufacturers estimate to NHS Hertfordshires population, it would cost Â£290k for drug plus about Â£160k for activity plus cost of associated drugs. Â With this level if investment, NHS Hertfordshire would be unable to develop pulmonary rehabilitation services for its population and would not be able to increase the number of hospice beds (8 beds planned). We would like to bring to the NICE our experience that the Costing template does not accurately reflect all the costs charged by providers and usually underestimates cost pressures.
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8	

(Proposed date of review of guidance)	
Date	8/9/2011 11:58:00 AM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Agree with these recommendations
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	In this indication this technology is not a cost effective use of NHS resources. The Appraisal Committee concluded that the most plausible ICER for eribulin monotherapy was in excess of Â£68,600 per QALY gained compared with treatment of physician?s choice. This ICER took into account a patient access scheme agreed by the Department of Health and the manufacturer of Eribulin. Eribulin monotherapy improves median overall survival by only 2.5 months compared with alternative treatments. Eribulin has a less favourable toxicity profile than alternative treatments. Treatment-related serious adverse effects were more common in the Eribulin group than the treatment of the physician?s choice. There were limitations to quality of the research available. There was only one RCT available (the EMBRACE trial) which provided the majority of the evidence about clinical effectiveness. The RCT did not report on health related quality of life, and this information had to be obtained from weaker sources (small non-comparative phase II trials of eribulin. Eribulin does not fulfil the end-of-life criteria, as it did not extend life by at least 3 additional months in the overall trial population.
Section 5 (Implementation)	The exact number of people who would be eligible to receive Eribulin (if approved) in preference to alternatives is uncertain. There are estimated to be 23 cases of advanced breast cancer per 100,000 population each year. Only a small proportion of these will require third line (or subsequent) therapy (i.e. the indication for which Eribulin is approved). Based on manufacturer?s estimates of the proportion of individuals with advanced breast cancer who receive third or subsequent line chemotherapy, about 3 people per 100,000 population each year might be eligible for Eribulin. The clinical specialist advising the Committee noted that due to its toxicity profile, Eribulin was unlikely to displace capecitabine or vinorelbine in the existing treatment pathway, and would be given after these

	therapies.
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	8/8/2011 3:36:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	No
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Agree
Section 2 (The technology)	End of life criteria (as laid down by NICE) not fulfilled, and the ICER is in excess of Â£68k even when patient access scheme is taken into account. It has little to recommend it over existing treatments as an infusion requiring hospital treatment Of the patient access schemes in place, most are not returning the money to the NHS that was predicted through NICE gudiance, and most are complicated to administer and audit. It requires a lot of NHS professional time - clinical and non clinical, and this is not taken into account by NICE.
Section 3 (The manufacturer's submission)	Only one RCT - no quality of life data - which is what youre loking for in a treatment at this stage, especially with the toxicity associated withthis treatment
Section 4 (Consideration of the evidence)	Agree - but also to emphasis that toxicity can adversely affect end of life and other treatments are available
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	Agree
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	8/8/2011 2:46:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	Network perspective from [redacted] Cancer Services: If used, this drug would be used between 3rd and 5th line. Increasing numbers of patients are fit enough for chemotherapy at that time and many would currently be offered an alternative chemotherapy schedule (as in the published trial). A guesstimate for the network would be around 30 -50/year. (But this would probably increase with time as clinicians became more familiar with use). Currently patients who might be eligible for eribulin are offered other chemotherapy drugs so this would have potentially little additional service impact in terms of capacity. The drug is administered as a short IV infusion on days 1 and 8 so may free up a bit of time on the chemo day unit (assuming it was replacing an IV treatment as opposed to oral e.g capecitabine or oral vinorelbine).
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	8/5/2011 1:40:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am in agreement with committees recommendations
Section 2 (The technology)	From local anecdotal experience, reimbursement under patient access schemes are not well implemented by local hospitals as it constitutes significant extra administrative burden for no obvious benefit for those undertaking the extra burden (usually hospital pharmacists). If this technology will be agreed this will have significant impact and opportunity costs in our local health economy as it will reduce the funding available for the development of a hospice centre that aims to provide care for the same group of patients that could benefit from this technology.
Section 3 (The manufacturer's submission)	Eribulin does not fulfil the end-of-life criteria, as it did not extend life by at least 3 additional months in the overall trial population. The manufacturer has reported that the median extension in survival in region 1 (North America, Western Europe, and Australia) was 3.1 months, but the Committee judged that it was more appropriate to consider the results of the trial as a whole. Eribulin meets the other end-of-life criteria, as it is indicated in patients with a short life expectancy (less than 24 months), and is likely to be indicated for a small population. However, the Committee noted that even if the technology had met all of the end-of-life criteria, the high ICER meant that it would still not be considered a cost-effective use of NHS resources.
Section 4 (Consideration of the evidence)	This technology is not a cost effective use of NHS resources. The Committee concluded that the most plausible ICER for eribulin monotherapy was in excess of Â£68,600 per QALY gained compared with treatment of physician?s choice. This took into account a patient access scheme agreed by DH and the manufacturer. Eribulin monotherapy improves median overall survival by 2.5 months compared with alternative treatments. One international multicenter phase III RCT in 762 patients found that eribulin monotherapy improved median overall survival to 13.1 months, from 10.6 months with treatment of the physician?s choice. The treatment of the physician?s choice in the comparator group was vinorelbine in 24.0%, gemcitabine in 18.1%, capecitabine in 17.3%, taxanes in 15.0%, anthracyclines in 9.4%, other chemotherapy in 9.8%, and hormone therapy in 3.5%. Eribulin has a less favourable toxicity profile than alternative treatments. Treatment-related serious adverse effects were more common in the eribulin group than physician?s choice

	(TPC) group (11.7% vs. 6.9%), but discontinuations due to adverse events were lower with eribulin (13.3% versus 15.4%).
Section 5 (Implementation)	The exact number of people who would be eligible to receive eribulin (if approved) in preference to alternatives is uncertain. There are estimated to be 23 cases of advanced breast cancer per 100,000 population each year. Only a small proportion of these will require third line (or subsequent) therapy (i.e. the indication for which eribulin is approved). Based on manufacturer?s estimates of the proportion of individuals with advanced breast cancer who receive third or subsequent line chemotherapy, about 3 people per 100,000 population each year might be eligible for eribulin. The clinical specialist advising the Committee noted that due to its toxicity profile, eribulin was unlikely to displace capecitabine or vinorelbine in the existing treatment pathway, and would be given after these therapies.
Section 6 (Proposed recommendations for further research)	There were limitations to quality of the research available. There was only one RCT available (the EMBRACE trial) which provided the majority of the evidence about clinical effectiveness. The RCT did not report on health related quality of life, and this information had to be obtained from weaker sources (small non-comparative phase II trials of eribulin).
Section 7 (Related NICE guidance)	no comment
Section 8 (Proposed date of review of guidance)	this is acceptable
Date	8/1/2011 2:07:00 AM

Name	[redacted]
Role	NHS Professional
Other role	chief pharmacist
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Recommendation 1.2 does not mean that PCTs can or will be able to fund this treatment in current patients if it is not recommneded by NICE. Â To do so would disadvantage new patients.
Section 2 (The technology)	The DH may not consider that PAS constitute an excessive administrative burden on the NHS but that is not consistent with evidence in practice. Â From local anecdotal experience, reimbursement under patient access schemes are not well implemented by local hospitals as it constitutes significant extra administrative burden for no obvious benefit for those undertaking the extra burden (usually hospital pharmacists).
Section 3 (The manufacturer's submission)	If this technology were to be agreed this will have significant impact and opportunity costs in our local health economy as it would reduce the funding available for the development of hospice care that aims to provide for the same group of patients that could benefit from this technology
Section 4 (Consideration of the evidence)	Haemotological toxicity was common with eribulin, with grade 3 neutropenia occurring in 21.1% of participants, and grade 4 neutropenia in 24.1%. The full costs of managing this are not fully reflected in the costs considered by NICE. Â They do however represent a substantial cost for PCTs, over and above the costs shown. Adverse events that were more common with eribulin than with TPC included alopecia (44.5% vs. 9.7%), peripheral neuropathy (34.6% vs. 16.2%), and febrile neutropenia (4.6% vs. 1.6%). Alopecia was highlighted as an important consideration for patients at this stage of treatment as they may already have had hair loss earlier in the treatment pathway
Section 5 (Implementation)	For my PCT adding yet another, barely effective, line of therapy would mean paying for around 18 patients. Â Local experience suggests that this would be used after existing third-line alternatives. Â This could mean Â£500,000 a year taken away from care of people with dementia, and from patients with conditions where treatment could substantailly affect quality and length of life. Â This is not an appropriate use of resources.
Section 6 (Proposed recommendations for further research)	There was only one RCT available (the EMBRACE trial) which provided the majority of the evidence about clinical effectiveness. The RCT did not report on health related quality of life, and this information had to be obtained from weaker sources (small non-comparative phase II trials of eribulin). QoL studies for patients with late-stage breast cancer are needed in order to understand how quality of life is affcetd by these many extra lines of therapy
Section 7	lapatinib guidance?

(Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	This review date is after the planned end-date for teh Cancer Drugs Fund
Date	7/31/2011 10:31:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I agree with the appraisal committees preliminary recommendations on the basis that the drug fails to meet end of life criteria and would not be a cost-effective use of NHS resources.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	7/27/2011 10:26:00 AM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We would support these preliminary recommendations. Eribulin does not fulfil the end-of-life criteria, as it did not extend life by at least 3 additional months in the overall trial population. Please clarify 1.2 to say that patients already receiving eribulin "WITH NHS FUNDING" should have the option to continue therapy...etc. Privately funded patients should NOT have the option to continue treatment with NHS funding.
Section 2	

(The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	There were limitations to quality of the research available. There was only one RCT available (the EMBRACE trial). Eribulin monotherapy improves median overall survival by 2.5 months compared with alternative treatments. One international multicenter phase III RCT (the EMBRACE trial) in 762 patients found that eribulin monotherapy improved median overall survival to 13.1 months, from 10.6 months with treatment of the physician?s choice (HR 0.809, 95% CI 0.660 to 0.991). The treatment of the physician?s choice in the comparator group was vinorelbine in 24.0% of participants, gemcitabine in 18.1%, capecitabine in 17.3%, taxanes in 15.0%, anthracyclines in 9.4%, other chemotherapy in 9.8%, and hormone therapy in 3.5%. Eribulin has a less favourable toxicity profile than alternative treatments. Treatment-related serious adverse effects were more common in the eribulin group than the treatment of the physician?s choice (TPC) group (11.7% vs. 6.9%), but discontinuations due to adverse events were lower with eribulin (13.3% versus 15.4%).
Section 5 (Implementation)	The exact number of people who would be eligible to receive eribulin (if approved) in preference to alternatives is uncertain. We have not received any individual funding requests and therefore there appears to be no local demand for this treatment.
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	8/9/2011 4:57:00 PM

Name	[redacted]
Role	NHS Professional
Other role	Associate Director of Public Health
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We agree with the Appraisal committee?s preliminary recommendation that Eribulin should not be recommended for treatment of locally advanced or metastatic breast cancer in people whose disease has progressed after at least two chemotherapeutic regimens for advanced disease as it is not a cost effective use of NHS resources for this indication.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	In this indication we do not consider eribulin to be a cost-effective use of NHS resources for the following reasons Clinical Effectiveness - -there were limitations to quality of the research available. There was only one RCT available (the EMBRACE trial) which provided the majority of the evidence about clinical effectiveness. This RCT did not report on health related quality of life, and this information had to be obtained from weaker sources (small non-comparative phase II trials of eribulin). Health related quality of life is an important outcome measure in advanced cancer and failure to assess this is a serious ommission. Eribulin monotherapy improves median overall survival by 2.5 months compared with treatment of physician choice but does not fulfil the criteria for being a life extending, end of life treatment, as it did not extend life by at least 3 additional months in the overall trial population. Eribulin has a less favourable toxicity profile than alternative treatments.Cost effectiveness ? the ICER for eribulin is likely to exceed Â£68,000 per QALY gained compared with physician?s choice even when the patient access scheme is taken into account. Â Even if eribulin met the criteria for end of life treatment it would not be cost effective for this indication.
Section 5 (Implementation)	If eribulin were to be approved for this indication by NICE we have significant concerns regarding affordability for our PCT. The exact number of people who would be eligible to receive eribulin if it were to be approved in preference to alternatives is uncertain. There are estimated to be 23 cases of advanced breast cancer per 100,000 population each year. Only a small proportion of these will require third line (or subsequent) therapy (i.e. the indication for which eribulin is approved). Based on manufacturer?s estimates of the proportion of individuals with advanced breast cancer who receive third or subsequent line chemotherapy, about 3 people per 100,000 population each year might be eligible for eribulin. For our PCT we estimate that the cost of treating the eligible population would be Â£364,000 per annum which may be reduced to Â£300,000 with discount. With discounting this is still a very significant cost and would inevitably impact on other cancer

	services that the PCT commissions. As an example Â£ 300,000 equates to 2,300 radiotherapy fractions ? just under 4.5% of the radiotherapy fractions that our PCT commissions each year.
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	
Date	8/9/2011 4:39:00 PM

Name	[redacted]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	No
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	This is reasonable as eribulin is an expensive option but patients already on it should be allowed to continue
Section 2 (The technology)	This is a new agent and quite well tolerated. Toxicity is comparable with other agents.
Section 3 (The manufacturer's submission)	The manufacturers submission is appropriate. Trial was company-sponsored.
Section 4 (Consideration of the evidence)	This appropriate. The data are not srtrong but a very select group of patients may benefit from this treatment. It should not be used in patients who progress.
Section 5 (Implementation)	Eribulin is not currently funded in the North West. It has been considered and prioritised against other drugs and will be funded through the North West Cancer Drugs Fund for a highly selected group of patients.
Section 6 (Proposed recommendations for further research)	This is appropriate
Section 7 (Related NICE guidance)	Fulvestrant guidance will be welcome
Section 8 (Proposed date of review of guidance)	This is appropriate
Date	8/9/2011 3:56:00 PM

Please see below response from our [redacted], [redacted].

