NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

HEALTH TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on Eribulin for the treatment of locally advanced metastatic breast cancer

Decision of the Panel

Introduction

1. An appeal panel was convened on 13 February 2012 to consider an appeal against the Institute's Final Appraisal Determination (FAD), to the NHS on eribulin for the treatment of locally advanced metastatic breast cancer.

2. The Appeal Panel consisted of Mr Andy McKeon (Chair), Ms Mercy Jeyasingham (Non-Executive Director, NICE), Dr Hugh Annett (NHS Member), Dr Mercia Page (Industry Representative) and Mr John Morris (Lay Representative).

3. None of the members of the Appeal Panel had any competing interest to declare.

4. The panel considered an appeal submitted by the company Eisai Ltd.

5. The Appellants were represented by Mr Nick Burgin (Eisai Ltd), Mr Trefor Jones (Eisai Ltd), Dr Tony Patrikios (Eisai Ltd), Professor Chris Twelves (Eisai Ltd) and Dr Adela Williams (Legal Counsel, Arnold & Porter).

6. Professor Chris Twelves declared an interest as a principal investigator in the EMBRACE trial.

7. In addition the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel: Professor Peter Clark (Appraisal Committee Chair), Professor Jonathan Michaels (Appraisal Committee Vice Chair), Mr Meindert Boysen (Programme Director, Centre for Health Technology Evaluation), Ms Helen Knight (Technical Advisor, Appraisals) and Mr Bhash Naidoo (Associate Director, Research & Development).

8. All of the above declared no conflicts of interest.

9. The Institute's legal adviser Mr Stephen Hocking (DACBeachcroft LLP) was also present.

10. Under the Institute's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal.

11. There are three grounds under which an appeal can be lodged:

- The Institute has failed to act fairly
- NICE has formulated guidance which cannot reasonably be justified in the light of the evidence submitted
- The Institute has exceeded its powers

12. The Chair of the Appeal Committee (Dr Maggie Helliwell) in preliminary correspondence had determined that:

- The Appellant Eisai Ltd had valid grounds of appeal as follows:

Ground 1

1.1 The additional data submitted by Eisai in response to the Appraisal Consultation Document (ACD) were substantial and the Appraisal Committee's conclusions in relation to this material should have been subject to consultation.

1.2 The late disclosure of the supplementary report prepared by the Evidence Review Group (ERG) precluded proper consideration of the report by Eisai prior to the second meeting of the Appraisal Committee.

1.4 The Appraisal Committee has failed to consider a comparison of eribulin with Treatment of Physician's Choice (TPC) in the population of patients previously treated with capecitabine.

1.6 The Appraisal Committee's conclusions with respect to the costs of vinorelbine which should be used for economic modelling in this appraisal are inconsistent with the approach specified in NICE's procedures and unfair.

Ground 2

2.1 The Appraisal Committee's conclusions with respect to the adverse events associated with eribulin do not reflect a balanced and reasonable assessment of the available evidence.

2.2 The Appraisal Committee's decision to reject the analysis based on the data from Region 1 of the EMBRACE trial is unreasonable.

2.3 The Appraisal Committee's reliance on the calculation of overall survival for patients pre-treated with capecitabine, based on the ERG's methodology set out in its Addendum Report, is unreasonable.

13. Eribulin (Halaven, Eisai) has a UK marketing authorisation as a monotherapy 'for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease'. Prior therapy should have included an anthracycline and a taxane unless these were unsuitable for the patient. The recommended dose of eribulin as the ready to use solution is 1.23mg/m2 (equivalent to 1.4 mg/m2 eribulin mesilate), which is administered intravenously over 2-5 minutes on days 1 and 8 of every 21-day cycle.

14. The appraisal that is the subject of the current appeal provided advice to the NHS on eribulin for the treatment of locally advanced or metastatic breast cancer.

15. Before the Appeal Panel inquired into the detailed complaints the following made preliminary statements: Mr Nick Burgin on behalf of Eisai and Professor Peter Clark on behalf of the NICE Panel.

Mr Burgin said that it was important to be mindful that metastatic breast cancer is an incurable disease with poor prognosis. Hence the importance of therapy directed to extending the duration and quality of life. Also, survival of patients with this condition in the UK lags behind that of other European and North American countries. Current NHS treatment lacks an evidence base and eribulin would rectify this situation. Eribulin has a novel mode of action and has taken 25 years to develop. The Royal College of Physicians had written to express the unanimous agreement of expert opinion on the value of eribulin as a 3rd and 4th line treatment. The pivotal EMBRACE trial, which was carefully designed to model current treatment, comparing eribulin with TPC is well recognised as an appropriate and valid methodology. It demonstrated overall survival for patients treated with eribulin. The results of EMBRACE led to marketing authorisation in record time.

