Oxaliplatin and capecitabine for the adjuvant treatment of colon cancer – table of consultee comments

Section	Consultees	Comments	Action
Objective	Roche	As far as capecitabine is concerned, the objective as presently stated accurately reflects the extension to our Marketing Authorisation for this drug which we anticipate receiving next year. We have no comment to make on the objective as it pertains to oxaliplatin.	**No change** Need to check whether this information is CiC
	RCP	We think that it should be made clear in the title and subsequently in the narrative that the appraisal is looking at oxaliplatin in combination with 5FU + folinic acid and at capecitabine as a single agent.	**Amend scope** Title has been amended to show that both drugs will be appraised within their licensed indications.
	SCHARR	The Department of Health remit to NICE was "To appraise the cost and clinical effectiveness of the use of oxaliplatin, irinotecan and capecitabine as adjuvant therapy in colorectal cancer." Although there is no good evidence for rectal cancer, as these patients have been excluded from the major randomised controlled trials, expert advice suggests that the use of adjuvant chemotherapy is similar for patients with rectal and colon cancer. We recommend that rectal cancer should be included in the scope of the appraisal; our suggested title for the appraisal is "The use of oxaliplatin and capecitabine for the adjuvant treatment of colorectal cancer"	**No change** Drugs will be appraised within their licensed indications for use (Dukes stage Colon cancer).
	SCHARR	We require clarification as to whether patients with Dukes B2 (Stage II) colorectal cancer should be included in the scope? (See other considerations below)	**No change** Drugs will be appraised within their licensed indications for use (Dukes stage C Colon cancer).
	RCP	It is stated in the draft scope that the treatments under consideration may be compared. They can certainly be compared in terms of cost and resources required for administration but since they have not been compared directly in clinical trials attempts at comparisons of efficacy would have to be accompanied by appropriate caveats.	**Comment noted**

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	SCHARR#2	I don't think this enquiry should be restricted to Dukes C. There's a paradox here: MOSAIC (the oxaliplatin trial) included both C and B patients though the licence application has been for Dukes' C only. Conversely XACT (the capecitabine trial) included only Dukes' C but if licensed oncologists will want to use it for both B and C regardless of the licence. I think you should consider both drugs in both stages.	**No change** Interventions will be appraised within their licensed indications for use (Dukes stage C colon cancer)
Background information	SCHARR	Within the background section of the draft scope the text reads, "In 2000, there were approximately 22,000 new cases of colon cancer diagnosed in England and Wales." This statement is incorrect. It should read as follows "In 2000, there were approximately 19,000 new cases of colon cancer diagnosed in England and Wales."1	**Amend scope**
	SCHARR#2	Cancer service guidelines Page: 2 also say that "the place of chemotherapy in the treatment of patients with Dukes' stage B cancer must be a matter for discussion between patients and their oncologists", ie by implication at least some of these patients should receive it too.	**No change** Interventions will be appraised within their licensed indications for use (Dukes stage C colon cancer)
	SCHARR#2	6 months of 5FUFA treatment as the standard comparator - True, but many centres use the "QUASAR weekly" regimen which lasts 30 weeks.	**Comment noted**
The technologies	Sanofi	For oxaliplatin, the company name should be '=Sanofi-Aventis'.	**Amend scope**
	SCHARR#2	Sanofi Synthelabo, not Aventis	**Amend as above**
	Sanofi	The registration timelines for oxaliplatin can be updated to state: 'A Mutual Recognition Procedure was completed successfully in October 2004 which resulted in an extended indication: 'adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour'.	**No change** – confirms that the licensed indications for oxaliplatin are Dukes C colon cancer.

