

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Appraisal of cetuximab for the treatment of metastatic colo-rectal cancer

Decision of the Appeal Panel

1. Introduction

An Appeal Panel was convened on 27th November 2006 to consider appeals against the Institute's Final Appraisal Determination (FAD), to the NHS, on the use of cetuximab for the treatment of metastatic colo-rectal cancer.

The Appeal Panel consisted of Professor Sir Michael Rawlins (chair of the Institute), Professor Shah Ebrahim (non-executive director of the Institute), Dr David Webster (industry representative), Mr Bob Osborne (patient representative), and Professor Robin Ferner (Clinical Assessor and NHS Representative).

The Panel considered appeals submitted by:

Merck Pharmaceuticals ("Merck"), represented by Ms Denise Richards, Mr Stephen Ralston, Dr Maya Morris, Dr Mark Saunders, and Professor John Wagstaff;

Bowel Cancer UK and CancerBackup (jointly), represented by Mr Ian Beaumont, Mr David Taylor, and Mr Peter Telford.

In addition, the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel: Professor Andrew Stevens (chair of the appraisal committee), Professor David Barnett, Dr Peter Clark, Dr Carole Longson, and Ms Zoe Garnett.

The Institute's legal advisor (Mr Julian Gizzi, Beachcroft) was also present.

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

There are three grounds on which a panel can hear an appeal:

- Ground 1: The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute’s Guide to the Technology Appraisal Process;
- Ground 2: The Institute has prepared guidance which is perverse in light of the evidence submitted;
- Ground 3: The Institute has exceeded its powers.

The chair of the appeals committee (Roy Luff, acting vice-chair of the Institute), had confirmed that the appellants had potentially valid grounds of appeal under Ground 2 as follows:

Merck – five points of appeal;

Bowel Cancer UK and CancerBackup – one point of appeal.

Before discussion began, each member of the Appeal Panel was asked to declare any relevant interests; none was declared.

2. Appeal on the ground that the Institute has prepared guidance which is perverse in light of the evidence submitted

2.1 Merck argued that the most appropriate position for cetuximab was as a third line treatment given the evidence presented, and that it was perverse of the Appraisal Committee to rule on the use of cetuximab as ‘second-line or subsequent’ treatment

Dr Morris, on behalf of Merck, acknowledged that the marketing authorization for cetuximab stated that cetuximab ‘in combination with irinotecan is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.’

She also acknowledged that approximately 20% of patients in the BOND study, submitted by Merck as evidence to the Appraisal Committee, had received cetuximab as part of second-line therapy.

Professor Stevens, on behalf of the Appraisal Committee, stated that the Appraisal Committee had considered that cetuximab would be used mostly as third-line therapy. However, the Appraisal Committee were bound by the Final Scope for the Health Technology Appraisal, and this stated that the interventions would be ‘appraised in accordance with their existing licensed indications. Guidance [would] only be issued in accordance with the marketing authorisation.’

The Appeal Panel found that the Appraisal Committee had regarded cetuximab as primarily, but not exclusively, a drug used in third-line treatment, and had assessed it according to the Final Scope. The Appraisal Committee was required to do this, and therefore could not be regarded as perverse.

The Appeal Panel therefore found that the Appraisal Committee’s assessment of the use of cetuximab had been consistent with its licensed indications and the Final Scope, and dismissed the appeal on this point.

2.2 Merck asserted that comparisons made by NICE with regards to best supportive care were inappropriate and biased against cetuximab

Professor Stevens, on behalf of the Appraisal Committee, advised that the BOND trial did not provide a direct comparison between cetuximab plus irinotecan and best supportive care. Therefore, to make the comparison, the Appraisal Committee had to use data for best supportive care derived from other trials. The data used were from the trials of Rao *et al*, Barni *et al*, and Cunningham *et al*. Merck had used an indirect comparison between cetuximab plus irinotecan and best supportive care that relied on adjusting the data from the Cunningham study.

Because of the uncertainties, Professor Stevens explained, the Appraisal Committee had additionally adopted a second approach. In this approach, the threshold method,

the incremental cost-effectiveness ratio of £30 000 per quality-adjusted life-year is fixed, and the survival with best supportive care is the variable that is calculated. By the threshold method, the mean survival with best supportive care would have to be below 1.7 months for the incremental cost effectiveness of cetuximab plus irinotecan to fall to the pre-specified value.