With this background Eisai were very disappointed with the conclusion of the FAD which Eisai considers to be based on inappropriate approaches. 1) The FAD questioned the safety of eribulin – it has side effects but these are predictable and manageable. 2) Consideration of eribulin by the Appraisal Committee had been inconsistent. The scope required comparison with individual treatments (vinorelbine, capecitabine and gemcitabine). The first Appraisal Committee compared eribulin with TPC and Eisai were requested to provide additional evidence. But, at the second meeting, comparison with TPC was rejected. The Appraisal Committee only evaluated comparison with vinorelbine. But, comparison with TPC demonstrates improvement on overall survival of 2.9 months for eribulin and this should have been considered. 3) For estimation of overall survival, the Appraisal Committee chose at its second meeting to rely on a methodology that was not recommended by the Decision Support Unit rather than the methods used by Eisai. Reliance was placed on a wholly new analysis by the ERG without allowing for

consultation or sufficient time for Eisai to give this proper consideration.

Consequently it was difficult to avoid the conclusion that alternative approaches were chosen simply because they gave a negative result on the cost-effectiveness of eribulin. Eisai has made eribulin available to the NHS at the lowest price in the world and it believed the FAD had let it and patients down and its conclusions were unreasonable.

Professor Clark said that, for this patient group, treatment is palliative in nature and it was necessary to balance benefit with the side effects of therapy. He noted that advanced breast cancer lacked robust therapies. The Appraisal Committee was pleased to see the pragmatic design of the EMBRACE design and was delighted that overall survival was the primary end point and that there was significant improvement in overall survival. The Appraisal Committee was disappointed however that quality of life was not assessed. Eribulin was clearly clinically effective. The main point of contention between the committee and the manufacturer was the estimation of mean overall survival. The Appraisal Committee considered all the issues raised by Eisai had been fairly dealt with as described in the FAD. Although clinically effective and providing a further treatment option, the Appraisal Committee's analysis was that eribulin was not sufficiently cost effective for NICE to recommend its use by the NHS.

Appeal by Eisai

Appeal Ground 1: The Institute has failed to act fairly

Appeal Ground 1.1: The additional data submitted by Eisai in response to the ACD were substantial and the Appraisal Committee's conclusions in relation to this material should have been subject to consultation.

16. Before presenting the case on this appeal point Dr Williams for Eisai expressed concern that appeal point 1.3 concerning the Appraisal Committee's approach to the estimation of overall survival benefit originally put forward by Eisai had not been considered a valid appeal point at initial scrutiny. Eisai believed this had been an incorrect decision and asked if Eisai would be permitted to raise the point during the appeal. The Chair, Mr McKeon, noted that the point had been fully considered and rejected by the Chair of NICE's Appeal Committee at initial scrutiny and it was not now possible for it to be considered by the panel. (The full text of appeal point 1.3 and the reasons for its rejection at initial scrutiny are included as an appendix to this decision letter.)

    Dr Williams then introduced the Eisai case in relation to appeal point 1.1, saying that at its first meeting, and as reflected in the ACD, the Appraisal Committee indicated it would find further analysis helpful. Consequently Eisai submitted pre-specified analysis for the post-capecitabine

population with two further estimates of overall survival. NICE obtained a further ERG report that was considered at the second Appraisal Committee meeting. This consideration led to six paragraphs in the FAD, one third of the Appraisal Committee's conclusions. Despite this substantial new material there was no second round of consultation. That is, one third of the conclusions of the FAD were not subject to consultation. NICE has an obligation to consult. While recognising that the procedures gave discretion to the Appraisal Committee chair whether or not to consult for a second time, he must exercise this discretion fairly and it was unfair that Eisai and eribulin received considerable criticism without Eisai having the opportunity to respond.

17. Professor Clark for the Institute explained that the Appraisal Committee did not ask for a post-capecitabine analysis. The ACD reflected the Appraisal Committee's three main conclusions, namely to use all of the intention to treat (ITT) population for all regions for analysis, to use the ERG modelling of overall survival for eribulin compared with TPC, and to compare eribulin with TPC rather than with single comparators. These had been consulted on. The conclusions were fully endorsed by the Royal Colleges and the manufacturer was the only body not to accept them and to challenge the modelling of overall survival. At the second Appraisal Committee meeting the manufacturer's second submission and the ERG report on it had been considered and there had been vigorous debate with the manufacturer. The two main concerns for the Appraisal Committee had been the uncertainties introduced to the analysis if the population base was narrowed and the exacerbation of this if the analysis was further restricted to the post-capecitabine group. In terms of these two issues, the Appraisal Committee already knew what the views of the professional bodies representing oncologists were. The Appraisal Committee did not consider that truly new material had been introduced or that there was a change in the evidence base and did believe that their decision was responsive to and still properly informed by the first consultation. In terms of ICERs, the one in the FAD is the same as in the ACD. As a consequence of all these considerations the Appraisal Committee thought it appropriate to issue the FAD without further consultation.

