ERG comments on manufacturers response

Summary

The ERG agrees that the cumulative effect of the three revisions to the model parameters in the manufacturer's response did not significantly change the ICER values. The ERG believes that even with the modifications in the manufacturers' response the ICERs are still associated with some uncertainty. The ERG comments on each of the areas of uncertainty discussed in the manufacturer's response are included below.

1) The NHS resource cost of operating APAS and the subsequent effect on the ICER

The manufacturer's response details research with pharmacists, NHS business managers, and NHS finance and operations experts. This research identified the employee time required to set up and administer the APAS. The details were provided in a worksheet in appendix C. This worksheet is unclear and includes links to values in external worksheets so the ERG was unable to check these calculations. The analysis spreads the costs of initial set-up activities over 3 years. It is not clear to the ERG what the appropriate timeframe is over which to spread these set-up costs.

The ERG can verify that based on an estimated cost per patient of operating the APAS over years 1 to 3 is of £57 and £67 for B-XELOX and B-FOLFOX respectively the marginal ICERs increase by £164 and £113 respectively.

2) The operation of the APAS in the context of an intermittent treatment strategy

No comments.

3) Bevacizumab treatment duration in clinical practice and its effect on the ICERs

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The manufacturer's response states that "As recognised by the committee, intermittent treatment, such as that specified in the COIN study (Adams, 2009) is becoming more prevalent within UK clinical practice. This typically leads to a shorter treatment duration compared to the NO16966 study."

The model reflects the N016966 study in which both the protocol for the bevacizumab and comparator arms was continuous treatment. If intermittent treatment +- bevacizumab were modelled then we may see a shorter treatment duration with bevacizumab compared with the N016966 study but we would likely also see a shorter treatment duration with XELOX/FOLFOX. As this would reduce the costs in both intervention and comparator arms the effect on the ICER is unclear. It is also unclear how intermittent treatment would effect the time spent in the PFS and OS states.

The manufacturers response stated that "It was considered that should bevacizumab be given positive NICE guidance it is likely to be added to the treatment strategy that is currently being employed, either intermittent treatment or continuous." In contrast, one of the ERG clinical advisors suggested that although they currently use intermittent treatment they would administer B-XELOX of B-FOLFOX continuously because that is where the evidence base lies.

The manufacturer's response states that "It would also be expected that if treatment with oxaliplatin was stopped due to either a planned break or unacceptable toxicity then treatment with bevacizumab would also typically be stopped at this time." The ERG note that this differs from the trial protocol. This clinical debate is drawn to the attention of the committee.

Real world evidence of bevacizumab treatment duration

The ERG group comment that although real world evidence may demonstrate shorter treatment duration than was seen in the trial. There is an inevitable tension between modelling the internal consistency of the trial and the external reality of real world clinical practice. However, the conventional approach to economic modelling would be to reflect the trial situation as this enables the source for both costs and efficacy to be the same.

4) The incremental pharmacy and administration cost associated with adding bevacizumab to XELOX or FOLFOX

The manufacturer's response includes a time and motion study to provide a more precise estimate of the cost of preparing and administering bevacizumab. Appendix B states that the study included only 3 patients and was undertaken at one institution (the Mount Alvernia Hospital in Guildford). The ERG suggests that such a small sample size which just includes one hospital may not accurately reflect the time required. The manufacturers response suggest reducing bevacizumab preparation and administration costs from £42 to £31 but it is unclear precisely where this was altered within the model. When the model was modified by the ERG to reflect this change the marginal effect on the ICERs was slightly different to that in the manufacturer's response.

5) The health state utility values used in the economic model

The ERG agrees that varying the post progression utility value has little effect on the ICER. The ERG agrees that reducing the PFS post treatment utility value may make the model more realistic. The marginal effect on the ICERs of changing this utility values has been verified by the ERG.

Other points

The manufactures response states that:

" In section 4.14 the ACD states: "*Nevertheless, the Committee understood from the ERG that the ICERS for both B-XELOX and B-FOLFOX increased if bevacizumab treatment continued beyond that of oxaliplatin."* It appears that this conclusion was drawn based on the results of the sensitivity analysis conducted by the ERG (section 3.25, ACD). Additionally it is not clear as to whether the committee considered the impact of the price cap on the cost of increasing treatment duration. "

The ERG reported that the ICERs for both B-XELOX and B-FOLFOX increased significantly if bevacizumab treatment continued beyond that of oxaliplatin and if survival was still assumed to be as in the trial (i.e. the additional month of bevacizumab treatment did not alter survival). The ERG analysis did not originally include the 12 month price cap within the calculations. This analysis has now been repeated to include the price cap and for an additional 1 month of bevacizumab the ICERs increase from £36,354 to £45,958 for B+XELOX vs. XELOX and from £40,090 to £31,452 for B-FOLFOX vs FOLFOX. The ERG wishes to emphasize that this was an exploratory analysis which assumes no difference in survival is caused by the additional month of bevacizumab, and as such is likely to over-estimate the true ICER. This exploratory analysis highlights that due to the structure of the APAS the incremental cost of continuing bevacizumab after oxaliplatin cessation is almost three times the incremental cost of adding bevacizumab to oxaliplatin.