Mr Ralston and Dr Morris, on behalf of Merck, explained that they had new data suggesting a median survival of 4.5 months with best supportive care in patients eligible for third-line treatment for metastatic colo-rectal cancer, and provided some information on two relevant trials, one unpublished and one published only as an abstract. Mr Ralston and Dr Morris accepted that those data had not been before the Appraisal Committee when they had made their decision, but argued that the new data justified the assumptions made by Merck in deriving the likely survival with best supportive care.

Professor Stevens reminded the Appeal Panel that mean survival data were required for the economic analysis, and that the mean survival of patients receiving best supportive care in the study by Rao *et al* was 8 months, while the median was 6.1 months. Even a mean (not median) survival of 4.5 months with best supportive care would be substantially longer than the threshold value of 1.7 months below which cetuximab would become acceptably cost-effective.

Mr Telford, acting *pro bono* for Bowel Cancer UK and CancerBackup, invited the Appeal Panel to find that the new data provided by the company at the Appeal Hearing should be taken into account, since it was desirable that the decision be informed by the latest information.

The Appeal Panel were satisfied that, while there were difficulties in making indirect comparisons between cetuximab plus irinotecan and best supportive care, the Appraisal Committee had used two independent methods to make the comparison, and that neither method, when applied to the data submitted by Merck to the Appraisal Committee, allowed the Appraisal Committee to conclude that the drug treatment would be of acceptable cost-effectiveness. The Appraisal Committee could

not, therefore, be said to have acted perversely regarding the estimation of survival with best supportive care.

The Appeal Panel also concluded that it was not reasonable for the Appraisal Committee to consider or make amendments to decisions in the light of new evidence as it became available, because this would lead to a continuous process that could never be completed. A decision maker can only take a decision on the basis of the evidence before it at the time of its decision.

The Appeal Panel therefore decided that the Appraisal Committee had not been perverse in its methods of making comparisons of cetuximab plus irinotecan with best supportive care, and dismissed the appeal on this point.

2.3 Merck proposed that patients within the group eligible for cetuximab plus irinotecan should undergo a CT scan at 6 weeks and only if that scan demonstrated complete or partial response at that time, should the patient continue treatment

Mr Ralston described how Merck now proposed a set of rules whereby patients should only continue treatment with cetuximab plus irinotecan if the CT scan six weeks after the start of treatment showed complete or partial response, and that otherwise treatment should be discontinued. He accepted that these rules were different from the rules submitted to the Appraisal Committee by Merck.

Professor Stevens explained that the Appraisal Committee had considered the rules submitted to them by Merck. The rules that Merck now proposed were based on the outcome in just 27 patients. They were derived from an analysis of subgroups after the event, and Ms Richards accepted that there had been no study to show whether the rules, based on the BOND cohort, could be shown to work in practice.

Professor Barnett explained that the results obtained by Merck were not unexpected: if models of different scenarios were constructed, some scenarios could appear of

acceptable cost-effectiveness. However, none of the clinicians who appeared before the Appraisal Committee had suggested the rules that Merck now proposed.

Dr Saunders explained that patients with ‘stable disease’ as assessed on CT scans included those whose tumours had changed in size by +20% to -30%. He and Professor Wagstaff agreed that they would continue to treat patients with stable disease whose tumours had decreased in size with treatment, even though this fell short of ‘partial response.’

The Appeal Panel decided that Appraisal Committee could not be regarded as perverse for failing to consider data that had only been provided at the appeal hearing.

The Appeal Panel also took the view that the proposed rules were based on a *post hoc* sub-group analysis that had never been validated, and that did not reflect the practice of expert clinicians.

The Appeal Panel therefore decided that the Appraisal Committee had not been perverse when it failed to consider the new continuation rules presented at the appeal hearing and dismissed the appeal on this point.

2.4 Merck claim that Cetuximab is an effective and cost effective treatment option for the third line treatment of mCRC when strict criteria are applied to the use of Cetuximab in combination with irinotecan

Mr Ralston stated that Merck recognized that there was an error in the extrapolation technique used to calculate overall survival in the model that Merck had submitted to the Appraisal Committee. They had now applied a different method, and obtained the same values as those in the independent assessment provided to the Appraisal Committee. However, results from the model depended on assumptions about survival with best supportive care, the utility, and the rules by which treatment was stopped or continued. When Merck applied the model under the rules provided to the appeal hearing, and when the survival with best supportive care was assumed to be 4.6 months, then the treatment would be cost-effective.

Professor Stevens reminded the Appeal Panel that, using the data from the study by Rao *et al*, the cost of treatment with cetuximab plus irinotecan would be approximately £100,000 per quality-adjusted life-year.

Dr Morris stated that only half the patients studied by Rao *et al* had received both irinotecan and oxaliplatin before entry to the trial, and they therefore differed from the patients recruited in the BOND study.