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	SCHARR	We would like to clarify with NICE that Sanofi-Synthelabo (Sanofi-Aventis group) manufacture oxaliplatin (Eloxatin®). The scope reads, "Capecitabine is currently licensed for first-line monotherapy of metastatic colorectal cancer. A submission has been made to EMEA to extend the licensed indications to include adjuvant treatment after surgery of patients with Dukes' C colon cancer." We would like to be provided details of any further progress concerning the extended licensing of capecitabine, for example anticipated timescales for licensing.	**No change recommended** MB to advise SCHARR of up to date licensing information
Population	SCHARR#2	Though, as I said above, if adopted there would be no logical reason for giving capecitabine to Dukes' C patients and FU/LV to Dukes' B patients in the same unit – that would be just silly.	**No change** Interventions will be appraised within their licensed indications for use (Dukes stage C colon cancer)
	Cancer Bacup	We recommend that the wording of the details relating to oxaliplatin under the heading 'The technologies' are updated to include the recent change to the licensing of this drug, which now includes use in an adjuvant setting.	**Amend scope**
	SCHARR	The scope focuses on "people with Dukes' stage C colon cancer after complete surgical resection of the primary tumour" We require clarification as to whether the scope should include patients with Dukes B2 colorectal cancer? (See other considerations below)	**No change** Interventions will be appraised within their licensed indications for use (Dukes stage C colon cancer)

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	SCHARR	Oxaliplatin is currently licensed for the treatment of metastatic colorectal cancer in combination with 5FU/FA. Based on data from the MOSAIC trial,2,3 oxaliplatin successfully completed A Mutual Recognition Procedure in Europe in September 2004 and resulted in an extended indication: 'adjuvant treatment of stage III (Dukes' C) colon cancer after complete resection of primary tumour'. We recommend that Dukes B colorectal cancer be included in the appraisal even though there is less evidence. The MOSAIC trial2 provides evidence on patients with Dukes' B and Dukes' C colon cancer. It is not yet clear whether results from this trial will be disaggregated for these two groups of patients, therefore the assessment team may have no choice but to appraise evidence for stage B and C together. If the appraisal includes only stage C cancer, this means that the results of the MOSAIC trial2 would be confounded by the population. As between 33% - 60% of patients with stage B disease are currently given adjuvant chemotherapy off-license (variable by centre), and results from the QUASAR trial4,5 will not be available until 2009/10, it would clearly be worthwhile to extend the remit of the assessment to include this group (even if NICE doesn't make any recommendations for this group of patients).	**No change** Interventions will be appraised within their licensed indications for use (Dukes stage C colon cancer) Although guidance can only be issued in line with the licensed indications for use it would be interesting if the Assessment Group were able to assess the cost effectiveness of the interventions in Dukes stage B and C colon cancer.

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	RCP	There is a problem with rectal cancer. It is generally agreed that patients with rectal cancer derive similar benefits from adjuvant chemotherapy to those with colon cancer and data from the QUASAR trial supports this. At present oncologists worldwide do not differentiate between colon and rectal cancer when deciding whether or not to recommend adjuvant chemotherapy following surgery. However, because patients with rectal cancer often have radiation in combination with chemotherapy delivered synchronously as part of their initial therapy, rectal cancer patients have often been omitted from the large adjuvant trials in order to produce a 'cleaner' study. The consequence of this is that there are limited data to support the use of post operative adjuvant chemotherapy in rectal cancer but no reason to suppose that the results would be any different from those seen in colon cancer. Would the NICE appraisal be willing to extrapolate the data to rectal cancer? This would accord with the wording in para 3 of the draft scope document where it is stated that at present six months of adjuvant chemotherapy with 5FUFA is seen to be the standard treatment for both colon and rectal cancer. This implies that NICE do accept that they should be regarded as one disease for the purposes of deciding whether or not toe recommend adjuvant chemotherapy.	**No change** Interventions will be appraised within their licensed indications for use (Dukes stage C colon cancer)
	NHS-QIS	The scope itself has been reasonably well framed. There is however one important omission. Many oncologists now recognise that, within Dukes stage B (outwith the draft scope), there is an identifiable sub-population of patients who have poorer prognosis and who should be considered for adjuvant chemotherapy. In our jargon these are the bad B's. These patients can be identified by some (or all) of the following histopathological features: pT4 (peritoneal involvement); poor differentiation; extensive extra-mural vascular invasion. Most of us would discuss adjuvant chemotherapy with such patients and it is inappropriate to exclude them from the scope of the review.	**No change** Interventions will be appraised within their licensed indications for use (Dukes stage C colon cancer)
Current Standard Treatments	Cancer Bacup	We suggest that 'no adjuvant chemotherapy' as a comparator is removed as this is not appropriate in this appraisal. Standard therapy for Dukes C colorectal cancer includes adjuvant chemotherapy.	**Amend scope** as the effectiveness of current treatment is not being evaluated