[redacted] supports NICE in that this technology is not recommended for the following reasons

1- It does not fulfil end-of-life criteria in that it did not extend life by 3 months or more in the overall trial population

2- The trial evidence for health related quality of life was derived from low grade evidence i.e. small non-comparative phase 11 trials

3- Eribulin is associated with more serious adverse effects than other standard therapy.

4- Eribulin is not a cost effective use of NHS resources at £68,000 per QALY

[redacted]
[redacted]
NHS Luton
[redacted]
[redacted]
[redacted]
Tel: [redacted]
e-mail: [redacted]

Eribulin for the treatment of locally advanced or metastatic breast cancer

Appendix: Additional evidence in response to the Appraisal Consultation Document (ACD)

August 2011

Eisai would like NICE to consider the use of eribulin within its licensed indication for post capecitabine patients in the management of locally advanced or metastatic breast cancer (MBC). This population is narrower than that proposed in the submission and we demonstrate a more favourable cost-effectiveness ratio in this restricted population. Sensitivity analysis across a number of possibilities demonstrates that the ICER ranges between £26,000 to £41,000 (without end of life), and with end of life after adjusting utilities well below £30000.

Clinical evidence

In response to the ACD, Eisai are presenting here additional evidence from the EMBRACE trial in the form of the results from the pre-planned stratification group of patients who had received prior treatment with capecitabine.

In the pivotal phase III EMBRACE trial, patients were pre-stratified according to:

- geographical region,
- HER2 status,
- **and prior treatment with capecitabine**

In the pivotal phase III EMBRACE trial **74% of patients had received prior capecitabine**.

Treatment practice in MBC has evolved with the use of the taxanes in the earlier 'adjuvant' setting. This has left an obvious void of evidence in the metastatic setting if a re-challenge with a taxane is not an appropriate course of action. Whilst the evidence is sparse, capecitabine is utilised in later stages of breast cancer. This was proven in our own EMBRACE study where over 74% of patients had received prior capecitabine. In light of this the evidence for eribulin in patients treated post-capecitabine is very significant as it offers this relatively small group of women with an evidence-based option proven to extend survival.

Primary outcome

Overall survival was defined as the time from the date of randomisation until death from any cause.

Table 1

Parameter (Post capecitabine)	Treatment Group	
	Eribulin (N=370)	**TPC (N = 184)**
Number of patients who died	291	154
Median	395 days	308 days
(95% CI)	(355,421)	(235, 356)
Hazard Ratio (95%CI)	0.787(0.645;0.961)	
p value (log rank)	0.018	

Median overall survival is significantly improved in patients assigned to eribulin vs. TPC by 2.9 months in the post capecitabine population.

This proposed positioning for eribulin fits with current NICE guidelines (NICE Clinical Guideline 81), which states that systemic chemotherapy should be offered in the following sequence:

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

Considering that capecitabine is used earlier in MBC, it is reasonable to expect that eribulin will be used after capecitabine; thus the most relevant comparator is vinorelbine.

As stated in the NICE guidelines '*The level of evidence on the use of vinorelbine as a monotherapy or in combination with other agents is generally of very poor quality consisting mainly of low patient number, non-comparative phase II trials or small RCTs. As such, the findings from these studies should be interpreted with caution. The majority of patients were believed to have had prior anthracycline therapy'.*

'No evidence was available for the effectiveness of third-line therapy, so both capecitabine and vinorelbine monotherapies were <u>assumed</u> to work as well as for second-line therapy'.

It should be stressed that in the pivotal phase III EMBRACE trial, eribulin is the first single agent that has shown a significant improvement in overall survival in patients with advanced MBC pre-treated with an anthracycline and a taxane. None of the currently available cytotoxic agents have shown this in this population.

<u>Validity of the Incremental Benefit</u>

The nature of using a study that has treatment of physician's choice (TPC) means that no one drug made up the majority of the comparator arm. Necessarily, this reduces the power of the study to detect incremental benefit compared to individual drugs.

However, a meta-analysis can show that the performance of the drugs used in the TPC arm is consistent with the performance they demonstrated in other clinical studies. With the evidence base for eribulin, one can compare the median duration of survival of patients taking eribulin with those that took the relevant drug in the EMBRACE trial and those that took that particular drug in all studies. (Appendix 1)

Table 2

Improvement in overall survival of eribulin vs. vinorelbine (EMBRACE trial- ITT Population)	**Improvement in overall survival of eribulin compared to the meta-analysis results**
4.2 months	4.33 months

When the median overall survival gain that was seen in the EMBRACE trial that evaluated eribulin vs. vinorelbine is compared to a recently published meta-analysis in The Lancet Oncology medical journal in May 2011, it is clear from the above analysis that the estimated difference in median overall survival demonstrated in the EMBRACE trial for vinorelbine is consistent with a meta-analysed estimate in a similar patient population. (Appendix 1)

These results provide confidence in the estimated mean differences generated from the modelling of the EMBRACE trial for the cost effectiveness analysis for vinorelbine.

End of life

Based on NICE's supplementary advice on end-of-life treatment, eribulin meets these criteria. That is, it is indicated for a relatively small number of patients, the medicine is indicated for the treatment of patients with a diagnosis of a terminal illness and who are not, on average, expected to live for more than 24 months, and eribulin provides an additional extension of 3 months of life compared to current NHS treatment:

- In the post capecitabine population the mean survival gain is 2.97 to 3.19 months vs. TPC (using 35-50% prediction)
- In the eribulin vs. vinorelbine (post capecitabine) population the mean survival gain is 4.5 to 4.9 months (using 35-50% prediction).

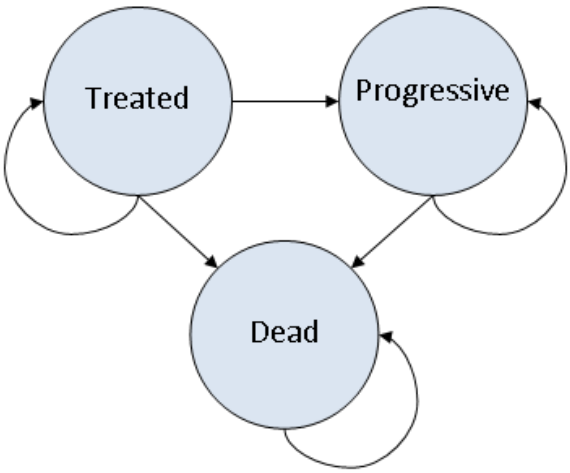
In this context, the Committee should consider the innovative nature of the treatment and the fact that none of the available treatments have shown an overall survival benefit at this stage of the treatment pathway in MBC. . Furthermore, the increment must be considered in the context that this is the most advanced breast cancer population for which NICE has been asked to provide guidance (eribulin is the first and only agent registered in this population). Secondly, the difference is compared to an active control. Had the study been compared to placebo (a valid option given the absence of registered alternatives) it is clear that the incremental benefit would have exceeded 3 months. However, Eisai and the EMBRACE investigators sought to compare eribulin to a more relevant and active comparator and this approach must be encouraged.

Economic Analysis of Eribulin

Model Design

A semi-Markov state transition model was developed in Microsoft Excel to model the lifetime clinical and economic outcomes for a hypothetical cohort of patients with locally advanced or metastatic breast cancer. The model structure was adapted from published economic evaluations of breast cancer treatments.

Figure 1



All patients in the model were initially assigned to the treated health state, comprising both stable and responsive patients. Patients remained on the assigned treatment drug until disease progression or death.

Model Assumptions

Model construction and analysis employed the following key assumptions:

- Patients enter the model when they initiate treatment.
- Every 21 days (model cycle length) patients faced a risk of transition among health states based on tumor status or death.
- Patients in the treated state may develop treatment-related toxicities.
- Patients in the progressive state remain in this state until death.
- Patient utilities are a function of the health state and incidence of treatment-related toxicities.
- The risk of disease progression or death from the treated state is independent of tumor response.

Establishing Transition Probabilities

Transition probabilities were derived from data for overall survival (OS) and time to treatment progression (TTP) based on patient-level data from the EMBRACE trial.

These probabilities were evaluated at the end of each model cycle—21 days in the base case, corresponding to the eribulin dosing cycle—to inform transitions and consequent state assignments for the subsequent cycle. Cycles continued until all patients were in the dead state.

Each health state was associated with health-care resource costs that were assigned in each model cycle. Patients in the treated health state also incurred the costs of drug ingredients and administration, as well as grade 3 and grade 4 treatment-related toxicities. Each health state also had a corresponding utility that was assigned to estimate effectiveness. In the case of the treated state, different utilities for stable and responsive disease were used and weighted by the proportion of patients responding.

Estimating Overall Survival

The EMBRACE trial Overall Survival update, which is the basis for the economic analysis, was undertaken on 77% of events.

A recent report by Latimer et al for the NICE Decision Support Unit summarises and reviews the methods available for estimating the probability of survival for patients for an economic analysis which draws data from a censored trial data set. These include:

- Using the patient data to undertake a trial analysis-type where transition is determined by the actual probability of transition at the corresponding time-point in the clinical trial.
- Parameterising the comparator arm and applying a hazard ratio to estimate the treatment arm or parameterising both arms of the clinical trial.
- Using the Kaplan-Meier data up until the data become unstable after which time transition probabilities are derived from a curve estimated from the patient level data. This method is known as the Liverpool Reviews and Implementation Group (LRIG) method.

Latimer provides evidence that the most common examples are the parameterisation of the two arms of the study and the proportional hazards method, where one arm of the trial is parameterised. Less common is the trial analysis type approach and least common are hybrid approaches including the LRIG method.

The Liverpool Review and Implementation Group method was used by the Evidence Review Group in their report on eribulin.

Like all alternative options, this approach requires significant assumptions. For example, Latimer et al discuss the importance of determining when to apply the parameterised curve and to stop using the Kaplan-Meier curve as the results it produces have become too uncertain.

For this reason, the outcomes of the mean are determined by at what point the extrapolation is attached to the non-parametric curve. The decision made by the ERG about where the non-parametric curves stops and the parametric curve starts was arbitrary and sensitivity analysis is not fully explored.

What was not discussed by Latimer et al is the importance of stratification. As illustrated below, analyses by stratification should be done if one is not to estimate a treatment effect using a method which controls for strata. The cox regression analyses that generate the hazard ratios for informing the proportional hazards analyses in the submission were conducted using a method that controlled for stratification.

A recent paper by Ekman *et al.* discusses the issue and suggests the following:

1) Analysts should perform and report results under a range of specific standard extrapolation assumptions to increase comparability across studies.
2) The choice of a base-case approach in any particular study should be guided by knowledge about the biology of the indication under evaluation and the mechanism of action of the treatment.

As acknowledged by the ERG, there are no rules for establishing where to attach a parametric curve to a Kaplan-Meier curve. However, by attaching the parametric curve to the end of the non-parametric curve, the analyst is assuming proportionality from that point on and bases that proportional difference on that final point of the curve. As one moves along the Kaplan-Meier curve, the data are more heavily censored. Therefore, the basis for establishing the validity of the proportional difference is reduced.

In addition, there will be sources of discontinuity in the proportional relationship that relate systematically to the source of the censoring. For the EMBRACE trial, the Region 1 dataset is more complete because patient recruitment started earlier. Therefore, the proportional relationship, once established, is more consistent compared to region 2 and 3 where, the proportional relationship varies far more along the Kaplan-Meier curve. Please see an illustration of the point below.

Table 3

ITT Population	**Difference in Overall Survival (Days)**		
Proportion of Curve Parameterised	Region 1	Non-Region 1	All Regions
10%	87	24	58
20%	93	16	62
25%	83	45	62
30%	89	44	75
35%	94	49	77

The proportional benefit varies more for non-region 1 than for Region 1. This is driven in part by data from outside of Region 1 being far more heavily censored due to later enrolment.

If the lack of proportionality relates to difference quantities of censoring between different strata in the study, it is reasonable to continue an established relationship between eribulin and comparator arm calculated using a large sample size than attach the curve to a point where, due to a collapse in the sample size, the established relationship has broken down. Alternatively, it is appropriate to use data where sources of changes in proportionality at the right side of the Kaplan-Meier curve have been removed – such as an analysis restricted by strata, i.e. the Region 1 analysis.

In addition, it will surely be noted that the difference in life expectancy gain is greater in Region 1 compared to non-Region1 patients. The reason for this difference can be understood when considering a breakdown of the results as seen below.

Firstly, the using a comparison between regions one can clearly see the improved performance of the TPC arm in the Non-region 1 stratum and the improved performance of the eribulin arm in the Region 1 stratum.

Table 4

	Degree of Parameterization	Eribulin Survival in Months	TPC Survival in Months	Difference (Months)	Difference (Days)
Non-Region 1	10%	17.22	16.43	0.79	24.18
	35%	17.57	15.96	1.61	49.05
Region 1	10%	17.90	15.02	2.88	87.56
	35%	17.77	14.67	3.10	94.17

However, when the analysis introduces a second stratum – prior use of capecitabine, one can see that the results even out significantly, suggesting that the prior treatment of patients outside of Region 1 was different and, when that had previously been treated similarly to Region 1 patients, their performance normalises and is even, proportionally speaking, better.

Table 5 Difference in Overall Survival by Strata

	Degree of Parameterization	Eribulin Survival in Months	TPC Survival in Months	Difference (Months)	Difference (Days)
Prior Cape R1	35%	17.56	14.66	2.90	88.23
Prior Cape NR1	35%	16.30	14.02	2.27	69.14
Prior Cape All Regions	35%	17.23	14.26	2.97	90.30

For these reasons detailed above, the economic analysis will use a base case of parameterisation of 35% to predict overall survival. Nevertheless, analysis of overall survival will be done with varying levels of parameterization.

Region 1 analyses, which don't vary greatly with the proportion of the curve parameterised, are also provided.

Curves for TTP are not parameterised. The approach to TTP is in line with the ERG.

Functional Form of the LRIG Extrapolation

The ERG utilised an exponential functional form to fit a curve to the end of the Kaplan-Meier curve. The choice of this functional form was not explained and does not seem to relate to the functional form which fits the data. When tested using the AIC and BIC criteria the appropriate curve for the TPC arm is the log

logistic. When extrapolating beyond the trial period the exponential function form will tend to generate a small incremental benefit than the log logistic functional form from any given proportional difference.