Professor Stevens explained to the Appeal Panel that there were uncertainties in the model, because parameters came from different sources, and some had to be derived. There were several reasons for the differences between models. These included the use of different values for utility, and for survival with best supportive care. The application of different rules for continuing or stopping treatment also affected the results obtained.

Professor Stevens also explained that the cost per treatment was very high, so that small changes in the continuation rules made substantial changes to the estimates of cost-effectiveness. The Appraisal Committee had not seen or tested the model used to calculate Merck's new estimates, and so did not know how Merck had derived the figures they presented.

The Appeal Panel decided that the new model provided by Merck was unevaluated, and had not been before the Appraisal Committee at the time the Committee made its decisions.

The Appeal Panel therefore decided that the Appraisal Committee had not been perverse when it failed to consider the results derived from the model and dismissed the appeal on this point.

2.5 Merck presented the overall costs per patient applying the restrictive six weeks continuation rule, and showed that the total cost to the National Health Service was relatively small

Professor Stevens explained that the Appraisal Committee was not allowed to take the budgetary impact of treatments into account, and had not done so.

The Appeal Panel decided that since the Appraisal Committee was prohibited from considering the budgetary impact of its recommendations, it could not have acted perversely in omitting to consider that impact.

2.6 Bowel Cancer UK and CancerBackup appealed on the grounds that cetuximab is a third-line treatment for metastatic colo-rectal cancer, and not a ‘second-line and subsequent treatment’ as stated in the Final Appraisal Document

Mr Beaumont, on behalf of Bowel Cancer UK and CancerBackup jointly, explained that he was representing the views of patients with metastatic colo-rectal cancer, that cetuximab was an advance in treatment, and that the Appraisal Committee were perverse in appraising cetuximab as second-line therapy rather than third-line therapy.

Mr Taylor described the benefit he had derived from cetuximab therapy.

Mr Beaumont read out a statement from a patient with advanced metastatic colo-rectal cancer who had not been treated with cetuximab, but who might benefit.

Mr Telford put forward the view that the more important the decision, the higher the threshold for reasonableness. He cited Sir Thomas Bingham MR in R v Ministry of Defence ex p Smith who said “The more substantial is the interference with human rights, the more the court will require by way of justification before it is satisfied that the decision is reasonable...” and argued that the Institute’s guidance was in breach of articles 2 (right to life) and 3 (prohibition of inhuman or degrading treatment) of the European Convention on Human Rights.

These were new arguments not advanced in Bowel Cancer UK and CancerBackup’s joint appeal submission and more properly the subject matter of Ground 3 of the grounds of appeal than Ground 2. The Appeal Panel considered them nevertheless, but were not persuaded by Mr Telford’s arguments.

A successful complaint under articles 2 and 3 is highly unlikely in relation to the general standard of healthcare available, the financial arrangements for such care and the policies governing its organisation and delivery within a state. In the Appeal Panel’s view, the guidance in this case was well within the margin of appreciation allowed to decision-makers. Furthermore, the domestic courts have taken the view

that they cannot make judgments about how health authorities decide to allocate a limited budget, even when a child's life expectancy is concerned (R v Cambridge District Health Authority ex p B). The judgment in R v Swindon NHS Primary Care Trust ex p Rogers also cited by Mr Telford did not deviate from this principle.

The Appeal Panel decided that this point of appeal by Bowel Cancer UK and CancerBackup was substantially the same as the first point of appeal by Merck. The Appeal Panel therefore found that the Appraisal Committee had made their assessment of the use of cetuximab in accordance with the licensed indications and the Final Scope, as they had a duty to do, and dismissed the appeal on this point.

3. Conclusion and effect of the Appeal Panel's decision

The Appeal Panel has dismissed the appeals by Merck Pharmaceuticals and the joint appeal by Bowel Cancer UK and CancerBackup, having found that the Institute had not prepared guidance that was perverse in light of the evidence submitted.

The determination that cetuximab in combination with irinotecan is not recommended for the second-line or subsequent treatment of metastatic colorectal cancer is therefore unchanged.

People currently receiving cetuximab should have the option to continue therapy until they and their consultants consider it appropriate to stop.

The Appeal Panel recommended that the guidance on this technology should be considered for review before May 2009 in the event that new evidence makes an earlier review desirable.

There is no possibility of further appeal within the Institute against this decision of the Appeal Panel. However, the decision of the Appeal Panel and the Institute's decision to issue the Guidance may be challenged by an interested party through an application to the High Court for permission to apply for judicial review. Any such application must be made promptly and in any event within three months of this Decision or the issuing of the Guidance.