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	Sanofi	We suggest that a comparison with no adjuvant chemotherapy in this treatment setting is no longer a valid comparison. A number of independent randomised phase III trials have reported significant benefits of 5FU-based treatment versus no treatment in the adjuvant setting.123 The correct baseline comparison is therefore adjuvant chemotherapy with established flourouracil-containing regimen.	**Amend scope** to remove no adjuvant chemotherapy.
	Roche	Adjuvant chemotherapy with (an) established fluorouracil-containing regimen" is an entirely appropriate comparator although it is fairly non-specific given that there are many possible 5-FU containing regimens. In England and Wales, the most widely used regimen, by far, is the Mayo clinic regimen of low-dose folinic acid and 5-FU administered as 30 doses over 6 months.	**No change**
	Roche	We do not believe that "no adjuvant chemotherapy" is an appropriate comparator treatment. It is already well accepted that 5-FU based chemotherapy offers a clinically useful survival benefit to patients with complete surgical resection of their primary (Dukes' C) tumour so that in the absence of any contraindications to chemotherapy in general, or fluoropyrimidines in particular, such treatment should routinely be offered. "No adjuvant treatment" is therefore not a suitable alternative to existing treatments in patients suitable to receive them. Additionally, since both of the treatments under assessment in the technology appraisal are fluoropyrimidine-based cytotoxic regimens, which either include or generate 5-fluorouracil, they are not suitable for patients who would be considered unsuitable for current regimens and for whom "no adjuvant chemotherapy" would be the current standard of care.	**Amend scope** to remove no adjuvant chemotherapy.
	SCHARR	We would like to clarify with NICE that "no adjuvant chemotherapy" is probably inappropriate for fit patients with node positive disease, however, "no adjuvant chemotherapy" is a possible option for elderly or frail patients with poor performance status and significant past history.	**Amend scope** to remove no adjuvant chemotherapy.
	SCHARR#2	No adjuvant therapy - this technology only applies to patients who under current guidance would receive FU/LV	**Amend scope** to remove no adjuvant chemotherapy.
Other Considerations	SCHARR	We recommend that progression free survival is omitted, as it is a poor outcome marker.	**No change** – this was an outcome measure of the capecitabine trial

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	RCN	We consider that the outcomes should also include Patient preference Data.	**No change** – this should be included in HRQoL measures
	RCP	In this section attention should be paid to the different resource implications of these treatments possibly using the capacity and demand tools currently being developed by the Cancer Services Collaborative Improvement Partnership. At present adjuvant chemotherapy for colorectal cancer is given using a relatively simple outpatient IV bolus schedule. Oxaliplatin + 5FUFA delivered using the De Gramont schedule is a much more complex treatment requiring 2- 4 hours in the day case unit for each of 24 visits + a central venous line. Thus a change to this therapy would require a considerable investment in pharmacy, chemotherapy nurse and day case facilities. Capecitabine on the other hand would result in a saving of resources in pharmacy and outpatients chemotherapy clinics if it was to replace IV 5FUFA.	**No change** Differences in the cost of administering treatment will be considered during the appraisal.
	RCP	It is stated in the draft scope that the treatments under consideration may be compared. They can certainly be compared in terms of cost and resources required for administration but since they have not been compared directly in clinical trials attempts at comparisons of efficacy would have to be accompanied by appropriate caveats.	**Amend scope for clarity** Trials have not been conducted that directly compare the two interventions. However, an incremental analysis should be performed which ranks the cost effectiveness of the interventions compared to standard treatment.
	Cancer Bacup	We believe that the appraisal should not consider the delivery of treatment such as bolus injection or continuous infusion as current practice states that oxaliplatin should be administered by infusion over a period of two to six hours.	**No change** – as the trials used different delivery methods of 5FUFA in the comparator arm (capecitabine trial - bolus [Mayo], oxaliplatin trial was infusion [de Gramont]) the effectiveness of different delivery methods must be taken into consideration.
	Cancer Bacup	We agree that the appraisal of irinotecan as adjuvant therapy in colorectal cancer should take place separately. The anticipated licensing timescale for irinotecan is not compatible with the appraisal of oxaliplatin and capecitabine for adjuvant colorectal cancer.	**No change**

