

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final Appraisal Determination

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

1 Guidance

- 1.1 The following are recommended as options for the adjuvant treatment of patients with stage III (Dukes' C) colon cancer following surgery for the condition:
- capecitabine as monotherapy
 - oxaliplatin in combination with 5-fluorouracil and folinic acid.
- 1.2 The choice of adjuvant treatment should be made jointly by the individual and the clinicians responsible for treatment. The decision should be made after an informed discussion between the clinicians and the patient; this discussion should take into account contraindications and the side-effect profile of the agent(s) and the method of administration as well as the clinical condition and preferences of the individual.

2 Clinical need and practice

- 2.1 Colon cancer is a malignant neoplasm arising from the lining (mucosa) of the large intestine (colon). Colorectal cancer (including cancers of the rectum as well as cancers of the colon) is the third most common cancer in the UK. Almost 30,000 new cases were registered in England and Wales in 2002, representing over 12% of all new cancer cases. The incidence of colorectal cancer increases with age. In people between the ages of 45 and 49 years the incidence is about 20 per 100,000. Among those aged 75 and above, the

rate is over 300 per 100,000 per year for men and over 200 per 100,000 per year for women.

- 2.2 In the UK, about 26% of patients diagnosed with colorectal cancer are classified as having stage III (or C1, C2 according to the modified Dukes' classification - patients whose tumour has spread to lymph nodes) disease at the time of presentation. These patients have an overall 5-year survival rate of between 25% and 60%. About two thirds of tumours develop in the colon and the remainder in the rectum. After a complete surgical resection (undertaken with curative intent), patients with stage III colon cancer have a 50–60% chance of developing recurrent disease.
- 2.3 The 2004 NICE guidance on cancer services¹ recommends that systemic chemotherapy should be offered to all patients who, after surgery for Dukes' stage C colon or rectal cancer, are fit enough to tolerate it; that a multidisciplinary team should ensure that adjuvant chemotherapy is scheduled to begin within 6 weeks of surgery; and that standard treatment is a 6-month course of 5-fluorouracil and folinic acid (5-FU/FA), given intravenously. 5-FU/FA can be given in regimens involving bolus doses or continuous infusions.
- 2.4 In clinical trials of adjuvant chemotherapy for colon cancer, the outcome of treatment is usually reported in terms of disease-free survival. This is commonly defined as the time from randomisation to either the first relapse, a second primary colon cancer, death from any cause (with no evidence of relapse), or when the patient is disease free (censoring time). In some trials, relapse-free survival is used as a secondary outcome measure and defined in the same way as disease-free survival, but excludes death unrelated to disease progression or treatment. Overall survival is also often reported as a secondary endpoint, but has disadvantages as an indicator of effectiveness.

¹ National Institute for Clinical Excellence (2004). Improving outcomes in colorectal cancers: manual update. *Guidance on cancer services*. Available from: www.nice.org.uk/csgcc

(In recurrent or advanced disease the activity of the adjuvant therapy may be masked by differences in subsequent therapy.) Pooled data suggest that 5-FU/FA regimens will increase disease-free survival at 5 years from 42% to 58%, and overall survival from 51% to 64%, when compared with surgery alone.

3 The technologies

Capecitabine

- 3.1 Capecitabine (Xeloda, Roche) is an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). It is licensed for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer, and for first-line monotherapy for metastatic colorectal cancer.
- 3.2 Capecitabine is contraindicated in patients with severe leucopenia, neutropenia or thrombocytopenia, and in patients with severe hepatic impairment or severe renal impairment. Dose-limiting toxicities include diarrhoea, abdominal pain, nausea, stomatitis and hand-foot syndrome (erythema and desquamation of the palms and the soles of the feet). Most adverse events are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced. For full details of side effects and contraindications, see the Summary of Product Characteristics.
- 3.3 The cost of 60 x 150-mg tablets and 120 x 500-mg tablets of capecitabine is £44.47 and £295.06, respectively (excluding VAT; *British National Formulary [BNF] 50*). For a person with a surface area of 1.75 m² receiving the recommended dose, the cost of treatment with capecitabine is £301.46 per cycle. Costs may vary in different settings because of negotiated procurement discounts.

