Comments from Merck Serono

1. Merck Serono believes that cetuximab plus BSC or in combination with irinotecan qualifies for consideration of the end-of-life criteria in the third line treatment of metastatic colorectal cancer for the following reasons:

- Cetuximab plus BSC or in combination with irinotecan offers an extension of life of more than three months. Effectively, the Karapetis et al. study shows statistically significant improvement of median overall survival for cetuximab plus BSC (9.5 months) versus BSC (4.8 months).

- Life expectancy of patients in third line treatment is less than 24 months.

- The patient population targeted by cetuximab plus BSC in third line treatment ranges from 260 to 390 patients. We understand that NICE considers the "small population" criteria per indication in this instance; we believe that this patient range could be considered as small for England and Wales.

- Additionally, no other treatments offering comparative benefits are available on the NHS in terms of improving life expectancy associated with an improvement in quality of life compared to BSC (Karapetis et al 2008; Au et al 2009);

PenTAG agrees that cetuximab plus BSC reaches the end-of-life criteria, subject to patient numbers. As noted above we confirmed that in this indication patient numbers will be below 400 per annum.

2. PenTAG's main disagreement with Merck Serono economic modelling is related to the input of mean treatment duration. We understand that mean duration of treatment is one of the key drivers of the economic case along with time in the progression-free and progressive disease health states.

In the PenTAG report the mean time on cetuximab plus BSC treatment is 4.8 months compared to 2.6 months in the company submission. Similarly a figure of 8.8 months was used by Pen TAG for cetuximab plus irinotecan compared to 4.4 months in the company submission.

To help resolve this difference, Merck Serono will endeavour to collect real life estimate of the treatment duration in current UK clinical practice.

3. In the cetuximab submission, Merck Serono reported the regression parameter for the Weibull function modelling the PFS and OS Kaplan-Meier curves of BSC and cetuximab plus BSC. The Assessment Report comments in this relation that: *"We did not use precisely the same PFS curve as Merck Serono, because this function is commercial in confidence (CiC). We specified that PFS follows a Weibull distribution, as this is a flexible function, widely used in cancer survival analysis."*

This has resulted in the BSC PFS curve presented by PenTAG (page 139) fitting the Kaplan Meier curve less well than that presented in the original submission by Merck Serono. This has the effect of artificially inflating the efficacy of best supportive care and subsequently skewing the ICER calculation in favour of BSC.

4. In the cost comparison of bevacizumab plus FOLFIRI against cetuximab plus FOLFIRI, clinicians in the second line setting would generally use bevacizumab at 10mg/kg plus FOLFIRI rather than 5mg/kg. Taking this dose into account, cetuximab plus FOLFIRI would save the NHS more than £9,000 per patient compared to the use of bevacizumab plus FOLFIRI which is in contrast to the data presented by the manufacturer of bevacizumab.

5. Since April 2011, KRAS testing is provided for free by Merck Serono ensuring that the best diagnostic test (PCR) is performed and accurately identifying patients suitable for cetuximab treatment.

Merck Serono would like to inform the Assessment Group and NICE that the KRAS testing is using the TheraScreen PCR assay (CE marked for In Vitro Diagnostics). In terms of sensitivity TheraScreen PCR will detect 1% mutant allele in a background of wild type in samples with 20% tumour.

References:

Au H.-J. Karapetis C.S. O'Callaghan C.J. et al. Health-related quality of life in patients with advanced colorectal cancer treated with cetuximab: Overall and KRAS-specific results of the NCIC CTG and AGITG CO.17 Trial. Journal of Clinical Oncology 2009; 27(11):1822-1828

Jonker D.J. Karapetis C. Harbison C.J. et al. High epiregulin (EREG) gene expression plus K-ras wild type (WT) status as predictors of cetuximab benefit in the treatment of advanced colorectal cancer (ACRC): Results from NCIC CTG CO.17 – A Phase III trial of cetuximab versus best supportive care (BSC). J Clin Oncol 27:15s, 2009 (suppl; abstr 4016)

Karapetis C.S. KRAS mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008; 359:1757-1765.