18. Mr McKeon asked if the Appraisal Committee had actively considered issuing a second appraisal consultation document. Professor Clark responded that this consideration was a normal part of the process. They look at the issues and consider the extent of changes and the likelihood of gaining from further consultation. In this case, if the manufacturer had not been present and contributing to the vigorous debate about the decision problems there might have been a stronger case for further consultation. Mr Boysen said that the Institute's Guidance Executive had accepted the Appraisal Committee's reasoning for not issuing a second ACD. Professor Clark expressed the view that the views of other consultees had already been made clear and confirmed that the Appraisal Committee had considered but not accepted any ICER other than the £68,600 per QALY gained quoted in the ACD and FAD. It was

noted that the manufacturer had opportunity to contribute to the debate of the issues but not to the determination of the conclusions as these were arrived at in a closed meeting. Dr Williams said that proper consultation requires that the question is put to consultees and for the latter to have sufficient opportunity to consider and respond but Eisai had not seen the conclusions before the FAD was issued. Given that the FAD contained so many conclusions not previously published it was not right to assume that no one else other than Eisai would have taken issue with the conclusions. As it was, Eisai were subject to criticism and had no proper opportunity to respond. Mr Jones for Eisai indicated he had been at the second Appraisal Committee meeting and there were issues raised and complicated questions that he would normally take advice on but this had not been possible. Professor Clarks reiterated his view that the meeting had fully covered the issues raised by Eisai in the second submission and the manufacturer's contributions to the debate at the meeting were substantial. Appraisal Committee members had commented on the value of those contributions.

19. The Appeal Panel noted that the manufacturer had responded to the ACD at length and provided substantial additional analysis. This had plainly been taken into account. It also noted the general principle that there is no obligation to conduct a second consultation just because new material has been submitted after a first consultation. Everything depended on the facts. The Appeal Panel then considered whether the manufacturer's responses had introduced substantial fresh evidence which cast existing issues in a new light, or a new issue of such significance that guidance could not fairly be published without a second consultation. It also considered whether the Appraisal Committee had itself substantially changed its position on what the main drivers of the decision were or on its conclusions. On the basis of the arguments it had heard it concluded that none of this was so. The essential issues and evidence driving the guidance had been fairly consulted on during the appraisal process. The Appeal Panel noted that the most fundamental evidence, the trial data, was of course unchanged. The manufacturer had submitted a new analysis. They were entitled to do so if that was how they considered they could best respond to a consultation. However, consultation is consultation on the appraisal carried out up to that point.

The Appeal Panel had in mind that the manufacturer had already had the chance to submit its preferred analysis as the basis of that appraisal. That analysis had been consulted on. The Appeal Panel was wary of encouraging the belief that submission of a new analysis has any inevitable effect other than the obligation to consider that analysis as a consultation response. It is unlikely in itself to give rise to obligations to reconsult. It may do so if the new analysis becomes the basis for the guidance, because then other consultees (but still not the manufacturer) may have lost the chance to comment on what has become the

operative analysis[1]. The Appeal Panel observed that here, the new analysis had been considered and commented on but not adopted. The fact that the Appraisal Committee had discussed and explained its reservations about this modelling should not be seized on as requiring further consultation on those reservations. It was notable that no other consultee felt that the failure to consult again was unfair. At the time of the appeal the manufacturer had submitted two analyses, had had each considered by the ERG, and had attended and played a part in two Appraisal Committee meetings. The Appeal Panel felt that the manufacturer had had a full, fair and informed chance to make whatever points it wished. If there was any unfairness, which the Appeal Panel did not believe there was, it had not been suffered by the manufacturer.

In reaching this conclusion the Appeal Panel noted that the points of contention between the manufacturer and the ERG had in any case been thoroughly aired at the second Appraisal Committee meeting which Eisai had attended and contributed to, and that the key conclusions reached by the Appraisal Committee in the ACD had general support from consultees, though not from Eisai. It noted that the Appraisal Committee chair had actively considered whether a second ACD should be issued but had concluded that there was insufficient new evidence to justify such a decision and the prolongation of the period before the appraisal could be concluded.

20. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 1.2: The late disclosure of the supplementary report prepared by the ERG precluded proper consideration of the report by Eisai prior to the second meeting of the Appraisal Committee.