Oxaliplatin

- 3.4 Oxaliplatin (Eloxatin, Sanofi-Aventis) is a water-soluble platinum-based cytotoxic drug that prevents DNA replication, and hence cell division, by cross-linking DNA. Oxaliplatin in combination with intravenous 5-FU/FA is licensed for adjuvant treatment of stage III (Dukes' C) colon cancer after complete resection of primary tumour, and for the treatment of metastatic colorectal cancer. Neurotoxic side effects can be dose limiting. Acute paraesthesias or dysaesthesias of the extremities, triggered or exacerbated by cold temperatures, occur in 85–95% of people within hours of oxaliplatin infusion. These symptoms are normally mild and resolve within hours or days. However, with increasing cumulative dose, peripheral sensory symptoms increase in duration and intensity. Symptoms may progress to functional impairment. Cumulative neurotoxicity is reversible in most, but not all cases, with regression of symptoms occurring in 4–6 months in about 80% of patients (see also 4.1.13). Other side effects include gastrointestinal disturbances and myelosuppression.
- 3.5 Oxaliplatin is contraindicated in patients who have myelosuppression before starting the first course, as evidenced by a baseline neutrophil count of less than 2×10^9 per litre and/or a platelet count of less than 100×10^9 per litre. It is also contraindicated in patients who have a peripheral neuropathy with functional impairment before the first course. For full details of side effects and contraindications, see the Summary of Product Characteristics.
- 3.6 The recommended dose for oxaliplatin is 85 mg/m^2 when given in combination with 5-FU/FA. It is administered as an intravenous infusion over 2–6 hours every 2 weeks (usually for 6 months) followed by an infusion of 5-FU/FA.
- 3.7 Vials containing 50 mg and 100 mg cost £165 and £330, respectively (excluding VAT, *BNF* 50). For a person with a surface area of 1.75 m^2 receiving the recommended dose, the cost of treatment with oxaliplatin is

£495 per cycle. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (Appendix A) considered evidence from a number of sources (Appendix B).

4.1 *Clinical effectiveness*

Capecitabine

- 4.1.1 One randomised, open-label, active-controlled trial with 1987 participants, the Xeloda - Adjuvant Chemotherapy Trial (X-ACT), investigated the efficacy and safety of capecitabine treatment versus 5-FU/FA treatment (bolus Mayo Clinic regimen) in the postoperative adjuvant setting in patients with stage III (Dukes' C) colon cancer. Apart from the protocol-specified analyses, ad hoc analyses were carried out at the request of the US Food and Drugs Administration (FDA).
- 4.1.2 For the primary endpoint of disease-free survival, the study was powered to establish non-inferiority, defined so that the upper limit of the 95% confidence interval (CI) around the hazard ratio (HR) was no more than 1.25. The median age of participants was 62 years in the capecitabine arm and 63 years in the 5-FU/FA arm.
- 4.1.3 After a median follow-up of 3.8 years, 35% of patients in the capecitabine arm had experienced disease recurrence (relapse or new occurrence of colon cancer) or died, compared with 39% in the 5-FU/FA arm. The hazard ratio for recurrence was 0.87 (95% CI, 0.75 to 1.00). Updated analyses, not specified in the protocol, showed that with longer follow-up (minimum 3 years and median 4.4 years) capecitabine remained at least as effective as 5-FU/FA.
- 4.1.4 Overall survival data were not mature at the time of the primary (specified) and secondary (ad hoc) analyses. However, at 3.8 years median follow-up,

80% and 77% of patients were alive in the capecitabine and 5-FU/FA arms, respectively.

- 4.1.5 Quality of life (QoL) was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), with global health status being the primary parameter for the QoL evaluation. In both treatment groups, scores for global health status were constant over time (from baseline to 25 weeks of trial treatment) and there were no major (statistically significant) differences between the two groups.
- 4.1.6 Severe stomatitis and hair loss were significantly more common in the participants treated with 5-FU/FA. In addition, neutropenia, as a clinical adverse event requiring medical intervention, was significantly less common in participants treated with capecitabine. The only treatment-related adverse events occurring statistically significantly more frequently with capecitabine than with 5-FU/FA were hand–foot syndrome ($p < 0.001$) and hyperbilirubinemia.
- 4.1.7 A submission by a professional organisation reports that ‘when given a choice, most cancer patients prefer oral instead of intravenous therapy, but only if the treatment is equally effective; patients cite increased convenience, less distress over repeated intravenous access and more control over their own treatment as major factors’.

Oxaliplatin

- 4.1.8 Two phase III, randomised active-controlled trials that compared oxaliplatin with standard treatment were identified by the Assessment Group. The first was the Multicenter International Study of Oxaliplatin/5-fluorouracil and leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial. (This was open-label and had 2246 participants – 60% with stage III and the remainder with stage II colon cancer) The second trial was the National Surgical Adjuvant Breast and Bowel Project (NSABP C-07) trial. (This had

2492 participants, 71% with stage III and the remainder with stage II colon cancer). The NSABP C-07 trial was only available in abstract form.

