NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer

Response to consultee, commentator and public comments on the ACD

Consultee	Section	Comment	Institute Response
Royal College of Physicians	1.2 Guidance	In our opinion this appraisal accords with the general view on the place of these treatments within the oncological community and would be well received by clinical staff and interested patient groups. The relevant evidence has been summarised and the reviews of clinical and cost effectiveness are appropriate. Our only additional comment would be that in the area of which patients are offered the various treatments available. The wording we would use is that capecitabine and or oxaliplatin + fluorouracil / folinic acid should be available for use where clinically appropriate for patients with stage III colon cancer ie not necessarily offered to all patients since there will be situations where they would not represent the best choice.	The remit of this appraisal is not to issue guidance on *whether* adjuvant treatment should be considered. Both treatments are recommended as **options**.
Institute of cancer research	1.1 Guidance	We acknowledge the committee's efforts in producing a comprehensive and well-considered report. The relevant clinical trial data have been thoroughly evaluated and the cost-benefit implications appropriately considered. The preliminary recommendations are a positive reflection of the currently available data which demonstrate that both capecitabine and oxaliplatin/5FU/LV are superior alternatives to 5FU/LV for the adjuvant treatment of Dukes' C colon cancer. The preliminary recommendations therefore endorse both capecitabine and oxaliplatin; recognising that for an individual patient there may be strong reasons to choose one over the other. Three further areas warrant further discussion, even though they may be technically beyond the remit of this NICE appraisal. The first is guidance for Dukes' B tumours - especially those with high risk features. It is well known that patients with T4 N0 tumours have poorer survival compared to T3 N1 tumours; demonstrating a fundamental deficiency in both the Dukes' and AJCC stage groupings for stratifying prognosis. While the X-ACT study only included patients with Dukes' C disease, the evidence from QUASAR1 strongly supports administration of adjuvant fluoropyrimidine therapy for patients with Dukes' B tumours. The MOSAIC study demonstrated a similar 3-year DFS benefit for	Noted. See NICE Guide to the Methods of Technology Appraisals (published April 2004) – section 6.1.6: 'The Appraisal Committee is not normally expected to make recommendations regarding the use of a drug outside its current licensed

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		Dukes' B tumours compared to Dukes' C tumours. The second area not addressed by the preliminary recommendations is that of rectal cancer. While the evaluated data relate specifically to colon cancer, there is no reason to believe that patients with Dukes' C (or B) rectal cancer would benefit less from adjuvant capecitabine or oxaliplatin. We feel it is important for NICE to address these areas at the same time as Dukes' C colon cancer, as unfortunately, further randomised evidence dealing specifically with Dukes' B or rectal tumours is unlikely to become available. The preliminary recommendations do not acknowledge the increasing data supporting the use of capecitabine instead of 5FU/LV as the fluoropyrimidine component of oxaliplatin therapy. The advantage of oral therapy with capecitabine as opposed to intravenous administration of 5FU/LV via a central line should not be underestimated.	indications as published in the manufacturer's Summary of Product Characteristics.
Clinical Expert 1	1.1 Guidance	Firstly, the summary did not mention use of the above drugs in the treatment of Dukes C rectal cancer. Whilst I am fully aware that the recent research quoted has looked at colon rather than colon and rectal cancer. There is very little doubt from numerous studies that the two groups of cancers behave in the same way. I can, therefore think of no reason why rectal cancer should not be treated in exactly the same way as colon cancer and I cannot think of a single oncologist with a specialist interest in this area who would disagree. The other point, which I made in my personal statement related to patients with poor prognosis tumours, especially those with positive resection margins or perforation found at the time of surgery. These patients may have Dukes B pathology. My understanding of the recent American CO7 Trial is that these patients would also potentially benefit from Oxaliplatin and 5FU chemotherapy. Certainly, when the data for both CO7 and the updated data on the MOSAIC Trial were discussed at the ASCO meeting in Orlando earlier this year, the authors were unwilling to distinguish between Dukes C patients and patients with poor prognosis colon cancer also included in the studies. I would be grateful if some attention could be given to considering the cost implications of treating this small, but significant group of patients. This would also be an excellent opportunity for NICE to recommend that this is one direction in which future clinical research should proceed, ie to see what difference, if any, there is in benefit between patients with poor prognosis Dukes B cancer and those with Dukes C cancer.	See NICE Guide to the Methods of Technology Appraisals (published April 2004) – section 6.1.6: 'The Appraisal Committee is not normally expected to make recommendations regarding the use of a drug outside its current licensed indications as published in the manufacturer's Summary of Product Characteristics.