21. Dr Williams for Eisai said this appeal point was related to the previous one where she had mentioned that following the submission of additional data by Eisai NICE had instructed the ERG to prepare a response. NICE procedures require the manufacturer to have 5 days to examine the ERG report but in this case there was no opportunity for Eisai to do so. Eisai were asked to check for factual errors and told their response would not be put to the Appraisal Committee in advance of the meeting; presumably they were to be informed orally. This would not have mattered so much if there had been a second consultation. But this lack of adequate time for preparation compounded the lack of consultation.

22. Professor Clark for the Institute explained that the NICE process allowed for checking for factual errors but not on matters of interpretation. An email had gone to Eisai a week before the meeting inviting them to

[1] It may also do so if the analysis, even if rejected, introduces new and relevant considerations (not merely new views on existing considerations) but this is not relevant here

correct any factual errors in the ERG report. NICE received Eisai's comments on the ERG report and Professor Clark had read them the night before the meeting. He regarded them to be addressing matters of interpretation and not factual points and that they related to issues that would be considered in detail at the meeting with the manufacturer present. Professor Clark said the manufacturer's points were all raised during the meeting, and that he had asked if they wished to raise any additional points at the end. The manufacturer had not raised any additional points. Professor Clark was satisfied that the Appraisal Committee had been aware of all of the issues raised by the manufacturer as dialogue was vigorous, prolonged and thorough between the Committee, the ERG and the manufacturer. The letter from the manufacturer had been copied to their legal counsel and Professor Clark made strenuous attempts to make sure all issues were aired and discussed at the Appraisal Committee meeting. The manufacturer's concerns were in his view addressed in the FAD. In response to Dr Williams, who noted that Eisai had been told written comments would not be put to the Appraisal Committee, Professor Clark said that he had also shared them with the vice-chairman.

23. The Appeal Panel sought clarification on a number of points and was told by Dr Williams that while Eisai had been given the relevant period to check for factual errors there was a grey area of understanding of what constitutes an error and what is a matter of interpretation. Eisai considered it was responding on points of fact and if they had been responding in substance the response would have been more substantial and detailed. Professor Clark clarified the process at this stage of the appraisal. It was not explicitly covered in NICE's process guides, which in fact referred to an earlier stage. He explained the importance of a factual errors check so Appraisal Committee members' time was not wasted discussing incorrect information. Mr Boysen explained that in relation to an ACD, NICE does not ask for clarification but allows new information to be submitted. In contrast, NICE does not consult on an ERG report but sends it to companies for error checking and to assist them. Dr Williams responded that it was a basic standard of administrative law that once NICE has accepted to consider new data there was a duty to treat consultees fairly. In clarifying his comment that the Eisai letter had 'raised issues that would have come up anyway' Professor Clark explained that he had a checklist of issues to be discussed and his recollection was that they were covered in his slides for the meeting although those slides were prepared in advance of the Eisai correspondence. However, he wished to assure the Panel that all the issues raised by Eisai were addressed. Dr Patrikios, who had been at the meeting, replied that he felt that he did not have sufficient opportunity to raise all Eisai's issues even though Professor Clark had asked towards the end of the meeting if there were other issues.

24. The Appeal Panel noted that Eisai accepted that the usual time for correction of factual errors had been given to the manufacturer by NICE. Much of the debate related to whether the Eisai response was on

matters of factual error or interpretation. However, the Appeal Panel was satisfied that the issues raised by Eisai in its response – whether matters of error or interpretation – had all been well aired and considered by the Appraisal Committee at its second meeting. The Appeal Panel did not consider that it was necessary for the entire Committee to have been provided with Eisai's comments in writing. It was appropriate and sensible that they were provided to the Appraisal Committee chair in advance, and that it was left to his judgement how many of the points were considered at the meeting and in what way as an aspect of his duty to manage the meeting fairly. Eisai were at the meeting, and were invited to say whether there were any issues that had not been covered which they wished to raise. They had not objected to the chair's conduct at the time. The Appeal Panel could see no grounds to conclude that the Appraisal Committee had not properly considered the relevant points made by Eisai.

25. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 1.4: The Appraisal Committee has failed to consider a comparison of Eribulin with TPC in the population of patients previously treated with capecitabine.

26. Dr Patrikios for Eisai said that at its first meeting the Appraisal Committee had concluded that the best comparator was TPC. Eisai had submitted evidence in response to the ACD on the post- capecitabine population provided with TPC, which was a pre-specified part of the EMBRACE trial and it was unfair not to use this and effectively ignore three quarters of the final population. Eisai raised its concerns with NICE and did not understand why the Appraisal Committee excluded the comparison of eribulin with TPC in the post-capecitabine population.