- 4.1.9 In the MOSAIC trial, oxaliplatin was combined with 5-FU/FA in the modified de Gramont regimen (an infusional regimen) and compared with 5-FU/FA alone (also given in the modified de Gramont regimen). In the NSABP C-07 trial, standard treatment consisted of 5-FU/FA administered via a bolus regimen (Roswell Park) and this was subsequently compared with oxaliplatin in combination with the same bolus regimen. In addition to the protocol-specified analyses, ad hoc analyses were carried out at the request of the FDA in the MOSAIC trial. The median age of trial participants was 61 years and 60 years in the oxaliplatin plus 5-FU/FA and the 5-FU/FA alone groups, respectively. NSABP C-07 did not report age at baseline. Quality-of-life data were not routinely collected within either trial.
- 4.1.10 In both trials the addition of oxaliplatin to 5-FU/FA, albeit administered via different regimens, led to a statistically significant reduction in rate of relapse when compared with 5-FU/FA monotherapy. Analysis of disease-free survival at 3 years showed a hazard ratio for recurrence of 0.77 (95% CI, 0.65 to 0.91) in the MOSAIC trial (median follow-up 37.9 months, intention to treat analysis), and 0.79 (95% CI, 0.67 to 0.93) in the NSABP C-07 trial (median follow-up 34 months, according to protocol analysis). Additional analyses on MOSAIC – requested by regulatory authorities – showed a 24% reduction in the rate of relapse (improved disease-free survival) at a median follow-up of 4 years (hazard for recurrence 0.76; 95% CI, 0.65 to 0.90).
- 4.1.11 Overall survival results for MOSAIC and NSABP C-07 are to be calculated at follow-up periods of 6 years and 5 years respectively. No mature data are available for MOSAIC at present and the interim 3-year and 4-year analyses report no statistically significant differences in overall survival between the study groups; 88.2% and 87.0% still alive at 38 months in the oxaliplatin plus 5-FU/FA, and the 5-FU/FA arms, respectively, and a hazard ratio for death of 0.89 (95% CI, 0.72 to 1.09) in the 4-year analysis favouring the addition of

oxaliplatin. The abstract of the NSABP C-07 trial did not report overall survival.

4.1.12 Only in the MOSAIC study were subgroups prespecified according to stage of the disease, with results reported separately. For participants with stage III colon cancer, the hazard ratio for recurrence was found to be 0.76 (95% CI, 0.62 to 0.92) at 3 years, and 0.75 (95% CI, 0.62 to 0.90) at 4 years. The percentages of people experiencing relapse or death in the oxaliplatin plus 5-FU/FA, and the 5-FU/FA arms were 26.9% and 33.5%, respectively. The hazard ratio for death for stage III patients in MOSAIC was 0.86 (95% CI, 0.66 to 1.11) at 3 years. Although the MOSAIC study was adequately powered to demonstrate improved survival outcomes in patients with stage II (40% of total population), or III (60% of total population) disease, the study was not powered to detect a therapeutic effect by subgroup.

4.1.13 In the MOSAIC trial more participants discontinued treatment because of adverse events in the oxaliplatin plus 5-FU/FA group (14.4%) than in the group receiving 5-FU/FA monotherapy (5.6%). Neutropenia and paraesthesia are the toxicities most reported for oxaliplatin plus 5-FU/FA. Grade 3 peripheral neuropathy was observed in 12.4% of patients during treatment (median number of cycles 12; equivalent to about 6 months of chemotherapy), and in 1.1% and 0.5% of patients at 12 months and 18 months follow-up, respectively. Other frequent adverse events in the oxaliplatin plus infusional 5-FU/FA group were diarrhoea, nausea and vomiting.

4.1.14 Grade 3 neurotoxicity was observed in 8% of patients receiving oxaliplatin plus bolus 5-FU/FA in the NSABP C-07 trial compared with 1% of patients receiving 5-FU/FA alone. After 1 year follow-up, grade 3 neuropathy in the oxaliplatin plus 5-FU/FA group remained in 0.5% of patients. The Assessment Group noted that the incidence of grade 3/4 diarrhoea in the combination arm was much higher than that observed in MOSAIC: approximately 40% and 11%, respectively.

- 4.1.15 A joint submission by professional organisations reports that oxaliplatin causes a unique cold-related peripheral neuropathy affecting over 90% of patients during treatment. Symptoms are still present to a greater or lesser degree 18 months after completing treatment in 24% of patients.
- 4.1.16 Another submission by a professional group refers to the combined incidence of grade 2 and 3 neurosensory symptoms as reported in the MOSAIC trial. It notes that 18 months after completion of treatment, 3.9% of patients had persistent debilitating symptoms.

Comparison of infusional and bolus regimes for 5-FU/FA

- 4.1.17 Three randomised comparisons of bolus versus infusional regimens have been published. Only two studies followed individuals for 5 years – a suitable proxy for long-term survival. The evidence reviewed suggests that infusional intravenous 5-FU-based adjuvant therapy is equivalent to, but has relatively less toxicity than, traditional bolus 5-FU/FA in extending survival and QoL. However, there are concerns about catheter-associated complications, patient inconvenience and the cost of infusional treatment. In the adjuvant setting, the weekly intravenous bolus 5-FU/FA for 30 weeks (QUASAR regimen) is most commonly used in the NHS in England and Wales. However, there remains significant geographical variation in the 5-FU-based regimens currently in use in the UK.