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	Sanofi	The draft scope indicates that treatments listed under 'interventions' can be compared with each other. We highlight here reasons why this is not appropriate and suggest an alternative evaluation framework for this appraisal. The clinical studies which led to the approval of oxaliplatin and capecitabine in this treatment setting have different designs that reflect the different study questions under evaluation. • The MOSAIC study was designed to detect the superior efficacy of treatment with infusional 5-FU/LV plus oxaliplatin compared to infusional 5-FU/LV alone, in the postoperative adjuvant setting. The X-ACT study was designed to detect equivalence of efficacy of oral capecitabine with bolus 5-FU/LV. • The MOSAIC study and the X-ACT study were therefore designed to answer different research questions and used different treatment comparisons. As a result, there are currently insufficient data to make a meaningful direct comparison between these interventions. It is important that this technology appraisal is designed (and the Assessment Group is directed) to evaluate the different roles of these two products in treating Duke's C colon cancer. In seeking better outcomes for patients with Duke's C colon cancer, the role of capecitabine as a replacement for 5-FU/LV, and the role of oxaliplatin in combination with 5-FU/LV, has led to Researchers investigating both products in combination with each other. • An appropriate evaluation should therefore consider the clinical and cost effectiveness of capecitabine compared to bolus 5-FU/LV and a separate consideration of the clinical and cost effectiveness of oxaliplatin (in combination with infusional 5-FU/LV) compared to infusional 5-FU/LV alone, until such time that the combination of capecitabine and oxaliplatin can be reviewed.	**Amend scope for clarity** Trials have not been conducted that directly compare the two interventions. However, an incremental analysis should be performed which ranks the cost effectiveness of the interventions compared to standard treatment.

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	Roche	In this section of the scoping document, it is stated that "treatments listed above under 'interventions' can be compared with each other". This seems an unusual proposal given that technology appraisals are intended to determine whether new interventions represent clinically and cost-effective advances relative to the current standard of care within the NHS. Comparison with other non-standard interventions does not seem to be useful in this context. For example when comparing two new interventions, one intervention might be considerably more cost-effective than the other but both might not be cost effective compared to the current standard of care. In other words, decisions on whether new treatments are to be made available on the NHS should depend solely upon whether they offer an advance on existing therapies, not how they compare with an intervention which does not represent the present standard of care.	**Amend scope for clarity** Trials have not been conducted that directly compare the two interventions. However, an incremental analysis should be performed which ranks the cost effectiveness of the interventions compared to standard treatment.
	SCHARR	The scope states, "If evidence allows, consideration should be given to different methods of delivering treatment such as bolus injection or continuous infusion." We believe that this is potentially another systematic review. However, feedback from clinicians has suggested that most UK institutions use a bolus rather than an infusional regimen, so it is not expected to add a great deal of complexity to the review. The impact on costs is likely to vary between regimens; this will be discussed within the review.	**No change** As trials of the two interventions used different methods of administration of 5FUFA in the control arm, the effects of different administration methods must also be taken into consideration. The Assessment Group may wish to consider using the Mayo delivery method for the base case analysis and De Gramont in a sensitivity analysis.
	SCHARR	We agree that irinotecan should be considered within a separate appraisal.	**No change**
	SCHARR	We require clarification on how the guidance will be issued for the three projects e.g. will the oxaliplatin/capecitabine guidance be superseded by the irinotecan/ bevacizmab and cetuximab guidance.	Guidance on the use of irinotecan/ bevacizmab and cetuximab should not supercede this guidance.