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NHSQIS1	1.1 Guidance	i) <u>Whether you consider that all the relevant evidence has been taken into account.</u> Probably – insofar as it goes. The problem being that we do not have the evidence we need to answer the real clinical questions. For example, the XACT trial used a control arm regimen that is widely-used in the USA but is not much used in the UK because it is known to be both toxic and relatively ineffective.	Noted and see also FAD 4.1.17.
		ii) <u>Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate.</u> I do not have access to the details of the economic models used in this report. Only the summary findings are presented. I would take issue with some of the assumptions that I am able to identify: eg it is incorrect to assume that time of relapse is irrelevant when calculating survival after relapse (long disease-free interval may indicate less aggressive disease and better survival after relapse, even if relapse is left untreated); site of relapse is important – lung alone is very different to liver + lung; management of relapse is more varied than accounted for in the models and so on….I do not understand the provenance of the figure for CQG of £56,780 (p15 para 1) this seems very different from £4805. The resource implications for the NHS are not given and therefore I cannot comment upon them.	Noted and see also FAD 4.3.5. This is the result of a sensitivity analysis restricting costs and benefits to only the duration of the clinical trial.
		iii) <u>Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.</u> No I do not. The recommendations fail to take into account several important issues. The Dukes classification system is not an appropriate basis on which to make decisions about adjuvant chemotherapy. There are identifiable patients with Dukes B tumours whose survival is lower that definable subgroups within Dukes C (see O'Connell et al JNCI 96; 1420 2004). Some of the apparent benefit of newer drugs and schedules may be confined to younger patients, the patients in the trials used for this guidance were much younger than UK patients with colorectal cancer. The trial results cannot be mindlessly extrapolated to UK practice. I share the authors concerns that they may be over-estimating the economic benefits of more intensive	See NICE Guide to the Methods of Technology Appraisals (published April 2004) – section 6.1.6: 'The Appraisal Committee is not normally expected to make recommendations regarding the use of a drug outside its current licensed indications as published in

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		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. A similar argument applies to co-morbidities. In populations with high prevalence of ischaemic heart disease, Capecitabine may be a dangerous option. Similarly, I would ask what is the relationship between oxaliplatin neuropathy and diabetes, do we know? Is it always safe to give adjuvant oxaliplatin to a diabetic or is there a risk of precipitating severe neuropathy? This guidance is all based on evidence from untypical patients and cannot, without considerable qualification, be safely used to inform clinical practice.	the manufacturer's Summary of Product Characteristics. See also FAD 1.2. See FAD 1.2.
NHSQIS2	1 Guidance	This is a comprehensive and well balanced review and I am not aware of any significant evidence not considered. The conclusions are clinically sensible and would be equally valid in Scotland.	Noted.
NHSQIS3	1 Guidance	I would support the conclusions of this report. Generally the consensus view in the UK is that patients with high risk, node negative disease (Dukes' B) should also receive adjuvant chemotherapy. Presumably, NICE's remit does not extend to non-licenced indications, but there will be a drift in this direction and a comment from NICE would have been helpful. Many centres will also wish to combine oxaliplatin with capecitabine, but this has not been considered … presumably for the same reason outlined above regarding licencing.	See NICE Guide to the Methods of Technology Appraisals (published April 2004) – section 6.1.6: 'The Appraisal Committee is not normally expected to make recommendations regarding the use of a drug outside its current licensed indications as published in the manufacturer's Summary of Product Characteristics.
Sanofi aventis	1.1 Guidance 4.1.15	We welcome this opportunity to review and comment on the Appraisal Consultation Document (ACD) on capecitabine and oxaliplatin in the adjuvant treatment of stage III colon cancer. We believe that all the relevant evidence has been taken into account, and that the summaries of clinical effectiveness are reasonable interpretations of the available evidence with the following caveats: The discussion of toxicities for both agents. The ACD makes several references to the main safety concern of oxaliplatin which relates to neurological impairment. It states that a joint submission by	