4.2 Cost effectiveness

- 4.2.1 The Assessment Group reviewed three published economic evaluations, two of which were submitted by manufacturers. It also presented its own three-state Markov model to estimate the cost effectiveness of oxaliplatin plus 5-FU/FA versus 5-FU/FA alone and of capecitabine versus 5-FU/FA alone.
- 4.2.2 In the Assessment Group model, hypothetical individuals were assumed to move between three states: alive without relapse, alive with relapse, and dead. Transition probabilities in the AG model and one of the manufacturer models were estimated from the disease-free survival curve and the

partitioned overall survival curves for patients with and without relapse. This joint modelling of disease-free and overall survival differs from the approach adopted in the model submitted by the manufacturer of capecitabine where there was independent modelling of relapse-free survival and overall survival with inconsistent results.

4.2.3 Key assumptions used in the Assessment Group model were as follows.

- Overall survival of people who relapse is assumed to be independent of the time of relapse.
- Overall survival of people who relapse is equivalent to that of patients who are initially diagnosed with advanced (stage IV – Dukes' D) colorectal cancer.
- All relapses occur within the 5 years following resection of the primary tumour.
- Overall survival of people alive and disease free at 5 years is similar to the survival in the general population, adjusting for age and sex.
- People who relapse are assumed to receive first-line 5-FU/FA followed upon progression by single-agent irinotecan.
- People receiving 5-FU/FA via the de Gramont regimen are assumed to receive their treatment on an outpatient basis.

All of these assumptions, except for the last two, are also used in the model submitted by the manufacturer of oxaliplatin. Instead of using the cost of a specific chemotherapy regimen to estimate cost of relapse, the manufacturer's model uses an average cost of relapse that is calculated from a distribution using costs of treatment for four different types of relapse.

4.2.4 Evidence for estimating preference-based utilities for the different health states is scarce. The submissions from the manufacturers of both drugs

based their utility estimates on a study of 173 patients with colorectal cancer (40 of whom had stage III disease). In this study, generic and cancer-specific quality-of-life tools were administered at regular intervals following diagnosis, starting at 13 months post diagnosis. Although the study did not differentiate between patients who relapsed and those who did not, both submissions used a disutility of approximately 0.2 for people who experienced relapse. In the manufacturer submission for oxaliplatin, utilities while on treatment were also corrected for adverse events.

- 4.2.5 The Assessment Group noted that because the study used in the manufacturers' submissions started long after diagnosis, and a relatively small proportion had stage III disease, they could only use data from this study to estimate the utility for people in remission (0.92).
- 4.2.6 From a second study that elicited utilities from 81 patients with colorectal cancer with all stages of the disease (including those with stage III undergoing resection and chemotherapy), utilities were taken for those people undergoing treatment without adverse events (0.7) and with adverse events (0.63), as well as for those who relapse (0.24).

Capecitabine

- 4.2.7 The key cost driver of the economic analysis submitted by the manufacturer was the difference in the drug acquisition and administration costs between the capecitabine and 5-FU/FA (Mayo Clinic regimen) arms. Acquisition costs were approximately £1400 higher for the capecitabine arm, whereas administration costs and costs associated with adverse events were lower for the capecitabine arm – approximately £4750 and £300 per patient for 5-FU/FA and capecitabine, respectively.
- 4.2.8 Primarily because of reduced drug administration costs associated with capecitabine (long-term costs assumed to be approximately equal), the manufacturer's submission concluded that capecitabine is cost saving compared with 5-FU/FA, costing on average £3653 less per patient.

Combined with lifetime extrapolated relapse-free and overall survival benefits treatment with capecitabine also leads to a gain of 0.75 quality-adjusted life years (QALYs) in the manufacturer's model. The one-way sensitivity analyses and extreme analysis showed that the only significant uncertain driver for varying cost effectiveness is the cost per administration visit. Scenario analyses on the regimen used for 5-FU/FA indicate that capecitabine remains cost saving whichever regimen is used.

4.2.9 In the Assessment Group model total cost savings from the use of capecitabine compared with the Mayo Clinic 5-FU/FA regimen are slightly less than those reported in the manufacturer's submission (£3320). This is primarily due to the differences between the two models in the costs associated with relapse and a difference in pharmacy costs between capecitabine and 5-FU/FA that was included in the Assessment Group model but not in the manufacturer's submission. The higher QALY gain associated with capecitabine in the Assessment Group model (0.98 QALYs) appears to be attributable to the different methods used to estimate survival. In all the one-way sensitivity analyses, capecitabine treatment results in a cost saving when compared with 5-FU/FA in the Mayo Clinic regimen.