Please see an illustration below:

Table 6 Difference in Overall Survival (Days)

Difference in Overall Survival (Days)		
Proportional Hazards Model	Eribulin ITT vs. TPC ITT	Eribulin Region 1 vs. TPC Region 1
Exponential Curve	117.6	117.3
Log Logistic	157.8	158.1

If there is no basis for using the exponential curve then the conclusions of the ERG are unsafe.

LRIG Analyses

The difference in mean duration of overall survival and results of cost utility analyses are presented for the following comparisons:

- Eribulin vs. TPC (All Regions)
- Eribulin vs. TPC (Region 1)
- Eribulin vs. TPC (Patients previously treated with capecitabine)
- Eribulin vs. Vinorelbine (All regions)
- Eribulin vs. Vinorelbine (Region 1)
- Eribulin vs. Vinorelbine (Patients previously treated with capecitabine)

Like the model detailed in the ERG report, the model estimates the overall survival curve as an exponential curve estimated using the probability of survival of patients remaining in the stable and progression states at each point after the first 100 days, the point at which the ERG hypothesised that the mathematical form of the survival curve has stabilised. While exploratory analyses showed the results were quite sensitive to the assumption of 100 days, variation around this assumption had not been explored by the ERG.

Proportional Hazards Model

This submission presents analyses based on the parameterisation of the comparator arm overall survival and the application of the cox regression hazard ratio to generate the eribulin arm. As is discussed in Guyot *et al*. the application of the hazard ratio to the parameterised TPC arm preserves the primary analysis that established efficacy and avoids the duplication of the measurement of incremental benefit which would, necessarily, generate a new measurement of efficacy which does not match the primary analysis.

Nevertheless, this method relies on the assumption of fully proportional hazards. As discussed above, deviation from proportionality also impacts the LRIG analysis. Therefore, it is more appropriate to use a model that relies on proportional hazards when sources of disproportionality of hazards have, to some extent, been removed. For this purpose, Region 1 is potentially more appropriate.

To generate the parameterised curve for the comparator arms, various functional forms were tested. An investigation of the AIC and BIC determined that the log logistic curve provided the best fit to the overall survival data in all cases. The curve fits are provided in Appendix 3.

The difference in mean duration of overall survival and results of cost utility analyses are presented for the following comparisons:

- Eribulin vs. TPC (All Regions)
- Eribulin vs. TPC (Region 1)
- Eribulin vs. TPC (Patients previously treated with capecitabine)
- Eribulin vs. TPC (All Regions) - Utilising exponential functional form for overall survival
- Eribulin vs. Vinorelbine (All regions)
- Eribulin vs. Vinorelbine (Region 1)
- Eribulin vs. Vinorelbine (All regions) - Utilising exponential functional form for overall survival

Model Parameters

Appendix 2 details the actions taken to amend the economic model.

Prediction of Overall Survival – LRIG Method

The estimated duration of overall survival for the eribulin arm compared to the TPC arm under the varying assumptions for when a curve is applied to the Kaplan-Meier data is set out below.

Table 7

Comparison	Percentage of Survival Curve Parameterised	Eribulin Expected Survival Months	TPC Expected Survival Months	Improvement in Life Expectancy in Months
Eribulin vs. TPC All Regions	20%	17.48	15.42	2.06
Eribulin vs. TPC All Regions	35%	17.70	15.16	2.55
Eribulin vs. TPC All Regions	40%	17.83	15.12	2.71
Eribulin vs. TPC Region 1	20%	17.94	14.87	3.07
Eribulin vs. TPC Region 1	35%	17.77	14.67	3.10
Eribulin vs. TPC Region 1	40%	17.94	14.10	3.84
Eribulin vs. TPC in Post Capecitabine Population	20%	17.34	14.49	2.85
Eribulin vs. TPC in Post Capecitabine Population	35%	17.23	14.26	2.97
Eribulin vs. TPC in Post Capecitabine Population	40%	17.82	14.46	3.36

As can be seen from the above table, the extension in overall survival compared to patients given TPC after previously receiving capecitabine is generally around 3 months. Given the variability in All Region data generated by censoring outside of Region 1, it can be argued that a higher percentage of parameterisation is appropriate.

As shown previously discussed on page 6, the gain in overall survival for Region 1 is not dependent on the extent of the parameterisation and is consistently over 3 months.

As discussed previously, the difference in the All Regions estimate of life gained is highly dependent on the percentage of the survival curve that is parameterised.

Table 8

Comparison	Percentage of Survival Curve Parameterised	Eribulin Expected Survival Months	Vinorelbine Expected Survival Months	Improvement in Life Expectancy in Months
Eribulin vs. Vinorelbine All Regions	20%	16.38	13.28	3.10
Eribulin vs. Vinorelbine All Regions	35%	17.36	13.48	3.88
Eribulin vs. Vinorelbine All Regions	40%	17.70	13.28	4.42
Eribulin vs. Vinorelbine Region 1	20%	17.63	12.89	4.74
Eribulin vs. Vinorelbine Region 1	35%	17.69	13.25	4.44
Eribulin vs. Vinorelbine Region 1	40%	17.98	13.12	4.86
Eribulin vs. Vinorelbine in Post Capecitabine Population	20%	16.78	12.54	4.24
Eribulin vs. Vinorelbine in Post Capecitabine Population	35%	17.51	12.97	4.54
Eribulin vs. Vinorelbine in Post Capecitabine Population	40%	17.87	12.65	5.21

A similar pattern is demonstrated when the same analysis is conducted on eribulin compared to vinorelbine. The difference lies in the scale of the incremental benefit, which is consistently over 3there months and more often around 4.5 months.

Prediction of Overall Survival – Proportional Hazards Method

Table 9

Comparison	Form of Comparator Survival Curve	Eribulin Expected Survival Months	TPC Expected Survival Months	Improvement in Life Expectancy in Months
Eribulin vs. TPC All Regions	Log Logistic	24.26	19.07	5.18
Eribulin vs. TPC All Regions	Exponential	20.78	16.92	3.87
Eribulin vs. TPC Region 1	Log Logistic	22.40	17.20	5.20
Eribulin vs. TPC Region 1	Exponential	19.31	15.45	3.86
Eribulin vs. TPC in Post Capecitabine Population	Log Logistic	23.26	17.71	5.55
Eribulin vs. TPC in Post Capecitabine Population	Exponential	19.61	15.62	3.99

Unlike the LRIG analysis, the proportional hazards analysis proves far more stable to data sources. This is because, just as was established by the ERG in their comparison of the hazard ratios of region 1 and the ITT analysis, there is very little detectable difference in the hazard ratios between the three analyses.

As discussed above, fitting the exponential curve provides a more conservative estimate of the mean incremental benefit.

The comparison to vinorelbine in all regions, and in patients previously treated with capecitabine is as follows:

Results of Cost Effectiveness Analysis – LRIG Method

Table 10

All Regions			
Eribulin vs. TPC - 35% Prediction	Eribulin	TPC	Increment
Total Cost	£22,503	£15,817	£6,686
Total QALYs	0.771	0.667	0.105
ICER			£63,761

Table 11

Region 1			
Eribulin vs. TPC - 35% Prediction	Eribulin	TPC	Increment
Total Cost	£21,879	£14,687	£7,192
Total QALYs	0.770	0.635	0.135
ICER			£53,199

Table 12

Post Capecitabine, All Regions			
Eribulin vs. TPC - 35% Prediction	Eribulin	TPC	Increment
Total Cost	£21,626	£15,260	£6,365
Total QALYs	0.749	0.620	0.129
ICER			£49,310

Table 13

Post Capecitabine, Region 1			
Eribulin vs. TPC - 35% Prediction	Eribulin	TPC	Increment
Total Cost	£21,250	£15,315	£5,935
Total QALYs	0.758	0.634	0.125
ICER			£47,562

Then results above illustrate that the incremental benefit is generally better in post capecitabine patients and Region 1 patients and the incremental cost of giving eribulin to post capecitabine patients is lower because capecitabine is rarely given again.

Results for the comparison to vinorelbine are seen below.

Table 14

All Regions			
Eribulin vs. Vinorelbine - 35% Prediction	Eribulin	Vinorelbine	Increment
Total Cost	£20,549	£14,360	£6,189
Total QALYs	0.747	0.585	0.161
ICER			£38,368

Table 15

Region 1			
Eribulin vs. Vinorelbine - 35% Prediction	Eribulin	Vinorelbine	Increment
Total Cost	£20,163	£13,300	£6,863
Total QALYs	0.756	0.568	0.188
ICER			£36,520

Table 16

Post Capecitabine, All Regions			
Eribulin vs. Vinorelbine - 35% Prediction	Eribulin	Vinorelbine	Increment
Total Cost	£20,673	£13,253	£7,420
Total QALYs	0.753	0.558	0.195
ICER			£38,005

Table 17

Post Capecitabine, Region 1			
Eribulin vs. Vinorelbine - 35% Prediction	Eribulin	Vinorelbine	Increment
Total Cost	£20,073	£13,160	£6,914
Total QALYs	0.753	0.550	0.203
ICER			£34,027

In region 1, 95% of patients randomised to vinorelbine had previously been given capecitabine. Therefore, there is no surprise that the results for post capecitabine/region 1 and Region 1 are quite similar.

Results of Cost Effectiveness Analysis – Proportional Hazards Method

Table 18

All Regions			
Eribulin vs. TPC – PH Log logistic Curve	Eribulin	TPC	Increment
Total Cost	£25,045	£17,362	£7,683
Total QALYs	0.998	0.804	0.194
ICER			£39,578

Table 19

All Regions			
Eribulin vs. TPC – PH Exponential Curve	Eribulin	TPC	Increment
Total Cost	£23,755	£16,588	£7,167
Total QALYs	0.882	0.732	0.150
ICER			£47,678

Table 20

Region 1			
Eribulin vs. TPC – PH Log logistic Curve	Eribulin	TPC	Increment
Total Cost	£23,642	£15,687	£7,955
Total QALYs	0.927	0.722	0.204
ICER			£38,903

Table 21

Region 1			
Eribulin vs. TPC – PH Log Normal Curve	Eribulin	TPC	Increment
Total Cost	£23,495	£15,627	£7,868
Total QALYs	0.911	0.716	0.195
ICER			£40,302

Table 22

Region 1			
Eribulin vs. TPC – PH Exponential Curve	Eribulin	TPC	Increment
Total Cost	£22,422	£15,056	£7,367
Total QALYs	0.823	0.663	0.160
ICER			£46,182

Table 23

Post Capecitabine			
Eribulin vs. TPC – PH Log logistic Curve	Eribulin	TPC	Increment
Total Cost	£23,957	£16,627	£7,330
Total QALYs	0.957	0.741	0.215
ICER			£34,037

Table 24

Post Capecitabine			
Eribulin vs. TPC – PH Exponential Curve	Eribulin	TPC	Increment
Total Cost	£22,550	£15,864	£6,686
Total QALYs	0.834	0.671	0.163
ICER			£40,952

Generally speaking, the incremental cost of treating patients with eribulin is less and the incremental benefit in QALYs is greater in the post capecitabine population.

Eribulin Versus Vinorelbine –Proportional Hazards Method

Testing using the AIC and BIC criteria of the parameterisation of the vinorelbine arm demonstrated that the log normal had a marginally better fit than other curves. Alternative function forms are also included in the analysis.

Table 25

All Regions			
Eribulin vs. Vinorelbine - PH Log logistic	Eribulin	Vinorelbine	Increment
Total Cost	£20,703	£14,591	£6,112
Total QALYs	0.763	0.598	0.166
ICER			£36,875

Table 26

All Regions			
Eribulin vs. Vinorelbine - PH Exponential Curve	Eribulin	Vinorelbine	Increment
Total Cost	£21,017	£15,169	£5,848
Total QALYs	0.803	0.637	0.166
ICER			£35,242

Table 27

All Regions			
Eribulin vs. Vinorelbine - PH Log Normal Curve	Eribulin	Vinorelbine	Increment
Total Cost	£20,270	£14,434	£5,836
Total QALYs	0.724	0.583	0.141
ICER			£41,480

Table 28

Region 1			
Eribulin vs. Vinorelbine - PH Log logistic	Eribulin	Vinorelbine	Increment
Total Cost	£22,227	£13,366	£8,861
Total QALYs	0.943	0.570	0.372
ICER			£23,810

Table 29

Region 1			
Eribulin vs. Vinorelbine - PH Exponential	Eribulin	Vinorelbine	Increment
Total Cost	£22,526	£13,703	£8,823
Total QALYs	0.970	0.599	0.371
ICER			£23,790

Table 30

Region 1			
Eribulin vs. Vinorelbine - PH Log Normal Curve	Eribulin	Vinorelbine	Increment
Total Cost	£21,373	£13,186	£8,188
Total QALYs	0.864	0.555	0.309
ICER			£26,475

The above analysis demonstrates that the proportional hazards model generates results that are quite stable around the £23,000 to £41,000 range. Generally, the results are consistent with the results generated in the LRIG model.

Unfortunately, no post capecitabine analysis (vs. vinorelbine all regions) was ready in time for this submission. However as mentioned 95% of patients in Region 1 had received prior capecitabine and the committee have confidence that they are unlikely to be greatly different from the Region 1 outcomes.

End of Life Analysis

An analysis was conducted for selected comparison with the implementation of the end of life guidance in accordance with the way NICE has previously recommended it be implemented. Details on this method were supplied in the previous submission.

