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Date	September 26th 2011
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Our ref. **Colorectal cancer (metastatic) 2nd line – cetuximab, bevacizumab and panitumumab: appraisal consultation document**

Dear Jeremy,

Merck Serono has reviewed the Appraisal Consultation Document (ACD) for cetuximab, bevacizumab and panitumumab in colorectal cancer (metastatic) in the pre-treated setting.

According to the ACD report, cetuximab is the technology offering the greatest chance of survival in terms of life extension compared to the other available technologies in this setting.

Cetuximab plus best supportive care prolonged life by 4.7 months in the third line or later setting relative to best supportive care alone while the second best technology (panitumumab) can offer between 2.7 to 3.2 months only.

As noted in the ACD, we understand from the Assessment Group's (AG) mixed treatment comparison that "*the results showed that patients who received cetuximab plus best supportive care would be expected to have significantly longer overall survival than those receiving panitumumab plus best supportive care (unadjusted HR 0.56, 95%CI 0.37 to 0.83; adjusted HR 0.63, 95%CI 0.41 to 0.97)*". We understand that the AG highlighted that the HR for overall survival for panitumumab from the Amgen trial may have underestimated the effectiveness.

The ERG critique highlights that the economic case developed for the use of cetuximab shows it is not cost-effective use of NHS resource. We agree that the technology is not cost-effective under the usual threshold range for acceptability.

Additionally, we applied for the Supplementary Advice of the End of Life (EoL) to be coherent with our evidence (i.e. CO17 study comparing cetuximab plus best supportive

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care versus best supportive care in the third line setting, a clinical study carried out following advice from the NICE TA118 guidance).

NICE is considering that cetuximab meets two out of the three End-of-Life criteria (i.e. population life expectancy less than 24 months and life extension beyond 3 months).

Small population" is the third criterion reported as not met. According to our computation the eligible population for the third line setting is 260 to 390 patients as outlined in our submission.

Please find below our specific comments:

1. ***Has all of the relevant evidence been taken into account?***

We believe all relevant evidence have been considered for this appraisal.

2. ***Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?***

Merck Serono trusts the summaries of clinical and cost effectiveness are reasonable interpretations in light of the available evidence.

3. ***Are the provisional recommendations sound and a suitable basis for guidance to the NHS?***

In relation to our application to the End of Life criteria, we acknowledge that the Committee agreed that cetuximab meet the following:

- "For metastatic colorectal cancer that has progressed after first line treatment, the Committee agreed that the technologies fulfilled the first criterion related to life expectancy"

- "Cetuximab plus best supportive care prolonged life by 4.7 months in the third line or later setting relative to best supportive care alone and therefore met the second criterion"

- The Committee concluded that "the cumulative population covered by the marketing authorisation for cetuximab was not small". However, the population outlined in the submission is 390 and therefore could be considered small and these patients will be disadvantaged by this recommendation.

Beside, all our licensed indications (see Appendix 1) have been appraised by NICE (see Appendix 2: TA118, TA145, TA150, TA172, TA176), and only 1670 patients can

currently benefit from cetuximab across England and Wales with NICE TA 176 (population obtained from TA176 costing template).

Adding these 390 patients, cetuximab cumulative population for recommended use would still be small approximately 2,100 patients.

Does that imply that technology licensed for a wide population should not explore efficacy in small population and seek potential NICE recommendation using the EoL?

4. ***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?***

No.

Sincerely,

[redacted]
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Appendix 1: Cetuximab's indications

Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer:

- in combination with irinotecan-based chemotherapy or FOLFOX4 *(for details, see section 5.1)*,
- **as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.**

Erbitux is indicated for the treatment of patients with squamous cell cancer of the head and neck:

- in combination with radiation therapy for locally advanced disease,
- in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.

Appendix 2 : NICE appraisals related to cetuximab

NICE TA176. Cetuximab for the first line treatment of metastatic colorectal cancer (August 2009).

NICE TA172. Cetuximab for the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck (June 2009).

NICE TA150. Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy (June 2008).

NICE TA145. Cetuximab for the treatment of head and neck cancer (June 2008).

NICE TA118. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (January 2007).