Oxaliplatin

4.2.10 Two published economic analyses that considered oxaliplatin plus 5-FU/FA in the adjuvant setting were included in the Assessment Report. One of these analyses was conducted from a non-UK perspective and used survival estimates from trials of oxaliplatin plus 5-FU/FA in advanced colorectal cancer that are unlikely to be representative of survival outcomes for patients receiving adjuvant chemotherapy. Further analysis by the Assessment Group of the marginal cost and survival results given in the paper suggested that the cost per life year gained of the addition of oxaliplatin to 5-FU/FA is £24,952. An abstract of another economic analysis was presented at the 2005 meeting of the American Society of Clinical Oncology (ASCO) and updated to form the basis of the manufacturer's submission to the appraisal (see 4.2.11 below).

The cost per life year gained associated with oxaliplatin plus infusional 5-FU/FA in this study was estimated to be US\$27,300.

4.2.11 The economic model submitted by the manufacturer was based on patient-level data from the MOSAIC trial. It used observed mortality and disease-free survival, as well as the relationship between disease-free survival and overall survival, to estimate the difference in overall survival between the two treatment arms. Data from MOSAIC that relate to the cohort of patients with stage III colon cancer were used to report a base-case cost per QALY gained (CQG) of £4805 for oxaliplatin plus infusional 5-FU/FA versus infusional 5-FU/FA alone, calculated over a 50-year time horizon. This CQG estimate consists of a difference in costs of £3267 and difference in benefits of 0.68 QALYs. When a one-way sensitivity analysis was performed, and benefits and costs were limited to those within trial data, the CQG increased to £56,780. There was no other one-way sensitivity analysis that resulted in a very different estimate from that of the base case – not even a doubling of the disutility for relapse (to 0.4). The manufacturer suggests that the difference between its base-case results (for stage II and III combined – CQG of £7210) and those of the published economic analyses is probably due to the lower drug acquisition costs of oxaliplatin in the UK compared with the US.

4.2.12 In an addendum to its submission the manufacturer presented a second cost-effectiveness analysis, now based on the NSABP C-07 trial. Equivalent efficacy (0.68 QALYs gained) was assumed for oxaliplatin plus bolus 5-FU/FA (Mayo Clinic regimen) and oxaliplatin plus 5-FU/FA (de Gramont). When combined with a cost difference of £4246 between oxaliplatin plus bolus 5-FU/FA (Mayo Clinic regimen) and 5-FU/FA alone (Mayo Clinic regimen), this analysis resulted in a CQG estimate of £6244 for oxaliplatin plus 5-FU/FA relative to 5-FU/FA.

4.2.13 Incremental benefits in the Assessment Group model were greater than those in the manufacturer's submission (1.33 versus 0.68 QALYs) when oxaliplatin plus 5-FU/FA (de Gramont) was compared with 5-FU/FA alone (de Gramont).

Reasons for this lie in the differences in methods used for long-term extrapolation of survival curves and utility estimates used for those people that relapse in the economic model. When incremental benefits were combined with a cost difference that was also greater than that in the manufacturer's submission (£3940) the Assessment Group model resulted in an estimated CQG of £2970. This cost difference arises because the manufacturer's model uses differential costs of relapse for the 5-FU/FA and combination arms, whereas the Assessment Group model uses costs of relapse unrelated to the intervention received in the adjuvant setting. Furthermore, unlike the manufacturer's submission, the Assessment Group model included differences in pharmacy costs between oxaliplatin plus 5-FU/FA and 5-FU/FA alone. Finally, by setting the model parameters to the worst-case scenario, the estimated CQG in the Assessment Group model was increased to £7587.

4.2.14 In the absence of studies directly comparing oxaliplatin plus 5-FU/FA (de Gramont) with capecitabine, the Assessment Group modelled indirect comparisons of oxaliplatin plus 5-FU/FA (de Gramont) versus capecitabine, and oxaliplatin plus 5-FU/FA versus bolus 5-FU/FA in the adjuvant treatment of stage III colon cancer.

- For the first comparison, two approaches were taken. The first used the absolute predicted long-term survival and cost data of the Assessment Group model, and the second used the marginal cost effectiveness of oxaliplatin plus 5-FU/FA (de Gramont) and of capecitabine against the comparator arms of MOSAIC and X-ACT, respectively. The estimated CQGs for oxaliplatin plus 5-FU/FA (de Gramont) compared with capecitabine were £12,874 (£16,283 additional costs and 1.26 QALYs) and £46,814 (£16,283 additional costs and 0.35 QALYs) for the first and second approach, respectively.
- The second comparison, using data from the MOSAIC and X-ACT trials, resulted in an estimated CQG of £5777 for oxaliplatin plus 5-FU/FA (de

Gramont) versus bolus 5-FU/FA (Mayo Clinic regimen), consisting of £12,963 in additional costs and 2.24 QALYs.