27. Professor Clark for the Institute explained that the onus for making the ICER case rested with the manufacturer. In its initial submission, Eisai wanted the Appraisal Committee to consider four analyses (for TPC and three separate comparator drugs) using a variety of methods. The Appraisal Committee had had to decide what the base case was. In the Eisai submission following the ACD the comparison of eribulin with vinorelbine had appeared to have been put forward as the base case. Subsequent communications with Eisai had confirmed that this was indeed the manufacturer’s base case. This was also the only comparison subject to a probabilistic analysis. Thus, both the Appraisal Committee and the ERG understood that the base case was eribulin compared with vinorelbine. At the second Appraisal Committee meeting the manufacturer was twice asked if there were any other issues not being discussed which the Appraisal Committee should consider. Professor Clark asserted that he had asked specifically "is eribulin against vinorelbine the only base case analysis?" The manufacturer did not suggest that the Appraisal Committee had overlooked a relevant comparison.

28. Responding to Professor Clark, Mr Jones explained that once the Appraisal Committee had decided that TPC was the most appropriate comparison Eisai wished to cover both TPC and vinorelbine in the post-capecitabine population, had presented analysis on both and considered it the responsibility of the Appraisal Committee to decide on appropriate comparisons. Dr Patrikios explained that Eisai provided two analyses with two methods and that the other analysis submitted was sensitivity analysis. Dr Williams was concerned that it did not appear that the Appraisal Committee had given consideration to the post-capecitabine sub-group – Eisai wanted it looked at but it seemed it was not. Professor Clark explained that there was information in his slide presentation summarising the manufacturer's submission and in their evidence. The Appraisal Committee had purposely chosen TPC across the whole population and this is why only one ICER applied.

29. The Appeal Panel deliberated upon what it was that the Appraisal Committee had been asked to consider in the manufacturer's post ACD submission. They noted the exchange of communications between NICE and Eisai and the related discussions at the meetings of the Appraisal Committee. The Appeal Panel accepted that, while there might have been an initial lack of clarity in understanding between Eisai on the one hand and the Appraisal Committee and the ERG on the other as to which was the base case from the manufacture, this was resolved early in the process. The Appeal Panel agreed that the Appraisal Committee had been told by the manufacturer that the new analysis which the manufacturer wanted the Appraisal Committee to consider was the comparison of eribulin against vinorelbine in the post-capecitabine population. The Appraisal Committee had done what the manufacturer had asked it to do. There was no unfairness in the Appraisal Committee not having done what it was not asked to do. In any event, the TPC ICERS in the manufacturer's submission were no lower and the Appraisal Committee's reservations about the vinorelbine analysis would seem to apply equally to the TPC analysis.

30. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 1.6: The Appraisal Committee's conclusions with respect to the costs of vinorelbine which should be used for economic modelling in this appraisal are inconsistent with the approach specified in NICE's procedures and unfair.

31. Dr Patrikios for Eisai said that within the NHS there was wide variation in how vinorelbine was used – oral or intravenous– but no consideration was given to the use of oral vinorelbine. The Appraisal Committee should have used the list price applying to different formulations. With respect to frequency of administration, again there was a lot of variation but the Appraisal Committee should have based its analysis on the licensing specification.

32. Professor Clark for the Institute explained that only one ICER for eribulin

in comparison with TPC had been used in the ACD. EMBRACE stipulated eribulin dosage and scheduling but could not stipulate dosage etc. in the TPC arm. The economic analysis had used the licensing specification scheduling although the clinical specialist had advised the Appraisal Committee that different scheduling regimes are used in the UK. Oral vinorelbine was a branded drug but intravenous vinorelbine was a generic drug. The manufacturer used generic products and the median of BNF prices in its submission but the ERG thought it unlikely that the NHS would use the more expensive formulations and the Appraisal Committee knew that the NHS brokered additional discounts for generic drugs. Different scheduling and cost were discussed but were not used in the economic comparison of TPC with eribulin.

33. In discussion, Dr Patrikios confirmed that Eisai had raised their concerns around scheduling and use of oral vinorelbine although Professor Clark did not think that scheduling had been raised during the consultation on the ACD. Professor Clark confirmed that the manufacturer's model used weekly scheduling and oral vinorelbine but also did a sensitivity analysis for intravenous vinorelbine. He confirmed that while it is known that vinorelbine was one of the drugs used in the TPC arm of EMBRACE, by the nature of a pragmatic trial it was very difficult to control for specific treatments and so the Appraisal Committee did not know the dose or scheduling for vinorelbine in the EMBRACE trial. Professor Clark confirmed that the ICER in play (i.e. ICER of approximately £68,000) used the scheduling specified in the licence and was based on intravenous and not oral vinorelbine using the cheapest BNF (i.e., non-discounted) prices. Mr Jones confirmed that Eisai had accepted this calculation for its re-submission. Dr Williams expressed concern that it was part of NICE procedures that procurement discounts were not taken into account but appeared to have been referenced in the FAD.

