Oxaliplatin and capecitabine for the adjuvant treatment of colon cancer - Response to consultee comments

Consultees	Comments/suggestions	ScHARR response to consultees comments
Colon cancer concern		No comment
Institute of Cancer Research		No comment
NHS Quality improvement Scotland	• 50 year time horizon I have problems with the economic analysis. The majority of patients with colorectal cancer are over 70 years old. They do not enjoy the prospect of a "50 year time horizon". I share the authors concerns that they may be over-estimating the economic benefits of more intensive treatment. If costs, both in terms of money and toxicity, are immediate, and if benefits are deferred by 5 to 10 years then this may, in an elderly population, be no bargain.	The mean age of patients within the MOSAIC and X-ACT trials was approximately 60 years, and the cost-effectiveness analysis is based upon this mean age. Whilst we acknowledge that the general colorectal cancer population is older than that observed in the trials, the cost-effectiveness analysis could be performed from the perspective of this more elderly cohort because patient-level data was not made available to the Assessment Group.
Roche		No comment
Royal College of Nursing		No comment
Royal college of Physicians		No comment
Sanofi-Aventis	• Disease-free and overall survival The importance of DFS as an appropriate (and perhaps the best) surrogate marker for long-term survival and /or cure, and the correlation observed between incremental improvements in DFS and overall survival benefits is widely accepted amongst the oncology community. In the MOSAIC trial, the link between DFS and survival benefit was clearly demonstrated…	Although this statistical initiative may turn out to be valid (a correlation is not enough to demonstrate the value of a surrogate endpoint), the primary goal should be to obtain direct evidence about the interventions effect on safety measures and true clinical outcomes. In a trial of adjuvant therapy, overall survival remains as the most reliable and meaningful cancer endpoint. Moreover the statement "In the MOSAIC trial, the link between DFS and survival benefit was clearly demonstrated…" is incorrect and misleading. For stage III patients only (subgroup data), the MOSAIC trial showed a statistically significant benefit in DFS at 37.9 months, 48.6 months and

<table>
<tr>
<td></td>
<td></td>
<td>56.2 months, however, no statistically significant benefit in OS was observed at 37.9 months, 48.6 months and 56.2 months (see table 1 and 2, below). These findings are similar to that of the overall population (patients with stage II and stage III colon cancer). Therefore, the (predictive) link between DFS and OS is not supported by the evidence from the MOSAIC trial.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Table 1. Disease free survival for stage III patients (sub-group analysis)
<table>
<tr><th rowspan="2">Median follow-up (months)</th><th colspan="2">Event rate</th><th rowspan="2">Hazard ratio (95% CI)</th><th rowspan="2">p-value</th></tr>
<tr><th>FOLFOX4</th><th>5-FU/LV (de Gramont)</th></tr>
<tr><td>37.9</td><td>181/672 (26.9%)</td><td>226/675 (33.5%)</td><td>0.76 (0.62 to 0.92)</td><td>NR</td></tr>
<tr><td>48.6</td><td>200/672 (29.8%)</td><td>252/675 (37.3%)</td><td>0.75 (0.62 to 0.90)</td><td>0.002</td></tr>
<tr><td>56.2</td><td>NR</td><td>NR</td><td>0.75 (0.62 to 0.89)</td><td>NR</td></tr>
</table>
NR, not reported

Table 2. Overall survival for stage III patients (sub-group analysis)
<table>
<tr><th rowspan="2">Median follow-up (months)</th><th colspan="2">Event rate</th><th rowspan="2">Hazard ratio (95% CI)</th><th rowspan="2">p- value</th></tr>
<tr><th>FOLFOX4</th><th>5-FU/LV (de Gramont)</th></tr>
<tr><td>37.9</td><td>104/672 (15.5%)</td><td>119/675 (17.6%)</td><td>0.86 (0.66 to 1.11)</td><td>NS</td></tr>
<tr><td>48.6</td><td>NR</td><td>NR</td><td>0.86 (0.68 to 1.08)</td><td>0.196</td></tr>
<tr><td>56.2</td><td>NR</td><td>NR</td><td>0.86 (0.69 to 1.08)</td><td>NS</td></tr>
</table>
NR, not reported; NS, not-significant</td>
</tr>
<tr>
<td></td>
<td>• Safety – neurotoxicity
The report emphasises the main safety concern of oxaliplatin which is neurological impairment. It states the ‘all grade’ neurotoxicity of >85%, and grade 3 neurotoxicity of >8%, and that although this does appear to improve within a one year time frame for the majority of patients, the report states that approximately 25% of patients in the MOSAIC trial had some form of neurological impairment even 18 months after treatment. Although this information is factually correct, we believe that the report needs to further differentiate between the various grades of neuropathy involved in order to provide a more balanced perspective and to avoid misinterpretation of the severity and</td>
<td>As noted by sanofi- aventis, the neurotoxicity information is factually correct, however, as suggested on page 55, the differentiation between various grades of neuropathy is provided in appendix 7, table 3 (page 194). We believe that the main text on page 56 (paragraph 2) presents a balanced overview of the severity and incidence of neuropathy.

Moreover, although grade 3 neurotoxicity improves 18 months after treatment (0.5% had grade 3 neuropathy), many patients are left with grade 1 residual neurotoxicity (19.8%), which is still a burden for patients.</td>
</tr>
</table>

	incidence of these side effects.	
	• Estimates of relative cost-effectiveness for oxaliplatin and capecitabine While we understand that such a comparison is of interest (and indeed NICE directed the Assessment Group to make this comparison), we assert and agree with the conclusions of the Assessment Group that insufficient data are available to make any conclusions derived from this comparison robust. The results generated are, therefore, of experimental interest only and are not sufficient to form the basis of guidance to the NHS. We therefore suggest that it is inappropriate to refer to these results in the Executive Summary of the report.	A comparison of oxaliplatin and capecitabine cannot be made directly in the absence of a trial comparing these two interventions. However, the AG were directed by NICE to consider such an incremental analysis, and we believe that the caution with which the results of this analysis should be interpreted was sufficiently emphasised within the executive summary.
	• Assessment of cost-effectiveness of treatment for Dukes stage B patients We also note that the Assessment Group have not included any assessment of the cost effectiveness of treatment for Duke's stage B patients within the report. While Duke's stage B is outside the scope of this appraisal the Institute at the scoping stage did direct the assessment group to consider Duke's stage B if the data allowed. An assessment of cost effectiveness for this patient group could have added further clarity to the overall consideration of adjuvant treatment for colon cancer in the NHS.	At the scoping stage, NICE did not direct the assessment group to consider Dukes stage B if the data allowed. As clearly highlighted in the final scope and the final protocol the aim of the assessment group was to "assess the clinical and cost effectiveness of oxaliplatin in combination with 5-FU/FA, and capecitabine monotherapy (within their licensed indications), as adjuvant therapies in the treatment of patients with Dukes' stage C colon cancer after complete surgical resection of the primary tumour, as compared to adjuvant chemotherapy with an established fluorouracil-containing regimen." Both oxaliplatin (in combination with 5-FU/FA) and capecitabine are not licensed for patients with stage II (Dukes B) colon cancer