LRIG Method

Table 31

All Regions Previous Capecitabine with EOL Criteria			
Eribulin vs. iv TPC -35% Prediction	Eribulin	TPC	Increment
Total Cost	£21,626	£15,260	£6,365
Total QALYs	0.829	0.620	0.209
ICER			£30,504

Table 32

Region 1 Previous Capecitabine with EOL Criteria			
Eribulin vs. iv TPC -35% Prediction	Eribulin	TPC	Increment
Total Cost	£21,250	£15,315	£5,935
Total QALYs	0.836	0.634	0.202
ICER			£29,311

Table 33

All Regions Previous Capecitabine with EOL Criteria			
Eribulin vs. Oral Vinorelbine -35% Prediction	Eribulin	Vinorelbine	Increment
Total Cost	£20,673	£13,253	£7,420
Total QALYs	0.875	0.558	0.317
ICER			£23,403

Table 34

Region 1 Previous Capecitabine with EOL Criteria			
Eribulin vs. Oral Vinorelbine -35% Prediction	Eribulin	Vinorelbine	Increment
Total Cost	£20,073	£13,160	£6,914
Total QALYs	0.883	0.550	0.333
ICER			£20,736

Proportional Hazards Method

Table 35

All Regions with EOL Criteria			
Eribulin vs. TPC – PH Exponential Curve	Eribulin	TPC	Increment
Total Cost	£23,755	£16,588	£7,167
Total QALYs	0.981	0.732	0.249
ICER			£28,733

Table 36

Region 1 with EOL Criteria			
Eribulin vs. TPC – PH Exponential Curve	Eribulin	TPC	Increment
Total Cost	£22,422	£15,056	£7,367
Total QALYs	0.922	0.663	0.259
ICER			£28,409

Table 37

All Regions Previous Capecitabine with EOL Criteria			
Eribulin vs. TPC – PH Exponential Curve	Eribulin	TPC	Increment
Total Cost	£22,550	£15,864	£6,686
Total QALYs	0.937	0.671	0.266
ICER			£25,111

Table 38

All Regions with EOL Criteria			
Eribulin vs. Vinorelbine – PH Exponential Curve	Eribulin	Vinorelbine	Increment
Total Cost	£20,597	£14,825	£5,772
Total QALYs	0.871	0.608	0.263
ICER			£21,959

Table 39

Region 1 with EOL Criteria			
Eribulin vs. Vinorelbine – PH Exponential Curve	Eribulin	Vinorelbine	Increment
Total Cost	£22,526	£13,703	£8,823
Total QALYs	1.213	0.599	0.615
ICER			£14,357

Sensitivity Analysis

It is clear from the analysis that eribulin is most cost effective in the patient population which alternatively would be given vinorelbine and particularly so in patients which had previously been given capecitabine. The sensitivity analysis will focus analysis on this patient group.

The following sensitivity analyses were performed:

- IV vinorelbine

Table 40

Previous Capecitabine			
Eribulin vs. iv Vinorelbine -35% Prediction	Eribulin	IV Vinorelbine	Increment
Total Cost	£20,673	£12,769	£7,904
Total QALYs	0.753	0.558	0.195
ICER			£40,488

Table 41

Previous Capecitabine With EOL Criteria			
Eribulin vs. iv Vinorelbine -35% Prediction	Eribulin	IV Vinorelbine	Increment
Total Cost	£20,673	£12,769	£7,904

Total QALYs	0.875	0.558	0.317
ICER			£24,932

The analysis using IV vinorelbine as the comparator demonstrates the average cost of the comparator arm is reduced slightly – by around £500. This increases the ICER to £40,488 from £38,005. Where the criteria previously set out by NICE for the EOL criteria are implemented, the ICER for the IV analysis is £24,932 compared to the oral vinorelbine, which is £23,403.

Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis was conducted on the scenario of treatment of patient who would otherwise get vinorelbine in Region 1.

Table 42 Eribulin vs. Vinorelbine in Region 1 Proportional Hazards Model

PSA Region 1			
Eribulin vs. Vinorelbine – PH Log Normal	Eribulin	Vinorelbine	Increment
Total Cost	£26,486	£16,568	£9,918
Total QALYs	1.309	0.838	0.472
ICER			£21,025

Figure 2 Scatter plot of ICERs – Eribulin vs. Vinorelbine in Region 1 Proportional Hazards Model

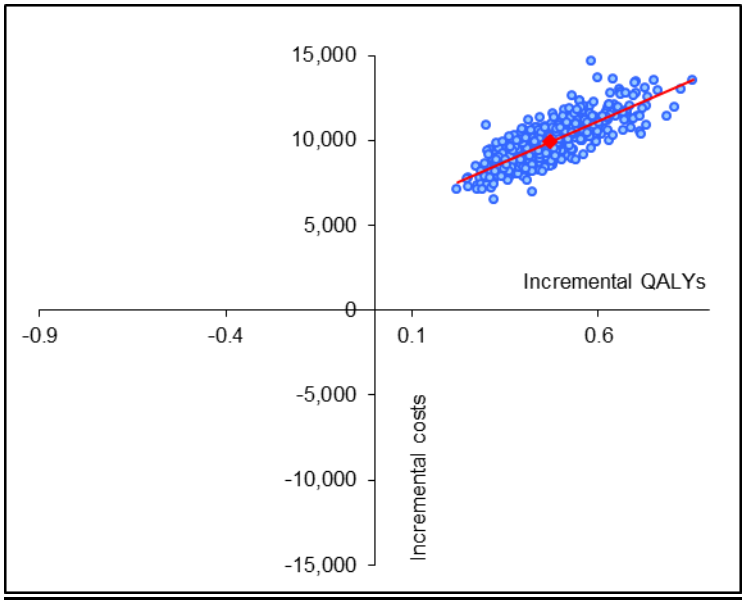


Figure 3 CEAC – Eribulin vs. Vinorelbine in Region 1 Proportional Hazards Model

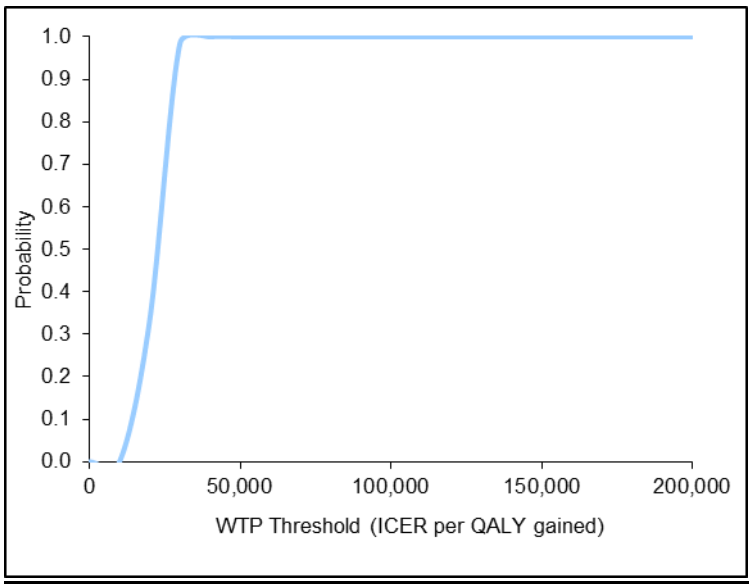


Table 43 Threshold Probabilities Eribulin vs. Vinorelbine in Region 1 Proportional Hazards Model

Willingness To Pay	Probability
0	0
£10000	0
£20000	0.334
£30000	0.984

Table 44 Eribulin vs. Vinorelbine in Patients with prior Capecitabine in All Regions

PSA Post Capecitabine			
Eribulin vs. Vinorelbine – 35% Prediction	Eribulin	Vinorelbine	Increment
Total Cost	£20,100	£13,148	£6,952
Total QALYs	0.756	0.549	0.207
ICER			£33,598

Figure 4 Scatter Plot of ICERs – Eribulin vs. Vinorelbine in Patients with prior Capecitabine in All Regions

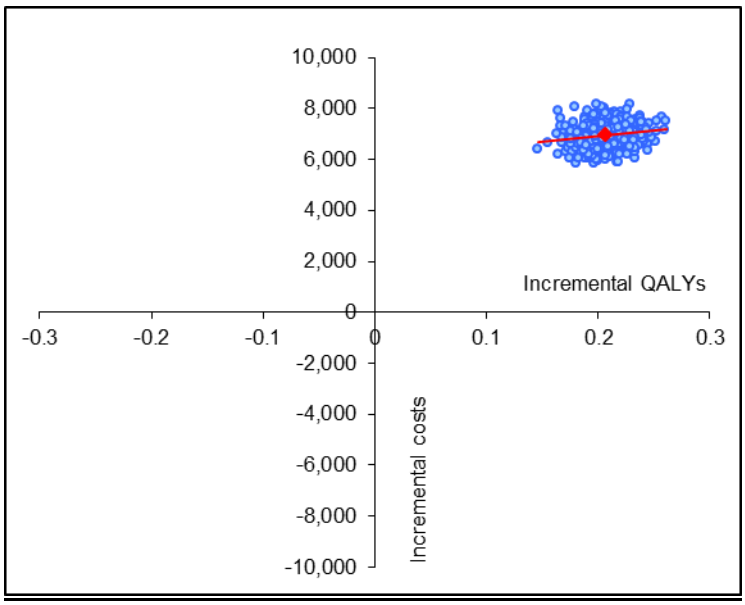


Figure 5 CEAC – Eribulin vs. Vinorelbine in Patients with prior Capecitabine in All Regions

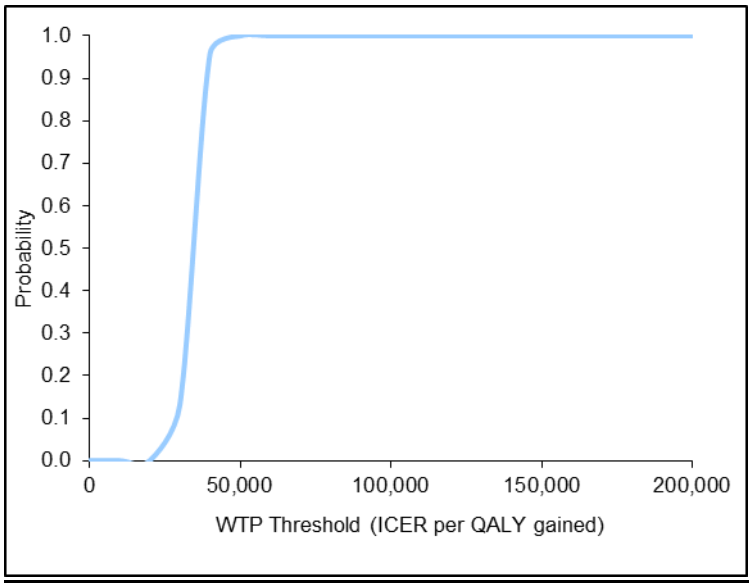


Table 45 Threshold Probabilities Eribulin vs. Vinorelbine in Patients with prior Capecitabine in All Regions

Willingness to Pay	Probability
£20000	0
£30000	0.132
£40000	0.958

Conclusions

Additional treatment options are needed for heavily pre-treated MBC patients whose disease progresses after receiving multiple therapeutic regimes. Eribulin is the only agent to date that has been shown to prolong the overall survival of heavily pre-treated MBC patients when administered as monotherapy, as reported in the phase 3 EMBRACE study. This now represents a new proven treatment for patients and physicians and an important role in breast cancer treatment. Considering that 74% of patients in EMBRACE had received prior capecitabine it makes clinical and economic sense for eribulin to be used after capecitabine.

There are several approaches to conducting survival analysis and two different methods have being presented here. The choice of model and extrapolation method has significant impact on comparative clinical effects and cost-effectiveness.

For the LRIG Method, various scenarios were explored to examine the effect of changing the point at which the extrapolated survival curve is attached to the non-parametric curve. These analyses revealed that the censoring of patients outside of Region 1, due to them not having died, seriously impacts the validity of an extrapolation from the end of the KM curve. Furthermore, analyses based on stratification factors reveals very significant differences between regions and based on previous treatment.

The hazard ratio generated by a traditional cox regression model accounts for stratification factors. Furthermore, it uses all available data to inform an estimate of the proportional difference beyond the trial period, not just the very end of the Kaplan Meier curve, where the power to detect a difference is very small. For this reason, the proportional hazards analysis was presented and this provides robust evidence for eribulin qualifying for the EOL criteria and demonstrating cost effectiveness of eribulin compared to the most appropriate comparator - vinorelbine.

This document has highlighted significant variation in approaches to modelling eribulin; however both approaches show that survival is increased beyond 3 months thus meeting the end of life criteria and the ICERs for both approaches for the post capecitabine and vinorelbine comparator group are below 30K when adjusting utilities as required for end of life analysis

References

Latimer, N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. Available from http://www.nicedsu.org.uk.

Ekman M et al. Extrapolation in trial based cost effectiveness modelling: in search of a standard. PCN162, 13th European ISPOR meeting

Guyout P et al. Survival Time Outcomes in Randomized, Controlled Trials and Meta-Analyses: The Parallel Universes of Efficacy and Cost-Effectiveness. Value in Health 2011 in press

Appendix 1

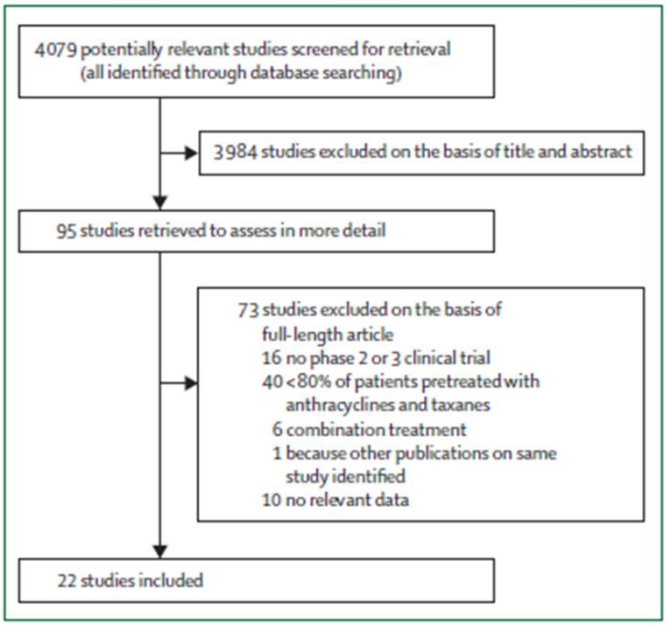
Meta-analysis of Survival Duration for Patients with Metastatic Breast Cancer – Comparison of Major Treatment Options.

The EMBRACE trial compared the efficacy of eribulin to treatments of physician's choice TPC for patients with heavily-pre-treated metastatic breast cancer. The nature of this condition is that, at this late stage, there is no standard of care. Therefore, patients and physicians choose from a spectrum of treatment options. As a result, no drug dominated the TPC arm, meaning that there is an increased uncertainty attached to the estimate of the treatment effect of eribulin compared to any one drug.