34. The Appeal Panel noted that the ACD had included the approach that was used in the FAD. It further noted that the ICER in play (i.e. ICER of approximately £68K) used the cheapest BNF prices rather than discounted prices. It also relied on the scheduling specified in the licence. The Appeal Panel rejected any complaint that the modelled benefit of vinorelbine might be overstated if dosages were reduced in clinical practice, because the data for vinorelbine's benefit came from a pragmatic trial where the dosing regimen was unknown. Further, FAD 4.10 made clear that these concerns were not included within the ICER of £68.000, but were merely cited as reasons for concluding that that was the most optimistic figure. Therefore even if the Appraisal Committee's approach on this point was unfair (which it was not) it was possible to see that the ICER would continue to be far above any level previously recommended.

35. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 2: NICE has formulated guidance which cannot be reasonably justified in the light of the evidence submitted

Appeal Point Ground 2.1: The Appraisal Committee's conclusions with respect to the adverse events associated with eribulin do not reflect a balanced and reasonable assessment of the available evidence.

36. Dr Patrikios for Eisai said that the FAD said that eribulin was more toxic and less well tolerated than the other comparator drugs. The Appraisal Committee relied upon a statement by their clinical specialist but Eisai believed the clinical specialist was misquoted and this was supported by a letter from the Royal College of Physicians that said 'the drug is remarkably well tolerated'. Professor Twelves said he had used the drug in a number of patients and had discussed it with colleagues and it is clear that eribulin was generally well tolerated. He was genuinely surprised by the FAD conclusions. It was inherent to the study design that it was difficult to compare toxicities between the two arms. But when high level comparisons of toxicities were examined they were effectively identical between the two arms of the study so it was difficult to justify the conclusion that one is more toxic. Patients receiving eribulin had already had other therapies, patients were on eribulin for nearly twice as long as other therapies and there was no excess of treatment related deaths. If anything eribulin was better tolerated. Professor Twelves did not view eribulin as unduly toxic and this was confirmed by patients.

37. Professor Clark explained that the Appraisal Committee had considered at length whether their conclusions were balanced and reasonable. That EMBRACE had not included an assessment of quality of life was a great pity. The Appraisal Committee had taken into account the views of the physician and nurse specialist. The Appraisal Committee agreed that high level comparisons were similar but noted differences in Grade 3 and 4 toxicity which were moderately higher in the eribulin arm. The Appraisal Committee gave particular attention to increased risk of peripheral neuropathy, neutropenia and alopecia while bearing in mind that one reason for more adverse events was increased duration of treatment with eribulin. All of these were noted and discussed but were not reported appropriately in paragraph 3.7 of the FAD, which should have included comparator data. Professor Clark conceded this paragraph should be re-drafted. With respect to the charge of misquoting the clinical specialist, his opinion was written before the meeting and was as reported in the FAD. Professor Clark accepted that patients and professional groups had said eribulin was well tolerated but the Appraisal Committee had put special weight on peripheral neuropathy, neutropenia and alopecia because of their implications for quality of life. There had been no feedback on toxicity in the consultation on the ACD.

38. In the following discussion Dr Williams said that Eisai had indeed given a substantial response on toxicity in its response to ACD. Her view

remained that paragraph 4.3 misquoted the clinical specialist's oral evidence to the Appraisal Committee. Noting that it was very difficult to compare adverse events between eribulin and TPC what should be looked at was the overall data as otherwise like was not being compared with like. But Professor Clark's view was that the clinical specialist's comparison of eribulin with vinorelbine and capecitabine referred to in paragraph 4.3 was based on trial data. Clarifying how adverse events were factored into the manufacturer's model used in the ICER, Professor Clark explained that only Grade 3 and 4 adverse events with a frequency of more than 10% were factored in. The events which the Appraisal Committee considered particularly significant (neutropenia, peripheral neuropathy, alopecia) were only included in the manufacturer's model to the extent to which they were Grade 3 or 4. Mr Jones explained that the process was to group adverse events as otherwise the modelling became too complex. It was a question of what the trial had power to detect a difference. Professor Clark confirmed that the £68,000 ICER was based on the manufacturer's model as far as adverse events were concerned.

