Single Technology Appraisal – Bevacizumab in combination with oxaliplatin and either 5FU or capecitabine for the treatment of metastatic colorectal cancer

PART 3 – RESPONSE TO NON-PRIORITY ERG CLARIFICATION QUESTIONS

The manufacturer provided an exploratory analysis in which all patients who received prior adjuvant therapy are excluded from the analysis. Is it possible to provide survival curves or ICERs relating to this exploratory analysis?

The further analysis referred to in the question investigated possible reasons for why patients in the FOLFOX+Placebo arm of the NO16966 study had far better outcomes than those in the other three non-bevacizumab arms of the study. The conclusion of this analysis was that the better than expected outcomes of these patients was largely driven by the subgroup of patients within that P-FOLFOX arm that had received prior adjuvant treatment. As discussed in part I of the response we do not consider that prior adjuvant treatment is predictive of the treatment effect of bevacizumab. Additionally there is no reason to believe that adding placebo to FOLFOX would confer a benefit in this patient population let alone the large difference in PFS and OS seen between the FOLFOX and P-FOLFOX arms of this study.

It is therefore reasonable to consider that there was an imbalance in an important prognostic factor between the P-FOLFOX patients that had received prior adjuvant therapy and the rest of the patients in the study. Prior adjuvant treatment was a stratification factor and so the arms are reasonably well balance in terms of the number of patients that received prior adjuvant treatment. However it was only discovered after commencing the NO16966 that disease free survival post surgery is also an important prognostic factor. Retrospective analysis has identified that the time from adjuvant treatment to randomization (a proxy of disease free survival) was longest in the P-FOLFOX arm and this may explain why these patient performed so well relative to the rest of the patients in the study.

Our original submission utilized all the patients across all 6 arms in the NO16966 in an attempt to dilute the impact of any imbalances between the arms and increase the precision of the results. Removing patients that had adjuvant treatment is another approach one could take to attempt to address the imbalance in the baseline characteristics mentioned above to estimate the treatment effect. However there are two benefits to pooling all the patients, 1) the precision of the parameter estimates are increased and 2) adjuvant treatment is known to be a prognostic factor and thus removing these patients may underestimate the baseline risk of the population of interest. When pooling the arms, as per our base case, the time from adjuvant treatment to randomization is balanced across the pooled groups (see table 2 below) strengthening the case for using this analysis for the base case.

Table 2: Time from adjuvant treatment to randomization

	FOLFOX	XELOX	P-FOLFOX	P-XELOX	B-XELOX	B-FOLFOX
N	**83**	**88**	**85**	**91**	**76**	**88**
Median time from start of adjuvant treatment to randomization in days (years)	613 (1.7)	687 (1.9)	913 (2.5)	843 (2.3)	725.5 (2.0)	813 (2.2)
	766 (2.1)*				**772 (2.1)***	
Median time from end of adjuvant treatment to randomization in days (years)	517	511	769	660	597	623
	614 (1.7)*				**610 (1.7)***	

*weighted average (mean) of the pooled arm's median values

The ICERs for the requested analysis (removing all patients that had prior adjuvant treatment) are consistent with the 6 arm pooled analysis (see table 3 below) previously presented. The estimated overall survival is slightly reduce when removing prior adjuvant patients reflecting the higher baseline risk of the subgroup that did not receive prior adjuvant treatment (see table 4).

Table 3: Summary of ICERs

	Analysis	Intervention	COMPARATOR: XELOX	COMPARATOR: FOLFOX-6
1	**Chemo+Bev vs Chemo+-Placebo (all 6 arms)**	**B-XELOX**	£35,912	Dominant
		B-FOLFOX-6		£36,569
2	**Chemo+Bev vs Chemo+Placebo (2*2 only)**	**B-XELOX**	£48,111	Dominant
		B-FOLFOX-6		£39,771
3	**XELOX+Bev vs XELOX+Placebo (2*2 only)** **FOLFOX+Bev vs FOLFOX+Placebo (2*2 only)**	**B-XELOX**	£35,662	Dominant
		B-FOLFOX-6		£62,714
4	**2*2 analysis without prior chemotherapy**	**B-XELOX**	£36,006	Dominant
		B-FOLFOX-6		£31,174

Table 4: Mean Overall survival (months)

Analysis	B-Chemo	Chemo	Difference
Chemo+Bev vs Chemo+-Placebo (all 6 arms)	[redacted]	[redacted]	[redacted]
2*2 analysis without prior chemotherapy	[redacted]	[redacted]	[redacted]

The conclusion from the results, in the context of the exploratory analysis presented in the part I of the response, is that the ICER when adding bevacizumab to either XELOX or FOLFOX is approximately £36,000 irrespective of whether patients received prior adjuvant therapy or not. For the reasons presented above we believe that analysis 1 offers the most robust approach to addressing the decision problem and estimating the incremental costs and benefits of bevacizumab.