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<tr><td></td><td>4.1.16</td><td>professional organisations reported that oxaliplatin caused a unique cold-related peripheral neuropathy affecting over 90% of patients during treatment, and that symptoms were still present to a greater or lesser degree 18 months after completing treatment in 24% of patients. Another submission by a professional group referred to the combined incidence of grade 2 and 3 neurosensory symptoms in the MOSAIC trial. It notes that 18 months after completion of treatment, 3.9% of patients had persistent debilitating symptoms.
Although such information is factually correct, we believe that guidance needs to differentiate the incidences of the various grades of neuropathy involved in order to provide a more balanced perspective and to avoid misinterpretation of the severity and incidence of these side effects.
As indicated in the table below, the fact that the vast majority of the neurosensory symptoms that developed either during treatment or at follow-up, were either Grade 0 or 1, needs also to be put into context when describing the incidence and severity at various stages of follow-up. For example, at 18 months follow-up, approximately 96 % of the incidences were grade 0 or 1, and only a small minority (0.5%) had grade 3 neuropathy at this stage.
Incidence of neurosensory symptoms (%)

<table><tr><th>Grade</th><th>6 month follow-up</th><th>12 month follow-up</th><th>18 month follow-up</th></tr><tr><td>0</td><td>59.0</td><td>70.5</td><td>76.3</td></tr><tr><td>1</td><td>31.9</td><td>23.6</td><td>19.8</td></tr><tr><td>2</td><td>7.8</td><td>4.8</td><td>3.4</td></tr><tr><td>3</td><td>1.3</td><td>1.1</td><td>0.5</td></tr></table>
It is our recommendation, therefore, to avoid misunderstanding, that section 4.1.15 (sentence 2) be re-worded to remove the word “ greater” (as all symptoms are reduced over time and therefore greater is factually incorrect) Section 4.1.15 (sentence 2) for clarity could read “ Symptoms are still present to a lesser degree 18 months after completing treatment with 76.3% of patients experiencing no symptoms, 19.8% of patients experiencing grade 1 neurosensory symptoms, 3.4% of patients experiencing grade 2 symptoms and 0.5% experiencing grade 3</td><td>Sections 4.1.13 and 4.1.14 of the FAD report the evidence presented for the ‘main toxicities’ in the Assessment Report – page 55.