39. The Appeal Panel considered the oral presentation of the reasons for the conclusions reached by the Appraisal Committee had been enlightening. It welcomed the acknowledgement by Professor Clark of shortcomings in paragraph 3.7 in the FAD. It accepted that a high level comparison of toxicity in the two arms of the trial showed little difference. It noted the evidence of Professor Twelves and the views of clinicians familiar with use of eribulin and of patients. Nevertheless the panel was persuaded that the Appraisal Committee had reasonable grounds for attaching weight to the relatively greater negative impact on quality of life that eribulin can give rise to due to greater frequency of neutropenia, peripheral neuropathy, and alopecia. The Appeal Panel also noted that the appeal ground was that the Appraisal Committee has formulated guidance that cannot reasonably be justified in the light of the evidence submitted. It was clear that even if the Appraisal Committee's views on adverse events had been unsustainable, (which they were not) because those views were not included in the calculation of the ICER as £68,000 the Appraisal Committee's guidance would have been unaffected.

40. The Appeal Panel therefore dismissed this appeal point.

Appeal Point Ground 2.2: The Appraisal Committee's decision to reject the analysis based on the data from Region 1 of the EMBRACE trial is unreasonable.

41. Dr Patrikios for Eisai explained that due to the regional differences in TPC a separate analysis in three regions was pre-specified for the EMBRACE trial. In region 1 (Western Europe and North America) 80% of patients in the TPC arm received capecitabine but a much smaller percentage did so in regions 2 (Eastern Europe) and 3 (Latin America). Patients in region 1 had four prior treatments but in regions 2 and 3 only two or three prior treatments. Also, region 1 represented the most

mature data and included 65% of the trial population. Also, for this region, it was more difficult to demonstrate survival improvement. These were a fundamental part of the trial design. Professor Twelves emphasised that pre-designation of the different regions was an inherent aspect of the trial design.

42. Professor Clark for the Institute explained that this had been a big part of the discussion at the first Appraisal Committee meeting. The two major considerations had been 1) whether there were differences in prognosis between the regions and 2) whether there were differences in clinical practice. The ERG analysis presented persuasive evidence that there was no difference in prognosis for the different regions. The clinical expert considered that the difference between UK clinical practice with areas within region 1 were no greater than differences between each region. The Appraisal Committee members were aware that one of the possible reasons that cancer outcomes were less good in the UK than in region 1 may be because of less expenditure and therefore were concerned with placing exclusive reliance on region 1 data. In addition, the oncology community submission stated that using overall ITT population was more appropriate to UK practice. The 2:1 randomisation reduced the number of patients on whom overall survival intervals could be calculated, making the analysis less robust if a subset of the ITT population was used. Professor Clark said the Appraisal Committee knew that the trial population included a large mix of prognostic factors and for this reason also were hesitant to select a single region. Also, the trial was designed, powered and reported for an ITT population covering all regions.

43. In discussion, Professor Clark re-confirmed the Appraisal Committee's judgement that the ITT population was the best comparator for the UK patient population and that there was no good reason for excluding region 2 and 3 populations from the analysis. Dr Williams reminded the panel that in using the ITT population for its licensing application Eisai was demonstrating clinical effectiveness, with which the licensing authority is concerned, and not cost-effectiveness which is the additional concern of NICE.

44. The Appeal Panel noted the efforts made to identify an appropriate comparator population for use in the UK. It was clear to the Appeal Panel that a very substantial body of expert opinion were of one mind that the better comparator for the UK patient population was the total ITT population of the trial. Whilst it is not for the Appeal Panel to second guess the opinion of experts, that opinion was rational and reasonable. First, the Appraisal Committee had rationally preferred to maximise the data on which it relied. Second, the Appraisal Committee had considered the relevance of that data and had rationally concluded that, at a minimum, the total trial data were no less relevant than the region 1 data. The Appeal Panel did not find it implausible that differences in clinical practice within region 1 might be comparable to the differences between the regions, or that there was any reason to doubt the ERG's

analysis and conclusion that prognosis did not differ between regions.

45. The Appeal Panel therefore dismissed this appeal point.

Appeal Point Ground 2.3: The Appraisal Committee's reliance on the calculation of overall survival for patients pre-treated with capecitabine, based on the ERG's methodology set out in its Addendum Report, is unreasonable.

46. Mr Jones for Eisai said that the interest was in comparison of overall survival between the arms of the EMBRACE trial. He explained that in modelling overall survival there were at least four approaches. The original submission by Eisai used one approach; the ERG followed this with another approach. The Eisai response to the ACD used the same approach as the ERG and another method. The ERG and the Appraisal Committee then rejected these models on the grounds of convergence. However, convergence of survival was never properly assessed by the ERG. The final decision of the Appraisal Committee was based on the original analysis which relies upon convergence not existing.