One way to investigate the validity of the treatment effect is to compare the way that each TPC drug has performed in other studies in comparable patient populations. This meta-analysis compares the median duration of survival demonstrated by patients treated with the three drugs which dominate the TPC arm: capecitabine, vinorelbine and gemcitabine as reported in the literature and in the EMBRACE trial with the median duration of survival in patients treated with eribulin and in patients treated with eribulin where they were considered for the alternative TPC comparator.

Available Data

A recent study by Oostendorp L et al in The Lancet Oncology medical journal undertook a review of the evidence for treatments for MBC drugs. Usefully, this study searched through over 4000 articles to identify 22 studies which tested drugs for patients at this stage of disease and therapy.



The authors found data available for the following drugs:

- Vinorelbine (9 studies)

- Gemcitabine (3 studies)
- Capecitabine (10 studies)
- Liposomal doxirubicin (1 study)
-

The results of the review of these clinical studies are set out below.

		Overall response n (%)	Stable disease n (%)	Progressive disease n (%)	Not assessable n (%)	Disease controlled n (%)	Median TTP (Months)	Median PFS (Months)	Median OS Months
Capecitabine									
Cameron et al, 2008	201	28 (14%)	59 (29%)	47 (23%)	67 (33%)	87 (43%)	4·3	NR	15·3
Pajk et al, 2008	23	2 (9%)	5 (22%)	10 (44%)	6 (26%)	7 (30%)	NR	2·8	9·3
Thomas et al, 2007	377	54 (14%)	175 (46%)	102 (27%)	46 (12%)	229 (60%)	NR	4·2	NR
Lin et al, 2006	37	12 (32%)	17 (46%)	NR	NR	29 (78%)	NR	5·9	9·5
Miller et al, 2005	230	21 (9%)/	NR	NR	NR	NR	NR	4·2	14·5
		44 (19%)							
Fumoleau et al, 2004	126	35 (28%)	44 (35%)	47 (37%)	0	79 (63%)	4·9	NR	15·2
Lee et al, 2004	38	10 (26%)	13 (34%)	13 (34%)	2 (5%)	23 (60%)	4·6	NR	18·1
Reichardt et al, 2003	136	21 (15%)	63 (46%)	52 (38%)	0	84 (62%)	3·5	NR	10·1
Blum et al, 2001	74	19 (26%)	23 (31%)	NR	NR	42 (57%)	3·2	NR	12·2
Blum et al, 1999	162	27 (20%)	54 (40%)	46 (34%)	8 (6%)	81 (60%)	3·1	NR	12·6
Weighted mean	..	..	..	..	..	57	3·9	4·2	13·5
Vinorelbine									
Seo et al, 2009	26	5 (19%)	9 (35%)	10 (38%)	2 (8%)	14 (54%)	NR	3·7	10·4
Pajk et al, 2008	24	3 (13%)	5 (21%)	8 (33%)	8 (33%)	8 (33%)	NR	2·6	11·0
Martín et al, 2007	126	33 (26%)	32 (25%)	58 (46%)	3 (2%)	65 (51%)	NR	4·0	16·4
Papaldo et al, 2006	33	9 (27%)	12 (36%)	12 (36%)	0	21 (63%)	6·0	NR	22
Toi et al, 2005	50	10 (20%)	19 (38%)	18 (36%)	3 (6%)	29 (58%)	3·8	NR	NR
Jara-Sánchez et al, 2003	47	9 (19%)	5 (11%)	32 (68%)	1 (2%)	14 (30%)	2·4	NR	7·7
Zelek et al, 2001	40	10 (25%)	9 (23%)	21 (53%)	0	19 (48%)	NR	NR	6
Udom et al, 2000	20	7 (35%)	3 (15%)	10 (50%)	0	10 (50%)	2·8	NR	NR
Livingston et al, 1997	40	10 (25%)	NR	NR	0	NR	3·0	NR	7·6
Weighted mean	..	..	..	..	..	49	3·6	3·8	12·6
Gemcitabine									
Modi et al, 2005	22	3 (14%)	1 (5%)	14 (64%)	4 (18%)	4 (19%)	NR	NR	9·5
Rha et al, 2005	41	8 (20%)	12 (29%)	18 (44%)	3 (7%)	20 (49%)	NR	4·5	11
Smorenburg et al, 2001	23	0	6 (26%)	NR	NR	6 (26%)	1·9	NR	7·8
Weighted mean	..	..	..	..	..	35	1·9	4·5	9·8

In order to combine the results of data from this review with the results of the EMBRACE trial, it is necessary to exclude results which were demonstrated in patients which were outside of the licensed indication for eribulin or where the nature of the patients could not be determined. The main reason for exclusion was that the patients in the study were not treated as third line in MBC. Many included patients having their second therapy for MBC. Nevertheless, it was necessary to include some studies which

included patients that were not third line. The rule used was that patients that were second line or earlier must not make up more than around 10% of the total.

Reference	Decision	Reason
Pajk et al, 2008	Excluded	50% had only 1 previous in MBC
Thomas et al, 2007	Excluded	Does not report survival
Martín et al, 2007	Excluded	Pooled first second and third line
Papaldo et al, 2006	Excluded	78% third line but only, 12% did not have previous taxane
Toi et al, 2005	Excluded	Does not report survival
Zelek et al, 2001	Excluded	Less than 80% had previous anthracycline. Undetermined how many 3rd line or later.
Udom et al, 2000	Excluded	Does not report survival
Modi et al, 2005	Excluded	22% second line MBC, the rest third line plus
Cameron et al, 2008	Excluded	Did not report lines of therapy
Pajk et al, 2008	Excluded	6/17 had only 1 previous treatment for MBC, rest had 2
Miller et al, 2005	Excluded	Restricted to patients with fewer than 3 lines
Fumoleau et al, 2004	Excluded	50/50 second and third line
Reichardt et al, 2003	Excluded	Number of previous MBC treatments not reported and median previous chemotherapies of only 2.

Uncensored data are available for the median duration of survival of patients who have died after being treated with individual drugs in the TPC arm. The results for Vinorelbine and capecitabine are as follows:

- 50 patients died who were treated with Vinorelbine – median survival of 8.3 months
- 39 patients died who were treated with gemcitabine – median survival of 10.2 months
- 35 patients died who were treated with capecitabine – median survival of 11.17 months

Corresponding data for patients treated with eribulin is as follows:

- Median OS for 98 patients treated with eribulin after being considered for vinorelbine but randomised to eribulin and have died: 12.62 months.
- Median OS for 78 patients treated with eribulin after being considered for gemcitabine but randomised to eribulin and have died: 13.7 months
- Median OS for 47 patients treated with eribulin after being considered for capecitabine but randomised to eribulin and have died: 15.84 months.

Combining these data in a meta-analysis produces the following results:

Vinorelbine

Reference	Patients (n)	Weighting	Duration (median months)	Weighted Duration (median months)
Seo et al, 2009	26	0.159509	10.4	1.658896
Jara-Sánchez et al, 2003	47	0.288344	7.7	2.220245

Livingston et al, 1997	40	0.245399	7.6	1.865031
EMBRACE	50	0.306748	8.3	2.546012
Total	163			
Weighted mean				8.290184
Eribulin Patients				12.62466
Difference				4.334473

Capecitabine

Reference	Patients (n)	Weighting	Duration (median months)	Weighted Duration (median months)
Lin et al, 200618	37	0.106936	9.5	1.015896
Lee et al, 200421	38	0.109827	18.1	1.987861
Blum et al, 200123	74	0.213873	12.2	2.609249
Blum et al, 199924	162	0.468208	12.6	5.899422
EMBRACE	35	0.101156	11.17	1.129913
Weighted mean	346			12.64234
Eribulin Patients				15.84
Difference				3.197659

Gemcitabine

Reference	Patients	Weighting	Duration	Weighted Duration
Rha et al, 200534	41	0.398058	11	4.378641
Smorenburg et al, 200135	23	0.223301	7.8	1.741748
EMBRACE	39	0.378641	10.12	3.831845
Weighted mean	103			9.952233
Eribulin Patients				13.70959
Difference				3.757356

It is clear from the above analyses that the estimated difference in median overall survival demonstrated in the EMBRACE trial particularly for vinorelbine is consistent with an analysed estimate of the duration that can expected when data from other studies are considered in the meta-analysis. These results give confidence in the estimated mean differences generated from the modelling of the EMBRACE trial for the cost effectiveness analysis.

References

Oostendorp, L.J.M., Stalmeier P.F.M., Donders, A.R.T., van der Graaf, W.T.A., Ottevanger, P.B. Efficacy and safety of palliative chemotherapy for patients with advanced breast cancer pretreated with anthracyclines and taxanes: a systematic review. The Lancet Published online May 27, 2011 DOI:10.1016/S1470-2045(11)70045-6

Appendix 2

Critique	ERG Report Page	Action
General		
Discount rate (should be 3.5% on both costs and health effects)	60	Updated
Correct use of a mid-cycle correction – minor error identified	68	Corrected
Costs of Chemotherapy/Chemotherapy Administration		
Model does not take account of BSA differences between patients but uses a fixed average value for all patients (ERG used BSA values from Sacco et al)	62	Utilized ERG estimates for drug cycle costs
Use of NHS Ref Costs 2008/2009 is out of date as NHS Ref Costs 2009/2010 were available at the time of writing	63	Updated
Manufacturer has ignored the different healthcare resource group costs appropriate to the first administration of a course of therapy (used subsequent cycles instead) – use cost per cycle from ERG report	63	Incorporated first administration
Costs of Supportive Care		
In PFS state, update the annual cost of monitoring and supportive care using NHS ref costs 2009/2010 and PSSRU Unit Costs of Health & Social Care 2010 (2915.34 vs. 2836.24)	64	Updated
In PPS state update the annual cost, assuming package of care per NICE guideline (5720.79 vs. 4059.82)	64	Updated
In terminal care, estimate cost of care per NICE guidance using Marie Curie report (4003.05 vs. 19711.85)	64	Updated
Health State and Utility Values		
Calculate expected utility values assuming mean age to 47 per the original York study (0.756 vs. 0.715 for stable; 0.823 vs. 0.790 responder; 0.496 vs. 0.443 progression)	65	Updated
End of Life ICER Adjustment		
Adjustment of utility value of additional life-years attributable to use of eribulin to match that of the general UK population, rather than patients with advanced or MBC. Six minor transcription errors were identified in the use of the UK population norms	68	Updated
Survival Estimation		

Use of Kaplan-Meier plot can become unstable and erratic when only small numbers of cases remain alive and uncensored curves	69	Incorporated survival estimates based on exponential curves plotted from the trial data and attached to the back of the survival curves

Unit Costs

The model uses the estimates of drug cost per cycle published in the ERG report.

Drug	Cost Per Cycle
Vinorelbine First Cycle	£715.72
Vinorelbine Subsequent Cycle	£944.51
Vinorelbine IV	£408.02
Gemcitabine	£676.20
Capecitabine	£306.83
Docetaxel	£1,265.74
Paclitaxel	£648.28
Nab-paclitaxel	£1,234.85
Doxorubicin	£235.62
Liposomal doxorubicin	£1,333.76

Infusion Cost

As mentioned in the summary, the infusion costs are updated and a first infusion cost is introduced for some agents.

Infusion Group	**HRG Cost**
First administration (oral)	£151.95
First administration (simple parenteral)	£206.74
Subsequent administration	£284.45

Based on the infusion costs calculated for the model, the table below details the infusion costs for each drug.

Drug	**First Cycle**	**Cycles 2 +**
Vinorelbine Oral	£455.84	£455.84
Vinorelbine IV	£775.65	£853.36
Gemcitabine	£491.20	£568.91
Capecitabine	£151.95	£151.95
Docetaxel	£206.74	£284.45
Paclitaxel	£206.74	£284.45
Nab-paclitaxel	£206.74	£284.45
Doxorubicin	£206.74	£284.45
Liposomal doxorubicin	£206.74	£284.45

Shares of Drugs That Make Up TPC

Vital to calculating the cost of the TPC arm is the shares of each drug that are assumed to be making up the TPC arm drug cost. Results are presented for all patients, i.e. the ITT population and for patients from all countries but stratified for patients with previous capecitabine. As can be seen from the table below, far fewer patients that had previously taken capecitabine then went on to take it in the TPC for the study. Therefore, this has implications for the drug and infusion costs.

Drug	All Patients	Previous Capecitabine
Vinorelbine	29.41%	35.80%
Gemcitabine	20.81%	23.46%
Capecitabine	20.36%	2.47%
Docetaxel	9.28%	12.35%
Paclitaxel	2.78%	3.70%
Nab-paclitaxel	6.49%	8.64%
Doxorubicin	0.00%	0.00%
Liposomal doxorubicin	10.86%	13.58%

Calculation of Weighted Cost of TPC Drug

Drug	**All Patients**	**First Cycle**	**Subsequent Cycles**
Vinorelbine Oral	29.41%	£715.72	£944.51
Gemcitabine	20.81%	£676.20	£676.20
Capecitabine	20.36%	£306.83	£306.83
Docetaxel	9.28%	£1,265.74	£1,265.74
Paclitaxel	2.78%	£648.28	£648.28
Nab-paclitaxel	6.49%	£1,234.85	£1,234.85
Doxorubicin	0.00%	£235.62	£235.62
Liposomal doxorubicin	10.86%	£1,333.76	£1,333.76
Weighted TPC Cost		**£774.20**	**£841.50**

Drug	**All Patients**	**All Cycles**
Vinorelbine IV	29.41%	£408.02
Gemcitabine	20.81%	£676.20
Capecitabine	20.36%	£306.83
Docetaxel	9.28%	£1,265.74
Paclitaxel	2.78%	£648.28
Nab-paclitaxel	6.49%	£1,234.85
Doxorubicin	0.00%	£235.62
Liposomal doxorubicin	10.86%	£1,333.76
Weighted TPC Cost		**£683.70**

Drug	Previous Capecitabine	First Cycle	Subsequent Cycles
Vinorelbine Oral	35.80%	£715.72	£944.51
Gemcitabine	23.46%	£676.20	£676.20
Capecitabine	2.47%	£306.83	£306.83
Docetaxel	12.35%	£1,265.74	£1,265.74
Paclitaxel	3.70%	£648.28	£648.28
Nab-paclitaxel	8.64%	£1,234.85	£1,234.85
Doxorubicin	0.00%	£235.62	£235.62
Liposomal doxorubicin	13.58%	£1,333.76	£1,333.76
Weighted TPC Cost		**£890.55**	**£972.47**

Drug	Previous Capecitabine	All Cycles
Vinorelbine IV	35.80%	£408.02
Gemcitabine	23.46%	£676.20
Capecitabine	2.47%	£306.83
Docetaxel	12.35%	£1,265.74
Paclitaxel	3.70%	£648.28
Nab-paclitaxel	8.64%	£1,234.85
Doxorubicin	0.00%	£235.62
Liposomal doxorubicin	13.58%	£1,333.76
Weighted TPC Cost		**£780.39**

Weight Cost of Infusion – TPC

As above, the weighted cost of infusions is calculated based on the distribution of drugs taken and the cost associated with infusing those drugs.