4.3 Consideration of the evidence

- 4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of capecitabine as monotherapy, and oxaliplatin in combination with 5-FU/FA in the adjuvant treatment of Dukes' C (stage III) colon cancer. It considered evidence on the nature of the condition and on the value that people with colon cancer, those who represent them, and clinical experts placed on the benefits of the two drugs in the adjuvant treatment of the condition. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.3.2 In reviewing the evidence of clinical effectiveness for both capecitabine and oxaliplatin the Committee noted that to date, no statistically significant benefit on overall survival of these interventions over their comparators has been reported from the trial populations of X-ACT, MOSAIC and NSABP C-07. However, the Committee considered it reasonable to assume that for the purpose of the economic model, the 3-year disease-free survival benefits reported in these clinical trials would predict 5-year overall survival benefits for the adjuvant treatment of people with stage III (Dukes' C) colon cancer.
- 4.3.3 The Committee considered the fact that participants in trials for adjuvant treatment of stage III colon cancer are often younger than those who would be treated in clinical practice. It heard testimony from clinical experts that it is reasonable to extrapolate these results to older patients, that appropriately selected older people show a relatively good tolerability profile to the drugs, and that the effect on overall survival in those older people in clinical practice is comparable to that seen in the younger trial participants. Additionally, the Committee heard evidence from the Assessment Group that, if an older cohort of people was used in the model that was more representative of the population under consideration, and survival benefits for this group were

assumed to be equivalent to those for the group of trial participants, the cost-effectiveness estimates would not materially change.

4.3.4 The Committee carefully considered the rates of adverse events reported for capecitabine and oxaliplatin in the three pivotal clinical trials. It particularly noted sensory neuropathy following treatment with oxaliplatin. It heard testimony from clinical experts that not only grade 3 but also grade 2 neuropathies can be severely debilitating, and continue long term in a significant percentage of patients. This is particularly problematic in adjuvant treatment. It further heard that 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.

4.3.5 The Committee considered the Assessment Group's assumptions and sensitivity analyses used in its economic model and noted the following points.

- They expressed some concerns regarding the utility values adopted, but accepted that these were the best available from the literature and gave a plausible set of results.
- They were concerned that the adverse effects of the drugs, particularly oxaliplatin-induced sensory neuropathy, could have been undervalued by the Assessment Group.
- They noted that recurrence of a tumour more than 5 years after first receiving adjuvant treatment is possible; however, the relevant sensitivity analysis from the economic model did not affect the cost effectiveness materially.
- They were aware that when findings from the FOCUS and GERCOR trials (which looked at advanced colorectal cancer) are used in estimating costs of relapse, these costs are likely to be an underestimate of the real costs; however, it was accepted that imputing higher costs of relapse would lead to more favourable cost effectiveness for capecitabine and oxaliplatin plus 5-FU/FA.

- They considered that the use of oxaliplatin in the adjuvant treatment of colon cancer could restrict its use in advanced colorectal cancer, but that this would depend on when the relapse was experienced after first use of the drug in the adjuvant setting. They were persuaded that it was most important to achieve the benefits of adjuvant treatment early in order to avoid or delay relapse.
- 4.3.6 Overall, the Committee accepted that capecitabine as monotherapy, and the combination of oxaliplatin plus 5-FU/FA, should be considered as cost-effective options for the adjuvant treatment of people with stage III (Dukes' stage C) colon cancer.
- 4.3.7 The Committee was mindful of the substantial uncertainty within the indirect comparisons reported in the economic analyses by the Assessment Group. It therefore did not consider the comparison between oxaliplatin plus 5-FU/FA and capecitabine to be informative for guidance.
- 4.3.8 The Committee was clear that, given the different toxicities of the drugs, particularly the risk of longer-term sensory neuropathy in oxaliplatin, the choice of therapy should be made in clear consultation with the patient, and in careful consideration of the patient's performance status.

5 Recommendations for further research

- 5.1 Research is needed to compare the effectiveness, tolerability, acceptability to patients and costs of the different oxaliplatin plus 5-fluorouracil regimens in the adjuvant setting (particularly those that combine oxaliplatin with oral forms of 5-fluorouracil).
- 5.2 The optimum duration of adjuvant therapy is not known. Shorter duration might potentially reduce the costs, inconvenience, toxicity and risks of adjuvant therapy, but large trials are required to determine whether there is any reduction in efficacy.
- 5.3 There is a need for future cancer trial protocols of the adjuvant treatment for stage III colon cancer to incorporate more detailed resource data collection strategies and to report summary statistics that are of use within economic valuations. The degree of adherence to treatment particularly needs to be factored in. Trials should also collect data on changes in health-related quality of life of participants, especially those related to adverse events.