47. Professor Clark for the Institute explained that in its first report the ERG truncated two survival curves and modelled using extrapolation. In the second report the ERG and the Appraisal Committee were newly concerned with the comparison of eribulin versus vinorelbine in the prior capecitabine-treated subgroup. The ERG were concerned that the number of patients in this analysis had fallen with consequently widened confidence intervals. For this analysis the overall survival Kaplan-Meier plot indicated that the survival of patients receiving vinorelbine and eribulin converged after two years. There was therefore no need to model at all as actual data trumps modelling. FAD paragraphs 4.12-4.14 contained a discussion of this, and set out the conclusion that survival gain could be estimated directly from the Kaplan Meier analysis without the need for parametric modelling. The Appraisal Committee examined the manufacturer's model in detail and interrogated the manufacturer and the ERG as to whether modelling was necessary. The plausibility of convergence was an important part of this discussion. The Appraisal Committee concluded that overall survival curves did converge and could see no reason for not accepting this.

48. Professor Michaels sought to clarify the relevance of the Decision Support Unit guidance on analysis in situations of incomplete survival data. He explained that the unit gave guidance if modelling was necessary. The main discussion was on whether plots for progression-free survival converged, which, if they did, meant modelling was not necessary. In this case only one patient survived beyond the trial follow up period. Modelling methods are generally to address the problem of truncation of data where patients survive beyond the trial period. That issue did not arise here so no modelling at all was needed to address it. All patients were captured in the curve fitting the actual trial data. Mr Jones said that the decision that convergence existed was never subject

to discussion at an Appraisal Committee meeting but it was the view of Professor Michaels that this was discussed at length. As progression free survival converged there was no reason to be suspicious of the conclusion that overall survival also converged. It was the responsibility of the manufacturer to test and justify its modelling approach and Eisai had failed to do this for the proportional hazard assumptions in its model. But Mr Jones said Eisai could not have predicted that the Appraisal Committee would have focussed on this point. Finally Professor Clark confirmed that the Committee did not rely on the ERG modelling method when considering the benefits of Eribulin compared to vinorelbine in the post capecitabine population.

49. The Appeal Panel noted the technical arguments favouring different approaches and the extensive analyses undertaken and presented by the manufacturer. It considered whether the Appraisal Committee was able to justify the approach it had adopted and was persuaded that this was so. It noted that the Appraisal Committee had given full and credible reasons for its approach, and that the conclusion that actual data made modelling (either by the ERG or the manufacturer) unnecessary was clearly justifiable. The reasons given for concluding that overall survival converged were clear and the conclusion justifiable. It considered whether the Appraisal Committee had been appropriately mindful of the Decision Support Unit guidance relating to situations of incomplete survival data analysis decision and accepted that it had done so. It noted that this guidance was not pertinent in the circumstance of this appraisal as reliance was placed on actual data rather than on modelling of overall survival.

50. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 3: The Institute has exceeded its powers

51. There was no appeal under this ground.

Conclusion and effect of the Appeal Panel's decision

52. The Appeal Panel dismissed all the grounds for appeal in this appraisal.

53. The Appeal Panel was mindful of the statement by Professor Clark that the discussion and decision of the Appraisal Committee on toxicity were not reported appropriately in paragraph 3.7 of the FAD. The Panel concurs with his expressed view that the FAD should include the comparator data to which Professor Clark referred and that this section of the FAD should be re-drafted. Consequential amendments may also be needed to paragraph 4.3.

54. There is no possibility of further appeal against this decision of the Appeal Panel. However, this decision and NICE's decision to issue the

final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of publishing the final guidance.

APPENDIX

.

Eisai's disallowed ground of appeal was that

The Appraisal Committee's approach to the estimation of the overall survival benefit associated with eribulin is not consistent with standards identified by the Decision Support Unit and the choices which form the basis for the estimation are unexplained and lack transparency.

this was raised under ground 1, unfairness.

Dr Halliwell's reason for finding this point invalid was:

[Eisai's] relevant comments were made in an additional document, submitted in August 2011 after the closure of comment on the ACD, which NICE agreed to accept. I have also noted that your additional document was the subject of a 19 page report prepared by the ERG in September 2011 which considers its arguments in some detail. I have every confidence that this material was available to and taken into account by the committee.

..., the issue here is possible unfairness. The Appraisal Committee's approach does appear to have been clear, and you had (and took) the chance to make comment on it. There seems to be no evidence that those comments were not taken into account. This seems to have satisfied the requirement that the committee acts fairly. I do not think this can be a valid appeal ground.

To this the Appeal Panel would add that in the course of discussing appeal point 2.3 the Appraisal Committee gave reasons for its choices, referred to reasoning contained in the FAD, and also confirmed that these issues were discussed with the manufacturer present at the Appraisal Committee meeting.