Drug	All Patients	First Cycle	Cycles 2 +
Vinorelbine IV	29.41%	£455.84	£455.84
Vinorelbine Oral	29.41%	£775.65	£853.36
Gemcitabine	20.81%	£491.20	£568.91
Capecitabine	20.36%	£151.95	£151.95
Docetaxel	9.28%	£206.74	£284.45
Paclitaxel	2.78%	£206.74	£284.45
Nab-paclitaxel	6.49%	£206.74	£284.45
Doxorubicin	0.00%	£206.74	£284.45
Liposomal doxorubicin	10.86%	£206.74	£284.45

TPC Vin IV		**£422.12**	**£484.01**
TPC Vin Oral		**£328.06**	**£367.09**

Drug	**Previous Capecitabine**	**First Cycle**	**Cycles 2 +**
Vinorelbine IV	35.80%	£455.84	£455.84
Vinorelbine Oral	35.80%	£775.65	£853.36
Gemcitabine	23.46%	£491.20	£568.91
Capecitabine	2.47%	£151.95	£151.95
Docetaxel	12.35%	£206.74	£284.45
Paclitaxel	3.70%	£206.74	£284.45
Nab-paclitaxel	8.64%	£206.74	£284.45
Doxorubicin	0.00%	£206.74	£284.45
Liposomal doxorubicin	13.58%	£206.74	£284.45
TPC Vin IV		**£475.80**	**£551.59**
TPC Vin Oral		**£361.30**	**£409.27**

Costs of Health States

Costs associated with supportive care health states are aligned to the ERG report as follows:

Health State	**Base**
Stable / Responsive	£2,915.34
Progressive	£5,720.79
End of life	£4,003.05

Adverse Event Costs

For this submission, the costs of adverse events were reassessed and redrafted. Details of the costs are as follows overleaf:

Cost of Grade 3 Adverse Events

Toxicity	Base	Min	Max	Description	Notes and Assumptions
Anaemia	£432.49	£206.73	£347.07	JA12A Malignant Breast Disorders with Major CC -- Day Cases HRG	
Anorexia	£-	£-	£-	Cost per grade 3 anorexia event.	No cost.
Diarrhoea	£128.67	£89.49	£144.71	370 Consultant Led: Follow-up attendance non-admitted face-to-face, medical oncology	Office visit.
Dyspnoea	£-	£-	£-	Cost per grade 3 dyspnoea event.	No cost.
Oedema	£551.80	£262.07	£934.43	DZ20Z Pulmonary Oedema -- Day Cases HRG	
Fatigue	£-	£-	£-	Cost per grade 3 fatigue event.	No cost.
Febrile neutropenia	£2,414.00	£2,414.00	£2,414.00	ERG Cost	
Heart failure	£-	£-	£-	Cost per grade 3 heart failure event.	No cost -- all assumed grade 4.
Hyperbilirubimaemia	£1,022.58	£174.88	£2,844.20	GC01B Liver Failure Disorders without Interventions -- Day Cases HRG	
Hypertension	£-	£-	£-	Cost per grade 3 hypertension event.	No cost.
Hypokalaemia	£286.95	£124.00	£324.77	KC05F Fluid and Electrolyte Disorders 69 years and under without CC -- Day Cases HRG	
Neuropathy	£-	£-	£-	Cost per grade 3 neuropathy event.	No cost.
Neutropenia	£-	£-	£-	Cost per grade 3 neuropathy event.	No cost.
Pain	£128.67	£89.49	£144.71	370 Consultant Led: Follow-up attendance non-admitted face-to-face, medical oncology	Office visit.
Peripheral neuropathy	£128.67	£89.49	£144.71	370 Consultant Led: Follow-up attendance non-admitted face-to-face, medical oncology	Office visit.
Pulmonary embolism	£292.36	166.36	£362.42	DZ09B Pulmonary Embolus with CC -- Day Cases HRG	
Stomatitis	£518.95	£219.23	£585.24	WA21W Other Procedures and health care problems with CC -- Day Cases HRG	
Thrombocytopenia	£425.54	£287.55	£480.32	SA12F Thrombocytopenia without CC -- Day Cases HRG	
Urinary tract infection	£128.67	£89.49	£144.71	370 Consultant Led: Follow-up attendance non-admitted face-to-face, medical oncology	Office visit.
Vomiting	£128.67	£89.49	£144.71	370 Consultant Led: Follow-up attendance non-admitted face-to-	Office visit.

				face, medical oncology	

Cost of Grade 4 Adverse Events

Toxicity	Base	Min	Max	Description	Notes and Assumptions
Anaemia	£432.49	£206.73	£347.07	JA12A Malignant Breast Disorders with Major CC -- Day Cases HRG	
Anorexia	£-	£-	£-	Cost per grade 4 anorexia event.	No cost.
Diarrhoea	£432.49	£206.73	£347.07	JA12A Malignant Breast Disorders with Major CC -- Day Cases HRG	Overnight stay, fluids.
Dyspnoea	£128.67	£89.49	£144.71	370 Consultant Led: Follow-up attendance non-admitted face-to-face, medical oncology	Outpatient visit.
Oedema	£551.80	£262.07	£934.43	DZ20Z Pulmonary Oedema -- Day Cases HRG	
Fatigue	£-	£-	£-	Cost per grade 4 fatigue event.	No cost.
Febrile neutropenia	£2,414.00	£2,414.00	£2,414.00	ERG Cost	
Heart failure	£520.73	£270.62	£569.51	EB03I Heart Failure or Shock without CC -- Day cases HRG	
Hyperbilirubimaemia	£1,022.58	£174.88	£2,844.20	GC01B Liver Failure Disorders without Interventions -- Day Cases HRG	
Hypertension	£-	£-	£-	None	No cost.
Hypokalaemia	£286.95	£124.00	£324.77	KC05F Fluid and Electrolyte Disorders 69 years and under without CC -- Day Cases HRG	
Neuropathy	£432.49	£206.73	£347.07	JA12A Malignant Breast Disorders with Major CC -- Day Cases HRG	
Neutropenia	£432.49	£206.73	£347.07	JA12A Malignant Breast Disorders with Major CC -- Day Cases HRG	
Pain	£128.67	£89.49	£144.71	370 Consultant Led: Follow-up attendance non-admitted face-to-face, medical oncology	Outpatient visit.
Peripheral neuropathy	£-	£-	£-	Cost per grade 4 peripheral neuropathy event.	No cost.
Pulmonary embolism	£292.36	£166.36	£362.42	DZ09B Pulmonary Embolus with CC --	

				Day cases HRG	
Stomatitis	£518.95	£219.23	£585.24	WA21W Other Procedures and health care problems with CC -- Day Cases HRG	
Thrombocytopenia	£425.54	£287.55	£480.32	SA12F Thrombocytopenia without CC -- Day Cases HRG	
Urinary tract infection	£482.07	£231.08	£519.79	LA04G Kidney or Urinary Tract Infections with length of stay 1 day or less without CC -- Day cases HRG	
Vomiting	£432.49	£206.73	£347.07	JA12A Malignant Breast Disorders with Major CC -- Day Cases HRG	

Utility

The utilities used for this analysis are as follows:

State	Base	Min	Max
Stable	0.756	0.620	0.810
Responsive	0.823	0.790	0.840
Progressive	0.496	0.330	0.650
End of life	0.160	0.130	0.250
w/ Anaemia	-0.124	no	no
w/ Anorexia	-0.124	no	no
w/ Diarrhoea	-0.103	no	no
w/ Dyspnoea	-0.124	no	no
w/ Oedema	-0.124	no	no
w/ Fatigue	-0.115	no	no
w/ Febrile neutropenia	-0.150	no	no
w/ Heart failure	-0.124	no	no
w/ Hyperbilirubimaemia	-0.124	no	no
w/ Hypertension	-0.124	no	no
w/ Hypokalaemia	-0.124	no	no
w/ Neuropathy	-0.124	no	no
w/ Neutropenia	-0.124	no	no
w/ Pain	-0.124	no	no

State	Base	Min	Max
w/ Peripheral neuropathy	-0.124	no	no
w/ Pulmonary embolism	-0.124	no	no
w/ Stomatitis	-0.151	no	no
w/ Thrombocytopenia	-0.124	no	no
w/ Urinary tract infection	-0.124	no	no
w/ Vomiting	-0.103	no	no

Appendix 3

Overall Survival Curve Parametric Fits - TPC ITT Population

Using the AIC criteria, it can be seen that the Log Logistic curve qualifies as having the best fit to the data.

Label of Model Statement	Convergence Status	Natural Log of Likelihood	days	Intercept	Scale Parameter for Distribution	k	aic	bic	First Shape Parameter for Distribution
Exponent	0 Converged	-309.58725	-1	6.20260	1.00000	1	621.17449	624.71182	.
Gamma	0 Converged	-300.62656	-1	5.85963	1.05112	3	607.25313	617.86513	0.16590
Weibull	0 Converged	-304.85224	-1	6.13643	0.79743	3	615.70448	626.31649	.
Logistic	0 Converged	-1105.1799	-1	350.07353	145.30025	2	2214.35980	2221.43446	.
Lnormal	0 Converged	-300.80054	-1	5.79739	1.09623	2	605.60107	612.67574	.
Llogistc	0 Converged	-300.73137	-1	5.78822	0.62386	2	605.46274	612.53741	.
Gompertz	0 Converged	-1128.4846	-1	481.20292	226.48445	2	2260.96912	2268.04379	.

Overall Survival Curve Parametric Fits - TPC Post Capecitabine Population

Using the AIC criteria, it can be seen that the Log Logistic curve qualifies as having the best fit to the data.

Label of Model Statement	Convergence Status	Natural Log of Likelihood	days	Intercept	Scale Parameter for Distribution	k	aic	bic	First Shape Parameter for Distribution
Exponent	0 Converged	-236.14524	-1	6.11881	1.00000	1	474.29047	477.53222	.
Gamma	0 Converged	-228.97252	-1	5.75302	1.06650	3	463.94504	473.67029	0.10888
Weibull	0 Converged	-233.12730	-1	6.06973	0.81705	3	472.25459	481.97983	.
Logistic	0 Converged	-852.08195	-1	327.78658	142.13153	2	1708.16389	1714.64739	.
Lnormal	0 Converged	-229.03720	-1	5.71025	1.09357	2	462.07439	468.55788	.
Llogistc	0 Converged	-228.87597	-1	5.69898	0.62392	2	461.75194	468.23544	.
Gompertz	0 Converged	-872.67199	-1	464.88239	231.24326	2	1749.34399	1755.82748	.

Overall Survival Curve Parametric Fits - TPC Region 1 Population

Label of Model Statement	Convergence Status	Natural Log of Likelihood	days	Intercept	Scale Parameter for Distribution	k	aic	bic	First Shape Parameter for Distribution
Exponent	0 Converged	-206.01749	-1	6.10722	1.00000	1	414.03498	417.12873	.
Gamma	0 Converged	-197.81182	-1	5.66743	1.05121	3	401.62363	410.90488	-0.08828
Weibull	0 Converged	-202.37492	-1	6.05983	0.79035	3	410.74984	420.03109	.
Logistic	0 Converged	-766.01551	-1	329.06530	141.28877	2	1536.03102	1542.21852	.
Lnormal	0 Converged	-197.84133	-1	5.70262	1.03496	2	399.68266	405.87016	.
Llogistc	0 Converged	-198.59560	-1	5.69739	0.60016	2	401.19121	407.37871	.
Gompertz	0 Converged	-783.81938	-1	462.62304	228.69374	2	1571.63877	1577.82627	.

Overall Survival Curve Parametric Fits – Vinorelbine Patients

Label of Model Statement	Convergence Status	Natural Log of Likelihood	days	Intercept	Scale Parameter for Distribution	k	aic	bic	First Shape Parameter for Distribution
Exponent	0 Converged	-68.81414	-1	6.06284	1.00000	1	139.62828	141.73915	.
Gamma	0 Converged	-58.93428	-1	5.21625	0.74340	3	123.86856	130.20118	-1.32926
Weibull	0 Converged	-64.33278	-1	5.96189	0.64263	3	134.66556	140.99818	.
Logistic	0 Converged	-265.69934	-1	304.78862	114.65818	2	535.39867	539.62042	.
Lnormal	0 Converged	-60.64422	-1	5.65752	0.77526	2	125.28844	129.51018	.
Llogistc	0 Converged	-61.74714	-1	5.63928	0.46663	2	127.49429	131.71604	.
Gompertz	0 Converged	-273.32785	-1	425.33649	198.10385	2	550.65571	554.87746	.

Overall Survival Curve Parametric Fits – Vinorelbine Patients Region 1

Label of Model Statement	Convergence Status	Natural Log of Likelihood	days	Intercept	Scale Parameter for Distribution	k	aic	bic	First Shape Parameter for Distribution
Exponent	0 Converged	-48.25499	-1	6.00943	1.00000	1	98.50998	100.24765	.
Gamma	0 Converged	-41.56227	-1	5.42777	0.75753	3	89.12453	94.33754	-0.67574
Weibull	0 Converged	-44.15183	-1	5.93968	0.61364	3	94.30367	99.51668	.
Logistic	0 Converged	-197.55974	-1	303.65671	110.32066	2	399.11948	402.59482	.
Lnormal	0 Converged	-41.96321	-1	5.64406	0.73840	2	87.92642	91.40176	.
Llogistc	0 Converged	-42.56873	-1	5.63551	0.43979	2	89.13747	92.61281	.
Gompertz	0 Converged	-203.69585	-1	422.43010	199.24604	2	411.39170	414.86704	.