Ongoing research (non-comprehensive list)

- 5.4 National Surgical Adjuvant Breast and Bowel Project (NSABP-C-08). *Phase III Randomized Study of Adjuvant Chemotherapy Comprising Fluorouracil, Leucovorin Calcium, and Oxaliplatin With Versus Without Bevacizumab in Patients With Resected Stage II or III Adenocarcinoma of the Colon*. US. NCT00096278.
- 5.5 National Cancer Research Institute (NCRI-QUASAR1). *Phase III Randomized Study of Adjuvant Chemotherapy with L-Leucovorin and Fluorouracil versus Observation in Patients with Resected Colorectal Cancer*. UK. NCT00005586.
- 5.6 North Central Cancer Treatment Group, National Cancer Institute, Eastern Cooperative Oncology Group. *Phase III Randomized Study of Oxaliplatin (OXAL) Plus 5-Fluorouracil (5-FU)/Leucovorin (CF) With or Without*

Cetuximab (C225) After Curative Resection for Patients with Stage III Colon Cancer. US. NCT00079274.

- 5.7 Schmoll HJ, Tabernero J, Nowacki M et al. Safety findings from a phase III trial of capecitabine plus oxaliplatin (XELOX) versus bolus 5-FU/LV as adjuvant therapy for patients with stage III colon cancer. Abstract 3523, presented at ASCO 2005.
- 5.8 Wein A, Lehnert T, Liersch T et al. (2004) Toxicity and safety of weekly high-dose 5-FU as 24-h infusion and folinic acid (AIO regimen) in adjuvant therapy of UICC stage III colon cancer. InTACT: A multicenter phase III trial. *Journal of Clinical Oncology* 22 (14S July 15 Supplement): 3586. ASCO Annual Meeting Proceedings (Post-Meeting Edition).
- 5.9 Coppola FS, Arca R, Ferro A et al. (2002) A phase III randomized trial (COLON-OXALAD) of adjuvant therapy for very high risk colon cancer (CC) patients (pts) with oxaliplatin (OXA) and bolus 5-fluorouracil (5-FU)/folinic acid (FA): a toxicity report. ASCO Annual Meeting: 656.

6 Implications for the NHS

The NICE Costing Unit is currently developing this section. A costing template and report will be available at the time of publication of the final guidance.

7 Implementation and audit

- 7.1 Clinicians with responsibility for treating people with stage III (Dukes' C) colon cancer should review their current practice and policies to take account of the guidance set out in section 1.
- 7.2 Local guidelines, protocols or care pathways that refer to the care of people with stage III (Dukes' C) colon cancer should incorporate the guidance.
- 7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.
- 7.3.1 A person with stage III (Dukes' C) colon cancer is offered the following as options for the adjuvant treatment following surgery for the condition:
- capecitabine as monotherapy
 - oxaliplatin in combination with 5-FU/FA.
- 7.3.2 The individual and the clinicians responsible for treatment decide jointly on the choice of adjuvant treatment after an informed discussion.
- 7.4 Local clinical audits on the management of colon cancer could also include measurement of compliance with accepted clinical guidelines or protocols or with the measures for the treatment of colorectal cancer that are suggested in *Guidance on cancer services: 'Improving outcomes in colorectal cancers'*.

8 Related guidance

- 8.1 NICE has issued the following related technology appraisal guidance.

Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer. Review of Technology Appraisal 33. *NICE technology appraisal guidance* no. 93 (2005). Available from: www.nice.org.uk/TA093

Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer. *NICE technology appraisal guidance* no. 61 (2003). Available from: www.nice.org.uk/TA061

Guidance on the use of laparoscopic surgery for colorectal cancer. *NICE technology appraisal guidance* no. 17 (2000). Available from: www.nice.org.uk/TA017

- 8.2 NICE is in the process of producing the following technology appraisal guidance.

The use of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (publication expected August 2006).

- 8.3 NICE has issued the following related cancer service guidance.

Improving outcomes in colorectal cancers: manual update. *Guidance on cancer services* (2004). Available from: www.nice.org.uk/csgcc

9 Review of guidance

- 9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

- 9.2 The guidance on this technology will be considered for review in June 2009.

Andrew Stevens
Chair, Appraisal Committee
January 2006

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets regularly and membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Darren Ashcroft

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences,
University of Manchester

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Mr Brian Buckley

Vice Chairman, InContact

Professor John Cairns

Public Health and Policy, London School of Hygiene and Tropical Medicine

Professor Mike Campbell

Statistician, University of Sheffield

Professor David Chadwick

Professor of Neurology, Walton Centre for Neurology and Neurosurgery

Dr Mark Chakravarty

Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK) Ltd

Dr Peter I Clark

Honorary Chairman, Association of Cancer Physicians

Dr Mike Davies

Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips

Public Affairs Manager, Medtronic Ltd

Professor Jack Dowie

Health Economist, London School of Hygiene

Dr Fergus Gleeson

Consultant Radiologist, The Churchill Hospital, Oxford

Ms Sally Gooch

Former Director of Nursing & Workforce Development, Mid Essex Hospital Services NHS Trust