As stated in section 4.1.15 of the FAD this a verbatim of the evidence provided in the joint submission by professional organisations and as such was part of the evidence base for the Committee.</td></tr>
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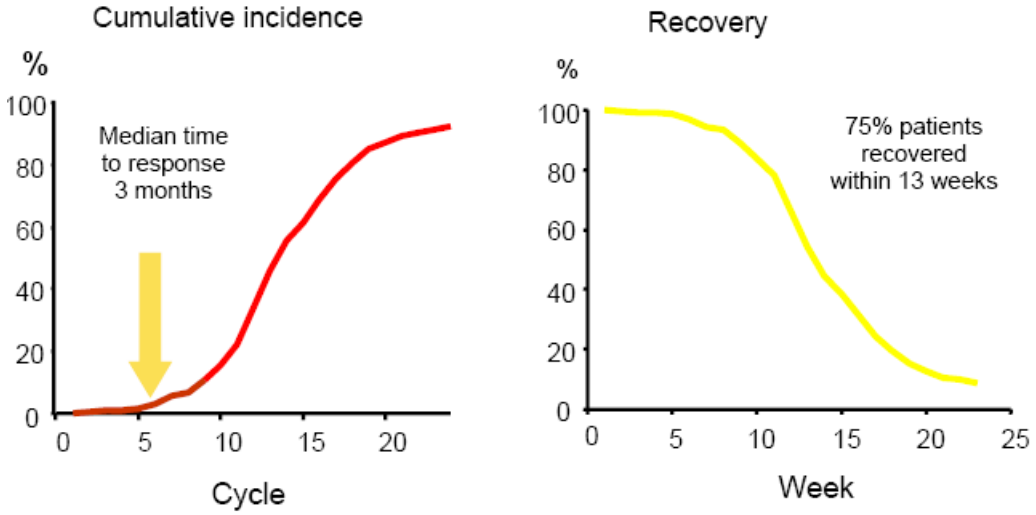
	4.3.4	symptoms. In addition, section 4.3.4 contains a sentence which states that "sensory neuropathy was not predictable". This is factually incorrect and we would recommend the deletion of this comment. There is considerable evidence supporting the view that the neuropathy associated with oxaliplatin is cumulative and predictable. (De Gramont A et al. J Clin Oncol 2000; 18(16):2938–2947). As a result, the duration and intensity of the symptoms naturally increase with the number of cycles, but equally, the neuropathy can be easily managed using a well established dose reduction strategy based on the grade of neurotoxicity seen.  de Gramont A *et al. J Clin Oncol* 2000; **18**(16):2938–2947 It is also worth considering the extensive experience that clinicians have had with oxaliplatin (and therefore managing the predictable side-effect profile) through the use of oxaliplatin in the metastatic setting.	The exact wording of 4.3.4 of the FAD is 'The appearance of sensory neuropathy was not predictable, but the degree to which individuals are affected by such adverse events depends to some extent on their fitness.' This is consistent with the comment made by the consultee. Noted.
	4.3.7 4.2.14	Comparison of technologies Section 4.3.7 clearly highlights "the substantial uncertainty with the indirect comparisons reported in the economic analyses by the assessment group" and stated that this comparison between oxaliplatin plus 5-FU/FA and capecitabine was not considered to be informative for guidance. We agree with this conclusion and therefore suggest that section 4.2.14 be removed from final guidance as it	All evidence presented and considered by the Appraisal Committee is to be included in the FAD; 4.2.14 constitutes no exception.

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	1.2 Guidance	could potentially cause confusion in the decision making process, which is clearly best placed between the patient and the clinician, as outlined in section 1. Informed patient, clinician choice Finally, we support the view that the choice of adjuvant treatment should be made jointly by the patient and the clinician responsible for treatment, after an informed discussion about the contraindications, the side-effect profile and the method of administration. However, we would also encourage this discussion to be about the clinical benefits afforded by the agents, as invariably the final decision on the choice of treatment for this group of patients who will undergo treatment with a potentially curative intent, tends to be based on the risk versus benefit assessment (both by the patient and the clinician). In conclusion, we consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS, and we would urge a more balanced account of the comparable toxicities and their impact on the patients for both agents.	
Welsh Assembly Government	2.2	Just one small comment from a pathology perspective. Paragraph 2.2 is factually incorrect. Dukes' classification of colorectal cancer only contains C1 and C2 categories. There is no C3 category.	Confusion had arisen with modified Astler-Coller C3. Corrected in FAD 2.2.
Roche	6 Preliminary views on resource impact for the NHS	Additional Information for the NICE Costing Unit To assist with the further development of Section 6 “Preliminary views on the resource impact for the NHS”, Roche would like to provide the following feedback for the attention of the NICE Costing Unit: - *full text made available to NICE costing unit.*	Noted and forwarded.
Web comment received from NHS professional	4 Evidence and interpretation	Am interested on the level of benefit in different patients according to age and wonder whether the evidence is relevant only to younger patients. In the MOSAIC trial published in the New Eng J Med the sub group analysis showed no advantage in patients over 65 (nearly 35% of the population). In the updated results patients over the age of 70 had an advantage but no figures were given about the numbers of patients over 70 which could therefore be very small, nor were their any updated results on patients over 65. Sanofi have not responded to my requests for information which make me concerned whether MOSAIC actually shows benefit for the more elderly patients i e those over 65. If you don"t have this information I feel it would be worth aquiring. What about rectal cancer. Do we need to do the same studies on patients with	See FAD 4.3.3. See NICE Guide to the Methods of Technology Appraisals (published April 2004) – section 6.1.6: ‘The Appraisal Committee is not normally expected to make recommendations regarding the use of a drug outside its current licensed indications as published in