Base Case Analysis – Eribulin

- The method chosen by the ERG to model the overall survival (the Liverpool Review and Implementation Group (LRIG) method) does not appear to have strong support in the literature and is open to arbitrary assumptions. Furthermore, the method is deeply unsuited to the modelling of data significantly affected by censoring. It is unclear how stratification factors have been taken into account. This is because the proportional difference breaks down towards the right of the Kaplan-Meier curve due to censoring. Thus there is very little evidence upon which to base the estimate of the treatment effect that is the basis for the extrapolation beyond the trial period. Necessarily, this leads to wildly variable estimates of differences in overall survival depending on which assumptions are made. The predicted difference becomes more stable further up the Kaplan-Meier curve. Analyses based on data that is much less censored, (i.e. Region 1) demonstrate a much more stable proportional difference.
- The best estimate of the difference between the treatment arm and the comparator arm is the hazard ratio estimated from a stratified cox regression model, because this analysis uses all available data on the effect of treatment; the LRIG method is strongly influenced by transition probabilities calculated from few, heavily censored, observations at the end of the Kaplan Meier curves.
- Where the cost effectiveness of eribulin is modelled using the proportional hazards method, the drug is demonstrated to extend life by a period greater than 3 months compared to TPC even when more conservative assumptions are made with respect to choice of functional form of curves (i.e. when the exponential functional form is used). Furthermore, the advantage is maintained in the population previously treated with capecitabine.
- The incorporation of the data from the EMBRACE study into a meta-analysis (See Appendix 1) demonstrates that the estimate of the median overall survival of patients taking vinorelbine in the EMBRACE trial is consistent with the performance of vinorelbine in similar patients in other studies. As we have a robust estimate from the meta-analysis of the median overall survival for comparable patients taking eribulin, the difference between eribulin and vinorelbine in the analysis of EMBRACE is significantly validated.
- The difference in mean overall survival, even when modelled using the LRIG method, demonstrates an expected improvement in overall survival of eribulin compared to vinorelbine that is well in excess of the three month benchmark for qualification for the end of life criteria (See Table 8).
- Whether the cost effectiveness of eribulin compared to vinorelbine is tested in All Regions or in the Region 1 sub-group, the analyses predict cost effectiveness ratios that are well within the bounds that have resulted in a recommendation for use by NICE in the past.
- With the above points in mind, the Committee is asked to consider that the base case for the cost effectiveness of eribulin as the analyses compared to vinorelbine. It should be drawn to the Committee's attention that in the EMBRACE trial the vast majority (around 95%) of patients that took vinorelbine in Region 1 had previously been treated with capecitabine. Therefore, it is reasonable that the analysis compared to vinorelbine in Region 1 is representative of the cost effectiveness in this patient population.

- The relevant tables for the bases case analysis are tables 28, 29 and 30. These demonstrate the cost effectiveness of eribulin in Region 1, with appropriate sensitivity analysis to the choice of functional form of the fitted curve. Hazard ratios fitted to these curves were provided in the original submission and in this additional data submission. The relevant survival curves for the analyses are provided in Appendix 3. All other changes made to the analyses are completely in line with the parameter assumptions used by the ERG model, as detailed in Appendix 2.

STA_Addendum

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Eribulin for the treatment of locally advanced or metastatic breast cancer

ADDENDUM

This report was commissioned by the NIHR HTA Programme as project number 10/19

Completed 13th September, 2011

CONTAINS IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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1 BACKGROUND

On 23rd June 2011, the National Institute for Health and Clinical Excellence (NICE) Appraisal Committee (AC) considered the evidence for use of eribulin (Halaven®) as a treatment for patients with locally advanced or metastatic breast cancer (LABC/MBC) who have received two or more chemotherapy (CTX) regimens. On 12th July 2011 NICE issued its Appraisal Consultation Document (ACD) which stated that "eribulin is not recommended for the treatment of locally advanced or metastatic breast cancer in people whose disease has progressed after at least two chemotherapeutic regimens for advanced disease".[1]

The manufacturer of eribulin (Eisai) made a successful request to NICE to submit new evidence at the ACD consultation stage for the appraisal of eribulin for the treatment of LABC/MBC, as permitted by the Single Technology Appraisal Process Guide.[2]

This document summarises an assessment by the Evidence Review Group (ERG) of the supplementary evidence submission provided by Eisai.

2 SUMMARY OF SUPPLEMENTARY EVIDENCE

2.1 Submission overview

The manufacturer's supplementary evidence submission included an appendix to the initial submission document together with an updated version of the EXCEL cost-effectiveness model.

The main focus of the new evidence submitted involves the restriction of the population considered for treatment to those patients previously treated with capecitabine, who constitute 74% of all patients included in the EMBRACE[3] clinical trial. The manufacturer argues that this is consistent with current NICE guidelines,[4] especially if vinorelbine is used as the primary comparator.

The main body of the supplementary evidence submission is taken up with discussions of different approaches to estimating survival outcome benefits within the economic model, and the differing results obtained with alternative assumptions. The objectives of these analyses are two-fold: to indicate the range of incremental cost-effectiveness ratios (ICERs) which can be generated under different scenarios, and also to establish the likely range of estimated gain in overall survival (OS) which can be attributed to use of eribulin, for use in the consideration of the NICE 'end of life' criteria.[5]

2.2 New clinical evidence

The manufacturer provides information for the post-capecitabine subgroup of EMBRACE[3] for median OS (the primary outcome of the trial), showing a significant improvement of 2.9 months (hazard ratio[HR]=0.787).

In addition, the manufacturer includes details of a meta-analysis of other clinical studies in which the median OS attributable to eribulin (4.33 months) is comparable to that indicated for eribulin vs vinorelbine in the EMBRACE[3] intention-to-treat (ITT) population (4.2 months), despite the small number of patients receiving vinorelbine in the EMBRACE[3] trial.

2.3 New economic evidence

Data inclusion

The manufacturer presents arguments against the employment of data from the whole EMBRACE[3] trial, preferring to use only Region 1 data (North America and Europe) arguing that data from Regions 2 (Eastern Europe, Russia and Turkey) and 3 (Latin America and South Africa) are less mature due to patient enrolment starting later, and that this leads to a bias which may underestimate the survival benefit from use of eribulin.

Projective modelling

The manufacturer presents arguments for earlier use of projective modelling (from 35% of patients remaining alive), rather than the ERG's approach which minimises the influence of projective modelling and maximises use of the unadjusted trial data. The manufacturer presents arguments to support alternative forms of projective modelling, and also argues against the simple exponential form employed by the ERG. In addition, the manufacturer indicates their preference for a proportional hazard approach to survival modelling, suggesting that this provides more stable results.

Model results

The manufacturer provides summary results for:

- 24 different OS modelling scenarios involving different populations, different comparators and different survival projection methods
- 21 different cost-effectiveness analysis model scenarios
- 9 different cost-effectiveness analysis model scenarios adjusted for increased utility values to represent 'end of life' thresholds
- a sensitivity analysis using the costs of intravenous (rather than oral) vinorelbine
- two probabilistic sensitivity analyses.

The ICERs reported range from £63,761 - £23,790 per QALY gained. The manufacturer's preferred scenarios reflect three proportional hazard projection models using different functional forms (log-logistic, exponential and log-normal) and are restricted to patients from Region 1 who had been planned to receive vinorelbine, with ICERs between £23,790 and £26,475 per QALY gained (Tables 28-30 in the Eisai document "Appendix: Additional evidence in response to the Appraisal Consultation Document (ACD)") .

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3 RE-DEFINING THE DECISION PROBLEM

3.1 New basis for evidence synthesis

Although the manufacturer's supplementary evidence submission does not explicitly redefine the decision problem for the appraisal it is clear from the first paragraph of the document, that a new basis is being proposed.

Whereas the initial manufacturer's submission imposed no limitation related to prior therapy, it is clear that the AC is being asked to consider only the use of eribulin in patients who have relapsed after previous treatment with capecitabine. In addition, the manufacturer has modified the comparator technology from "treatment of physician's choice" (TPC) to vinorelbine, on the basis that this more closely matches the stage within the current NICE guidelines[4] at which it is envisaged that eribulin may be used.

The ERG considers that both these alterations are reasonable and realistic in the UK context where capecitabine is widely used for LABC/MBC patients. However, there are likely to be practical implications for the analyses required to reflect these changes in order to rework estimates of clinical benefit and cost effectiveness. The reduction of the overall volume of admissible trial data by a quarter is likely to increase uncertainty in analytical results. In addition, the restriction of the comparator to less than 25% of the overall trial population suggests that it may prove impossible to obtain meaningful results for comparisons of clinical effectiveness, or as a basis for projective modelling of outcomes.

3.2 What base-case scenario should be used?

In line with the manufacturer's revised submission, it is appropriate that patients who had not received prior treatment with capecitabine should be excluded from consideration. In addition, the model calibration should initially be based on patients intended for treatment with vinorelbine prior to randomisation to eribulin or vinorelbine.

The manufacturer argues that data from Region 1 only should be used in the analysis, on the basis that centres in Regions 2 and 3 began recruiting at a later date, and that the greater degree of censoring would bias survival estimates and HRs. This is a curious supposition since techniques such as Kaplan-Meier and Cox regression analysis are specifically designed to take account of differing proportions of censoring within data sets. However, to test this hypothesis the ERG have applied Cox regression analysis to the OS data from the EMBRACE study, restricted to patients with previous experience of capecitabine therapy. The explanatory variables included in the analysis are the trial arm (eribulin or TPC), the recorded "Best Response to therapy", as well as the two remaining randomisation variables (HER2 status and Region). Using a step-wise procedure, the first variable

entered into the model was "Best Response to therapy" ($p < 0.001$). No more variables achieved the 5% significance level required, indicating that neither treatment, HER2 status nor geographical region could contribute significant additional explanatory power. When the analysis was repeated omitting the "Best Response to therapy" variable, only the trial arm (eribulin vs TPC) proved to be significant. Thus it appears that these two factors are sufficient to account for the observed results, and there are no grounds for distinguishing between subgroups of patients on the basis of either HER2 status or geographic region. The ERG therefore considers it is appropriate to use suitable trial data from all regions in calibrating the economic model.

On this basis, the newly submitted cost-effectiveness scenario results were examined to identify which mostly match these criteria. Amongst the scenarios using Kaplan-Meier values combined with long-term projective modelling, the closest equivalent yields the results shown in Table 16 of the re-submission with an ICER of £38,005. There are no equivalent scenarios based on proportional hazards (PH) modelling, since it was noted by the manufacturer that:

"Unfortunately, no post capecitabine analysis (vs. vinorelbine all regions) was ready in time for this submission. However as mentioned 95% of patients in Region 1 had received prior capecitabine and the committee have confidence that they are unlikely to be greatly different from the Region 1 outcomes."

It should be noted that the PH scenarios using data from all regions (Tables 25-27) yield greater ICERs than those using only Region 1 data (Tables 28-30): £35,242-£41,480 per QALY gained compared to £23,790-£26,475 per QALY gained. This indicates that using the data from all regions is likely to result in higher ICERs irrespective of whether patients not previously treated with capecitabine are excluded. In order to assess the relative impact of various changes made by the ERG to the economic model, the scenario represented by the manufacturer's Table 16 is used below as the starting point for comparison.

4 FURTHER ANALYSIS UNDERTAKEN BY ERG

4.1 Implementation of amendments and corrections previously identified

The original ERG report identified a series of logic errors and amendments and recommended that these should be applied to the manufacturer's model (Table 33). In each case the ERG has examined the re-submitted model to determine whether these changes have been correctly implemented by the manufacturer. In several cases it was found that changes had not been incorporated; in response, the ERG has applied the necessary alterations to the model to ensure that the impact of these factors can be properly understood. The results are shown in Table 1.

Table 1 ERG revisions to re-submitted cost-effectiveness model results

Scenario / changes	Eribulin		Vinorelbine		Incremental		ICER
	Cost per patient	QALYs per patient	Cost per patient	QALYs per patient	Cost per patient	QALYs per patient	
Table 16*	**£20,673**	**0.7530**	**£13,253**	**0.5577**	**£7,420**	**0.1952**	**£38,005**
+ discounting logic	£20,920	0.7640	£13,405	0.5652	£7,515	0.1987	£37,818
+ terminal period logic	£22,585	0.7302	£15,190	0.5346	£7,395	0.1955	£37,819
+ mid-cycle logic	£20,274	0.7320	£13,165	0.5366	£7,110	0.1954	£36,391
+ IV vinorelbine cost	£20,673	0.7530	£12,769	0.5577	£7,904	0.1952	£40,488
+ febrile neutropenia	£20,744	0.7529	£13,279	0.5577	£7,465	0.1952	£38,244
Table 16 revised*	**£22,522**	**0.7311**	**£14,812**	**0.5321**	**£7,710**	**0.1990**	**£38,737**

*Table 16 refers to manufacturer's revised submission

The net effect of applying all these modifications is very small, indicating that none of these concerns is likely to prove influential for decision-making.

4.2 New survival analysis

The major alterations made to the decision problem have the potential to lead to different methods in the estimation of patient outcomes as the relevant data subset is likely to exhibit reduced heterogeneity. In particular, omission of patients not previous treated with capecitabine and restriction of patients to those initially identified for treatment with vinorelbine result in reduced patient numbers, but may give important insights into the manner by which patient benefit accrues over time.

Examination of the OS Kaplan-Meier plot for this patient subgroup (Figure 1) is suggestive that the survival experience of patients receiving vinorelbine and eribulin may converge after about 2 years. However, the small number of patients in the comparison [redacted] means that this pattern could easily have arisen by chance. This is an important matter to resolve, since if the convergence can be confirmed from the trial evidence this would imply that an accurate estimate of survival gain could be obtained directly from the Kaplan-Meier analysis without need for any parametric projective modelling. Moreover, the magnitude of the estimated gain is likely to be considerably smaller than that obtained by accumulating additional benefit indefinitely (equivalent to the area of the gap between the two projective curves shown in **Error! Reference source not found.**).

