Addendum to PenTAG report: Estimated mean duration of cetuximab treatment and mean cetuximab dose intensity

Addendum to: ‘The effectiveness and cost-effectiveness of cetuximab (mono- or combination chemotherapy), bevacizumab (combination with (non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal 150 and part review of technology appraisal 118): a systematic review and economic model.’

Information on cetuximab treatment duration and dose intensity recently received

In our report, we stressed that the cost-effectiveness of cetuximab vs best supportive care (BSC) for patients with kirsten rat sarcoma (KRAS) wild-type (WT) status is very sensitive to the mean treatment duration of cetuximab, but that unfortunately Merck Serono could not provide us with this information from the RCT of cetuximab vs BSC,(Karapetis, Khambata-Ford et al. 2008) and that we could find not this in the literature. As stated in our report, Mittmann and colleagues(Mittmann, Au et al. 2009) published a cost-effectiveness model on cetuximab vs BSC in metastatic colorectal cancer (mCRC), including an analysis specifically for patients with KRAS WT status. We asked Mittmann and colleagues for the mean treatment duration of cetuximab and the mean dose intensity of cetuximab in the randomised controlled trial (RCT) of cetuximab vs BSC. They replied on 24th May 2011:

[redacted] and they replied on 25th May 2011:

[redacted]

While this vital information has not been published, and therefore not subject to critical review, we nonetheless have confidence in its accuracy because several of the authors of the Mittmann and colleagues paper were also authors on the two papers that reported the clinical results of the cetuximab vs BSC RCT.(Jonker, O'Callaghan et al. 2007; Karapetis, Khambata-Ford et al. 2008) Indeed the lead authors on these two papers are also authors on the Mittmann and colleagues paper.

Given that we received this important information from Mittmann shortly before submission of our report to NICE, we did not have time to fully integrate it in to our report. Instead, we now report our cost-effectiveness results using Mittmann's updated information.

Updated estimate of cost-effectiveness of cetuximab vs BSC using new information

Mean cost of cetuximab administration

We first estimate the mean cost of cetuximab administration using the new information. [redacted] In the RCT, four patients in the cetuximab arm did not receive cetuximab.[5] Given that there were 110 patients with KRAS WT status and 75 patients with KRAS mutant status assigned to the cetuximab arm, we estimate that, of the four patients who received no cetuximab, 2.4 of these were KRAS WT status. Hence, 98% of patients with KRAS WT status received at least one dose.

[redacted]

[redacted] doses assumed by Merck Serono. In our report, we stated that we assumed that cetuximab was taken for the entire duration of progression-free survival (PFS), and that we had found published evidence on the median duration of cetuximab treatment for all patients combined that was consistent with this assumption (see Section 7.1.3.1.2.2 of the main PenTAG report). In this Section, we also criticised Merck Serono's derivation of their assumed mean time on cetuximab treatment.

Next, we estimate the mean undiscounted cost of cetuximab administration per person as the cost per administration of cetuximab multiplied by the estimate mean number of doses = [redacted].

Finally, given that cetuximab is typically taken for less than half a year, discounted costs are very similar to undiscounted. We estimate the discounted cost as equal to the undiscounted cost, discounted over the mean time in PFS (= 0.40 years) = [redacted]

Mean cost of cetuximab acquisition

Next, we estimate the mean cost of cetuximab acquisition using the new information.

First, the cost of the first (loading) dose of cetuximab, which is given at 400 mg/m^{-2}, is £1,093, which is taken directly from our model. Given that we estimate that 98% of patients with KRAS WT status allocated to the cetuximab arm received the first dose, the contribution of the first dose to the mean acquisition cost of cetuximab per person is 98% * £1,093 = £1,069.

Next, the cost of each subsequent dose of cetuximab, which are given at the lower dose of 250 mg/m^{-2}, is £698. Note that the mean number of subsequent doses for those patients who received at least one dose is [redacted], where we subtract the single loading dose. The mean dose intensity, over all patients who had at least one cetuximab dose, is given by Mittmann as [redacted]

Combining this information, the contribution of the all subsequent doses to the mean acquisition cost of cetuximab is [redacted].

Therefore the total mean undiscounted acquisition cost is [redacted].

Finally, we estimate the total mean discounted acquisition cost as equal to the undiscounted cost, discounted over the mean time in PFS (= 0.40 years) = [redacted].

Updated cost-effectiveness of cetuximab vs BSC

Our new results, updated for the analyses above, are given in Table 1 and Table 2. The updated values are shown in the shaded cells. The updated ICER for cetuximab vs BSC is [redacted] per quality-adjusted life year (QALY),

[redacted]

Cost-effectiveness of cetuximab+irinotecan vs BSC

We stated in our report that there is considerable uncertainty in the treatment duration of cetuximab+irinotecan for patients with KRAS WT status. While Mittmann have provided no further direct evidence on this quantity, we believe that our assumption that cetuximab in the cetuximab+irinotecan treatment arm was taken for the entirety of PFS is supported by the information from Mittmann which shows that in the RCT of cetuximab vs BSC, cetuximab was taken for the entire duration of PFS.

Table 1. PenTAG results for patients with KRAS WT status using new data from Mittmann and colleagues

	CET	BSC
Life years (mean, undiscounted)		
Time on drug treatment	0.40	N/A
Progression-free	0.40	0.23
Post-progression	0.44	0.29
Total (mean)	**0.84**	**0.51**
Total (median)	0.75	0.40
QALYs (mean, discounted)		
Progression-free	0.32	0.17
Post-progression	0.29	0.19
Total	**0.61**	**0.36**
Costs (mean, discounted)		
KRAS test	£296	£0
Drug costs	[redacted]	£0
Drug administration	[redacted]	£0
Consultant monitoring appt.	£1,397	£0
CT scans	£178	£0
BSC in PD	£5,304	£3,496
AEs	£3,671	£2,760
Total	[redacted]	**£6,256**

AEs, adverse events; BSC, best supportive care; CET, cetuximab; CT, computed tomography; N/A, not applicable; PD, progressive disease; QALYs quality-adjusted life years

Table 2. PenTAG incremental results cetuximab vs BSC for patients with KRAS WT status using new data from Mittmann and colleagues

	CET BSC
Life years (mean, undiscounted)	
Progression-free	0.17
Post-progression	0.15
Total (mean)	**0.32**
Total (median)	0.35
QALYs (mean, discounted)	
Progression-free	0.15
Post-progression	0.10
Total	**0.25**
Costs (mean, discounted)	
KRAS test	£300
Drug costs	[redacted]
Drug administration	[redacted]
Consultant monitoring appt.	£1,400
CT scans	£200
BSC in PD	£1,800
AEs	£900
Total	[redacted]
Incr. cost LYG	[redacted]
Incr. cost QALY	[redacted]

AEs, adverse events; BSC, best supportive care; CET, cetuximab; CT, computed tomography; incr, incremental; LYG, life years gained; PD, progressive disease; QALYs, quality-adjusted life years

References

Jonker, D. J., C. J. O'Callaghan, et al. (2007). 'Cetuximab for the treatment of colorectal cancer.'

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Mittmann, N., H. J. Au, et al. (2009). 'Prospective cost-effectiveness analysis of cetuximab in metastatic colorectal cancer: evaluation of National Cancer Institute of Canada Clinical Trials Group CO.17 trial.' J Natl Cancer Inst **101**(17): 1182-1192.