Mr Sanjay Gupta

Stroke Services Manager, Basildon and Thurrock University Hospitals NHS Trust

Professor Philip Home

Professor of Diabetes Medicine, University of Newcastle upon Tyne

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Professor Peter Jones

Professor of Statistics & Dean Faculty of Natural Sciences, Keele University

Dr Mike Laker

Medical Director, Newcastle Hospitals NHS Trust

Dr George Levvy

Lay representative

Ms Rachel Lewis

Nurse Advisor to the Department of Health

Mr Terence Lewis

Mental Health Consultant, National Institute for Mental Health in England

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Neil Milner

General Medical Practitioner, Sheffield

Dr Ruairidh Milne

Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology

Dr Rubin Minhas

General Practitioner, Primary Care Cardiovascular Society

Mr Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Dr Ken Stein

Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens (Chair)

Professor of Public Health, University of Birmingham

B. NICE project team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Meindert Boysen

Technical Lead, NICE project team

Cathryn Fuller

Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by The School of Health and Related Research (ScHARR), University of Sheffield:

Pandor A, Eggington S, Paisley S et al. *The use of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer*, August 2005.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope and assessment report and the appraisal consultation document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturers/sponsors:

- Roche Products Ltd
- Sanofi-Aventis

I Professional/specialist and patient/carer groups:

- Association of Coloproctology of Great Britain and Ireland
- Beating Bowel Cancer
- Bowel Cancer UK
- British Oncology Pharmacy Association
- Cancer Research UK
- CancerBACUP
- CORE
- Department of Health
- National Council for Palliative Care
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Physicians

- Teenage Cancer Trust
- Tenovus Cancer Information Centre
- Welsh Assembly Government

II Commentator organisations (without the right of appeal):

- British National Formulary
- Institute of Cancer Research
- Medac UK
- MRC Clinical Trials Unit
- National Cancer Research Institute
- National Collaborating Centre for Cancer
- National Public Health Service for Wales
- NHS Quality Improvement Scotland
- Pfizer Ltd
- Wyeth Pharmaceuticals

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on oxaliplatin and capecitabine in the adjuvant treatment of Duke's C (stage III) colon cancer by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Olive Craven, Nurse Clinician, The Christie Hospital NHS Trust -Clinical expert, nominated by Royal College of Nursing
- Dr Edward Levine, Consultant Clinical Oncologist, The Christie Hospital NHS Trust – Clinical expert, nominated by Association of Coloproctology of Great Britain and Ireland
- Professor Chris Marks, Consultant Surgeon, The Royal Surrey County Hospital NHS Trust – Clinical expert, nominated by Association of Coloproctology of Great Britain and Ireland
- Dr Anand Sharma, Consultant Forensic Psychiatrist, The Edenfield Centre – Patient expert

Appendix C. Detail on criteria for audit of the use of capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer

Possible objectives for an audit

An audit on the adjuvant treatment of people with stage III (Dukes' C) colon cancer could be carried out to ensure that capecitabine and oxaliplatin are being used appropriately.

Possible patients to be included in the audit

An audit could be carried out on people with stage III (Dukes' C) colon cancer seen over a suitable time period for audit; for example, 6 months or a year.

Measures that could be used as a basis for an audit

The measures that could be used in an audit of capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer are as follows.

Criterion	Standard	Exception	Definition of terms
<p>1. A person with stage III (Dukes' C) colon cancer is offered the following as options for adjuvant treatment following surgery for the condition:</p> <p>a. capecitabine monotherapy and</p> <p>b. oxaliplatin in combination with 5-FU/FA</p>	<p>100% of people who have stage III (Dukes' C) colon cancer and to whom adjuvant treatment is offered</p>	<p>A. The person has a contraindication to capecitabine</p> <p>B. The person has a contraindication to oxaliplatin, 5-fluorouracil, or folinic acid</p>	<p>Clinicians will need to agree locally on how the offer of the treatment options is documented for audit purposes.</p> <p>Contraindications for capecitabine include severe leucopenia, neutropenia, thrombocytopenia, severe hepatic impairment or severe renal impairment.</p> <p>Contraindications for oxaliplatin include myelosuppression before the patient starts the first course of adjuvant treatment, as evidenced by a baseline neutrophil count of less than 2×10^9 per litre and/or a platelet count of less than 100×10^9 per litre, or peripheral neuropathy with functional impairment prior to the first course of adjuvant treatment.</p> <p>See the Summary of Product Characteristics for contraindications to 5-FU/FA.</p>
<p>2. The individual and the clinician(s) responsible for treatment decide jointly on the choice of adjuvant</p>	<p>100% of people who have stage III (Dukes' C) colon cancer and</p>	<p>None</p>	<p>Clinicians will need to agree locally on how the discussion and decision are documented for audit purposes. The</p>

treatment after an informed discussion	to whom adjuvant treatment is offered		discussion should take into account contraindications and the side-effect profile of the agent(s), the method of administration, and the clinical condition and preferences of the individual.
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Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the **criteria** **plus** number of patients who meet any **exception** listed}{\text{Number of patients to whom the **measure** applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.