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		rectal cancer or can we treat rectal cancer in the same way as colon cancer?	the manufacturer's Summary of Product Characteristics. See also FAD 1.2.
Web comment received from Health care other – pharmaceutical industry	1 Guidance	This document recommends that patients preferences are an important criteria and should be taken into account when deciding the type of Adjuvant treatment that should be received by the patient. Choice of therapy should be made jointly by the patient and the clinician after an informed discussion. NICE, patients and clinicians should consider published data relating specifically to patient preference. Ref 1: Annals of Oncology, Vol 15, Suppl 3, 2004, Abs/Poster 347 Simon W Gollins et al Objectives 1. patient preference for oral (Xeloda) versus i.v treatment: after experiencing both oral and out-patient de Gramont, 50% of patients would prefer to be treated with out-patient de Gr rather than oral.1 What is the impact on patient choice ? 2. patient satisfaction with treatment: patients were more satisfied with infusional 5fu (in-patient de Gramont) when they had experienced both oral and infusional 5fu1 . What is the impact of patient choice ? Patients making informed decisions about their treatment and so their outcome is clearly a difficult process. This emerging data is available for patients to evaluate with their clinician, it takes them a step closer to informed consent.	Noted.
	4.1.17	Section 4.1.17 states However, there are concerns about catheter-associated complications, patient inconvenience and the cost of infusional treatment. The data from Gollins et al and separately Ref 2 : Per Pfieffer Annals of Oncology, Vol 15, Suppl 3, 2004 , Abs 342 , (comparing oral to bolus 5fu) suggests a picture which is at odds with this conclusion. 62% patients preferred iv after experiencing both bolus and oral2 In most cases the strength of preference was very high.2 Why bolus ? Medicine interfered less with daily activity The patient had less diarrhoea It is claimed that patients prefer oral therapy but we conclude patients prefer a regimen with least toxicity2 Until this data was published in 2004 (ref 1,2) it has been unclear what the impact would be of choosing oral capecitabine or iv/infusional 5fu on the patients experience of cancer treatment and their outcome. For the first time it would appear that the patient would experience less inconvenience as they would prefer iv treatment rather than oral capecitabine.	Noted.
Bowel Cancer	1.2 Guidance	Bowel Cancer UK (formally Colon Cancer Concern) believes that this is an	Noted.

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UK		excellent review by NICE, which is going to allow clinicians to provide the best treatment options for their patients tailored to each individual patient"s circumstances. We warmly welcome it and congratulate NICE on it. We would like, however, included in the guidance the point that the choice of treatment made needs to be based on a discussion between the clinician and patient: a discussion that covers the clinical benefit that hopefully the treatment will provide as well as the method of administration and the side-effects of the treatment. Most of this is already covered in the first paragraph under the guidance bullets, but it does not mention discussing the clinical benefit specifically. We know from what patients and clinicans tell us that an important part of their discussions about treatment always centres around the balance between benefit and risk. At the moment the guidance does not cover this, it just talks about covering the risks. We would be grateful if this could be included.	

Reply received but no comments:

- Department of Health
- Royal College of Nursing