Figure 1

In the ERG report it can be observed (Table 31 and Figure 3) that the vinorelbine, gemcitabine and capecitabine subgroups exhibited similar mean OS and statistically significant survival gain. Although capecitabine is now excluded from consideration in this analysis, since all patients have received capecitabine previously, there remains the possibility of augmenting the vinorelbine data with additional gemcitabine patients if it can be shown that patient outcomes (OS and progression-free survival [PFS]) are sufficiently similar.

This hypothesis was tested by the log-rank test, and examination of the Kaplan-Meier plots. **Error! Reference source not found.** and **Error! Reference source not found.** illustrate the close correspondence between the vinorelbine and gemcitabine planned treatment cohorts for both arms of the clinical trial for OS.

Figure 2

Figure 3

Similar results were obtained for investigator PFS. As a consequence it was deemed appropriate by the ERG to pool the vinorelbine and gemcitabine cohorts to obtain more robust survival results with an 80% increase in patient numbers available for analysis.

Error! Reference source not found. and **Error! Reference source not found.** confirm the suspected convergence of eribulin and TPC trial arms when the larger pooled data set is analysed.

Figure 4

Figure 5

Table 2 shows the results of estimating the survival gain attributable to eribulin compared to TPC for both the planned vinorelbine subgroup, and the pooled vinorelbine and gemcitabine subgroups. The latter shows slightly larger estimated gains in OS (99 vs 85 days), and narrower confidence intervals as expected. In both cases the additional survival is split evenly between the pre- and post-progression periods.

These estimates of extended OS contrast strongly with modelled estimates from the manufacturer's Table 16 scenario (4.5 months) and preferred proportional hazards scenarios in Tables 28-30 (over 7 months).

Table 2 Kaplan-Meier survival estimates using the Area Under Curve (AUC) difference until survival curves converge

	Upper limit (days)	**Mean survival (days)**		**Survival gain (days)**		**Survival gain (months)**	
		TPC	**Eribulin**	**Mean**	**95% CI**	**Mean**	**95% CI**
Vinorelbine subset							
PFS	230	76	118	43	29 to 57	1.40	0.94 to 1.87
OS	**766**	**333**	**418**	**85**	**30 to 140**	**2.79**	**0.99 to 4.59**
PPS	N/A	257	299	42	2 to 82	1.38	0.07 to 2.70
Vinorelbine+gemcitabine pooled subsets							
PFS	381	94	141	47	31 to 63	1.54	1.01 to 2.07
OS	**827**	**341**	**440**	**99**	**57 to 142**	**3.27**	**1.88 to 4.65**
PPS	N/A	247	299	53	2 to 85	1.73	0.68 to 2.78

N/A=not applicable; PFS=investigator assessment PFS; TPC=treatment of physician choice; CI=confidence interval; PPS=post progression survival (estimated as the difference between OS and PFS)

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4.3 ERG revised cost-effectiveness results

Reference case utility values

It was noted in the first AC meeting that the utility values used by the manufacturer did not match the requirements of the NICE reference case. Subsequent to the meeting, Simon Dixon, a committee member unable to be present at the meeting, wrote to NICE staff drawing attention to the evidence previously presented at an earlier appraisal (see copy of his letter in Appendix 1). This used a value of 0.69 obtained from EQ-5D data collected in the EFG100151 clinical trial for pre-progression survival. Since this type of data would normally be considered more reliable than either figures obtained by standard gamble responses by non-patients, or inferred by mapping from a quality of life instrument, it is suggested that it should be used in place of the manufacturer's parameter value in the submitted model. The impact of this change is relatively minor. When applied to the scenario shown in Table 1, the ICER increases from £38,005 to £38,408 per QALY gained. When combined with all the other modifications in Table 1, the overall revised ICER increases from £38,737 to £39,137 per QALY gained. This additional amendment is included in the results shown below.

ERG survival estimates

In order to recalculate the impact of the Kaplan-Meier survival gains estimated by the ERG (Table 2), two sets of Kaplan-Meier have been added to the manufacturer's resubmitted model as alternatives to the original OS and PFS survival data for the vinorelbine subgroup and the pooled vinorelbine and gemcitabine subgroups.

Since there are insufficient patient data beyond the convergence point in each of the survival curves to allow any meaningful projection beyond this point, the Kaplan-Meier are terminated at that point (equivalent to all remaining patients dying at that time). This underestimates survival in both arms of the comparison by exactly the same amount so has no effect on either incremental costs or patient outcomes and so does not bias the calculation of the ICER in any way.

ERG revised cost-effectiveness estimates

Table 3 summarises the effect of these changes to the cost-effectiveness results generated by the modified decision model. The comparator in all cases is vinorelbine with its associated treatment costs and adverse event profile. The choice between using Kaplan-Meier survival estimates based on the small subgroup of patients with vinorelbine as the intended management or using the extended subgroup including also those intended for gemcitabine treatment has only a minor effect on the size of the estimated ICER (£53,538 vs £53,446 respectively). On the basis of minimising uncertainty (i.e. maximising the data set used for analysis) the ERG is inclined to prefer the use of the pooled subgroups.

Table 3 ERG revised cost-effectiveness model results including EQ-5D utility value and convergent Kaplan-Meier survival estimates

Scenario/changes	Eribulin		Vinorelbine		Incremental		ICER
	Cost per patient	QALYs per patient	Cost per patient	QALYs per patient	Cost per patient	QALYs per patient	
MS Table 16*revised	£22,522	0.7311	£14,812	0.5321	£7710	0.1990	£38,737
+ EQ-5D utility value	£22,522	0.7257	£14,812	0.5287	£7710	0.1970	£39,137
Vinorelbine subgroup survival	£20,633	0.6050	£13,623	0.4740	£7011	0.1309	£53,538
Vinorelbine/gemcitabine subgroup survival	£22,902	0.6455	£14,719	0.4924	£8184	0.1531	£53,446

*Table 16 refers to manufacturer's revised submission

N.B. Cost and QALY totals using Kaplan-Meier sub-group survival estimates are not directly comparable with other scenarios due to truncation of model at point of convergence. However, incremental cost and QALY estimates and ICERs are directly comparable with all other scenarios.

5 SUMMARY

The ERG welcomes the manufacturer's reorientation of their submission to restrict use of eribulin to those patients previously treated with capecitabine, rather than an unspecific comparison with any other treatment that a physician may choose. This appears to locate eribulin more clearly within the context of current NICE guidelines[4] for the treatment of breast cancer. However, the ERG considers that this restriction is likely to alter the characteristics of the data set selected for analysis from the pivotal clinical trial, with the prospect of eliminating at least some of the evident heterogeneity which makes projective modelling uncertain and contentious.

The ERG's own analysis of the data led to two important conclusions:

- that there is no basis for excluding any records from the data set on the basis of the location of trial centre (no regional bias);

- that it is likely that the net outcome benefits attributable to use of eribulin in terms of PFS and OS are limited to a specific time period from randomisation, and do not extend indefinitely.

The main consequence of these observations is that the most reliable estimates of benefit are obtained directly from the non-parametric Kaplan-Meier analysis of the trial data, obviating the need for any parametric projective modelling (as discussed at length in the manufacturer's resubmission) and avoiding the need for any regional exclusions of trial records.

On the basis of this much simpler approach to estimating cost effectiveness, the ERG has concluded that the most reliable estimated ICER for eribulin compared to vinorelbine in treating patients previously treated with capecitabine is £53,446 per QALY gained.

6 REFERENCES

1. National Institute for Health and Clinical Excellence. Breast cancer (advanced) eribulin: appraisal consultation document. 2011 [cited 2011 September 2011]; Available from: http://guidance.nice.org.uk/TA/Wave23/32/Consultation/DraftGuidance.
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3. Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011; 377(9769):914-23.
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5. National Institute for Health and Clinical Excellence. Supplementary Advice to the Appraisal Committees - End of Life Treatments. 2009; Available from: http://www.nice.org.uk/aboutnice/howwework/devnicetech/endoflifetreatments.jsp?domedia=1&mid=88ACDAE5-19B9-E0B5-D422589714A8EC6D.

7 APPENDIX

Appendix 1 Letter to NICE from Simon Dixon re: reference case utility values

Robert

I was unable to attend the Eribulin meeting, but wish to make a comment on the ACD. Is this best done through the public consultation process or at the next meeting? If use the consultation process, you could ask the manufacturer (or LRiG) to do the necessary analyses. My concern is that the manufacturer is now doing further analyses based on (what I suggest to be) the wrong estimates of QoL - it would be better if they did the analyses on the correct estimates. FYI, my comment is below:

Within the appraisal, the utility values used are based on those of Lloyd et al., which are non-reference case. However, in the absence of more appropriate evidence these have necessarily been accepted. The utility values used by the manufacturer are 0.715 for stable disease and 0.79 for response, which were revised upward by the ERG to 0.756 and 0.823, respectively.

However, reference case utility values for a similar patient population are available. In the suspended NICE appraisal of lapatinib for HER2 over-expressing breast cancer, the manufacturer provided EQ-5D utilities from the pivotal trial on which the appraisal was based (EFG100151). The pre-progression utility used by the manufacturer was 0.69, which is in essence an weighted average of stable and responding disease. This figure is considerably lower than that used in the eribulin appraisal and suggests a possible bias within the estimates of cost-effectiveness.

The key question then becomes, how similar are the patient populations in the respective appraisals?

The patient population for EFG100151 is advanced or metastatic HER2 over-expressing breast cancer who have received two prior therapies, whilst for EMBRACE it is locally advanced or metastatic breast cancer who have received at least two prior therapies.

The median age in EFG100151 is 52. The median age in EMBRACE is 56.

ECOG 0 at baseline in the lapatinib arm of EFG100151 is 58% and 43% in the eribulin arm of EMBRACE.

Median overall survival is 67.7 weeks for lapatinib (=474 days) in EFG100151 and 399 days for eribulin in EMBRACE.

All figures are taken from the publicly available ERG reports and/or manufacturer submissions.

This suggests that the reference case estimate of pre-progression utility from EFG100151 is suitable for the eribulin appraisal, and as such, is preferred to the figures employed by the manufacturer and the ERG.

Thanks, Simon.

From: [redacted]
Sent: 23 September 2011 15:21
To: Helen Knight
Subject: RE: CMU contracts and national acquisition costs of vinorelbine PROTECT - COMMERCIAL

Helen,

As requested, discounts are in the range 80-90%

Regards

[redacted]

From: Helen Knight [mailto:Helen.Knight@nice.org.uk]
Sent: 23 September 2011 14:53
To: [redacted]
Subject: RE: CMU contracts and national acquisition costs of vinorelbine PROTECT - COMMERCIAL

Hi [redacted],

Thanks for your quick response. It would be great if you could provide the range of discounts for me. I don't suppose you are free in the next 10 minutes for a quick chat? If so, you can call on my number below or if you give me your number, I will call you.

Best wishes,

Helen

Helen Knight
Associate Director - Appraisals (working days: Monday to Thursday)
Tel: 44 (0)161 870 3157

From: [redacted]
Sent: 23 September 2011 14:05

To: Helen Knight
Subject: RE: CMU contracts and national acquisition costs of vinorelbine PROTECT - COMMERCIAL

PROTECT – COMMERCIAL

Dear Helen,

The actual prices that are available to the NHS through CMU framework agreements vary by region [redacted]

You could derive a range from eMIT in terms of discount from BNF prices [redacted]

Please feel free to get in touch if you need anything more – but I am on leave after today until Thurs. next.

Regards

[redacted]

From: Helen Knight [mailto:Helen.Knight@nice.org.uk]
Sent: 23 September 2011 09:31
To: [redacted]
Subject: CMU contracts and national acquisition costs of vinorelbine
Importance: High

Hi [redacted],

Meindert Boysen passed me your contact details as I have an appraisal which is being discussed next week, where the comparator is vinorelbine. We have been made aware that IV vinorelbine is provided at a discount to the NHS, as detailed below:

BNF
Vinorelbine (Non-proprietary) - Concentrate for intravenous infusion, vinorelbine (as tartrate) 10 mg/mL, net price 1-mL vial = £29.00, 5-mL vial = £139.00

NHS CMU electronic Market Information Tool (eMIT)
Vinorelbine 10mg/1ml solution for injection vials / Packsize 1: Average price £5.11 (StdDev £3.46)
Vinorelbine 10mg/1ml solution for injection vials / Packsize 10: Average price £48.98 (StdDev 13.87)
Vinorelbine 50mg/5ml solution for injection vials / Packsize 1: Average price £23.09 (StdDev 21.40)
Vinorelbine 50mg/5ml solution for injection vials / Packsize 10 Average price £213.26 (StdDev 81.39)

I have a couple of questions that I would really appreciate you answering – along the lines of what Meindert asked last year.

- are these discounts/prices I have identified above consistently available across the NHS?

- is the period for which the discount/price range is available guaranteed? And if so, what is the period for which it will be guaranteed.

In addition, I would be keen to know whether, if needed, we would be able to use the above information on our documentation, or if not in the format above, perhaps quoting the range of the discounts from the BNF price or branded price? This will certainly be brought up in our Committee discussion next week.

If you could get back to be asap (the Committee meeting is on Tuesday) I would be extremely grateful. I am very sorry about the short notice. Please feel free to give me a call if you have any questions.

Best wishes,

Helen

Helen Knight
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ERG results with CMU prices (eribulin)

Scenario/changes	Eribulin		Vinorelbine		Incremental		ICER
	Cost per patient	QALYs per patient	Cost per patient	QALYs per patient	Cost per patient	QALYs per patient	
Vinorelbine subgroup survival (BNF prices)	**£20,633**	**0.6050**	**£13,623**	**0.4740**	**£7011**	**0.1309**	**£53,538**
(CMU single vial prices)	£20,633	0.6050	£12,255	0.4740	£8,379	0.1309	£63,986
(CMU multi-pack prices)	£20,633	0.6050	£12,235	0.4740	£8,398	0.1309	£64,132
Vinorelbine/gemcitabine subgroup survival (BNF prices)	**£22,902**	**0.6455**	**£14,719**	**0.4924**	**£8,184**	**0.1531**	**£53,446**
(CMU single vial prices)	£22,902	0.6455	£13,046	0.4924	£9,856	0.1531	£64,370
(CMU multi-pack prices)	£22,902	0.6455	£13,023	0.4924	£9,880	0.1531	£64,522