NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

The use of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members prior to the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. In order to allow sufficient time for the overview to be circulated to Appraisal Committee members prior to the first Appraisal Committee meeting, it is prepared before the Institute receives Consultees' comments on the Assessment Report. These comments are therefore not addressed in the Overview.

A list of the sources of evidence used in the preparation of this document is given in Appendix A.

This overview contained academic in confidence information, which has been removed.

1 Background

1.1 The Appraisal

This overview relates to the appraisal of the clinical and cost effectiveness of the use of oxaliplatin in combination with 5-FU/FA (5-fluorouracil in combination with folinic acid [parenteral]), and to capecitabine monotherapy in the adjuvant treatment of stage III (Dukes' C) colon cancer after complete surgical resection of the primary tumour.[1]

1.2 The condition

Colorectal cancer is a malignant neoplasm arising from the lining (mucosa) of the large intestine (colon and rectum). Colorectal cancer is the third most common cancer in the UK, with almost 30,000 new cases registered in England and Wales in 2002, and represents 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

[1] Irinotecan for this indication will be appraised at a later date, because it has not received its marketing authorisation in time to be considered now.

incidence is about 20 per 100,000. Among those aged 75 and above, the rate is over 300 per 100,000 per year for males while for women it is over 200 per 100.000 per year.

In the UK, about 26% of patients diagnosed with colorectal cancer are classified as stage III (or as C1, C2 and C3 according to the modified Dukes' classification) at presentation (see Table 1 below). 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 resection (undertaken with curative intent), patients with stage III colon cancer have a 50–60% chance of developing recurrent disease. Adjuvant chemotherapy is given after surgery, usually to patients whose tumour has spread to lymph nodes (stage III colon cancer) and for whom the benefit of chemotherapy has been clearly demonstrated.

Table 1 Staging of colorectal cancer, with 5-year survival.

Tumour/node/metastasis (TNM) status	Stage	Extension to	Modified Dukes'	5-year overall survival
T[a] in situ N[b]0 M[c]0	0	Carcinoma in situ	–	Likely to be normal
T1 N0 M0	I	Mucosa or submucosa	A	> 90%
T2 N0 M0	I	Muscularis propria	B1	85%
T3 N0 M0	IIa	Subserosa/pericolic tissue	B2	70–80%
T4 N0 M0	IIb	Perforation into visceral peritoneum or invasion of other organs	B3	
T1–2 N1 M0/T2 N2 M0	III	T2, N1: 1–3/N2: ≥ 4 lymph nodes	C1	25–60%
T3 N1 M0/T3 N2 M0	III	T3, N1: 1–3/N2: ≥ 4 lymph nodes	C2	
T4 N1 M0	III	T4, N1: 1–3/N2: ≥ 4 lymph nodes	C3	
Any T any N M1	IV	Distant metastases	D	5–30%

[a] Tumour
[b] Number of affected lymph nodes
[c] Number of metastatic sites

1.3 Current management

The 2004 Guidance on Cancer Services[2] 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 the multidisciplinary team (MDT) should ensure that adjuvant chemotherapy is scheduled to begin within 6 weeks of surgery; and that standard treatment has been a course of 5-FU/FA, given intravenously over 6 months.

The place of adjuvant chemotherapy in stage II (Dukes' B) colon cancer is subject to ongoing scientific discussion, as is its use in (lower) rectal cancers. Most of the trials of chemotherapy for adjuvant colorectal cancer exclude patients who have recently

[2] National Institute for Clinical Excellence. Guidance on Cancer Services. Improving outcomes in colorectal cancer. Issued June 2004. www.nice.org.uk/page.aspx?o=204541

had radiotherapy and as a result most patients with upper rectal cancers are excluded.

In advanced disease (stage IV or Dukes' D), a small benefit in terms of toxicity is seen with the infusional regimens of 5-FU/FA (for example, modified de Gramont) compared with bolus administration, but with equivalent efficacy. However, concerns have been raised about catheter-associated complications, patient inconvenience and expense 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. Pooled data suggest that 5-FU/FA regimens will increase disease-free survival (see below for definition) at 5 years from 42% to 58%, and overall survival from 51% to 64%, when compared with surgery alone.

Despite the apparent attractiveness of overall survival as an indicator of effectiveness, it has the disadvantage that in recurrent or advanced disease the activity of the adjuvant therapy may be masked by differences in subsequent therapy. Disease-free survival has thus become the outcome of choice in establishing clinical effectiveness of chemotherapy in adjuvant colon cancer. Disease-free survival is usually defined in clinical trials as the time between randomisation and the first relapse, a second primary colon cancer, death from any cause when no evidence of relapse was recorded, or the last date at which the patient was known to be free of disease (censoring time). It is argued that disease-free survival rates after 3 years follow-up (it is reported that most relapses occur within the first 3 years after curative surgery) accurately predict overall survival rates after 5 years. In some trials relapse-free survival is used as a secondary outcome and defined in the same way as disease-free survival but excluding deaths unrelated to disease progression or treatment.

The total cost to the NHS for surgical, adjuvant and palliative treatment is estimated to be more than £300 million per year for all colorectal cancer. The specific cost to the NHS of chemotherapies for adjuvant treatment of colon cancer is unknown.

2 The technologies

2.1 Capecitabine

Capecitabine (Xeloda, Roche) is an orally administered precursor of cytotoxic moiety 5-fluorouracil (5-FU) (see Table 2). Capecitabine is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer, and for first-line monotherapy of metastatic colorectal cancer.

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. Most adverse events are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced. See the Summary of Product Characteristics (SPC) for full

details of contraindications and adverse effects.

2.2 Oxaliplatin

Oxaliplatin (Eloxatin, sanofi-aventis) is a water-soluble platinum-based cytotoxic compound that cross-links DNA, preventing replication and hence cell division (see Table 2).

Oxaliplatin is licensed in the UK in combination with 5-FU/FA and is indicated for:

- adjuvant treatment of stage III (Dukes' C) colon cancer after complete resection of primary tumour
- treatment of metastatic colorectal cancer.

The British National Formulary (*BNF)* warns that treatment with oxaliplatin can lead to renal failure. Oxaliplatin is contraindicated in people who have peripheral neuropathy with functional impairment prior to the first course. Symptoms of peripheral sensory neuropathy can be persistent after the end of treatment. Neurotoxic side-effects (paraesthesia, dysaesthesia) are dose limiting, as are some of the gastrointestinal and haematological toxicities (see SPC for full details of contraindications and adverse effects).

Table 2 Summary of drugs included in this appraisal.

Generic name	Proprietary name	Manufacturer (MA holder)	Dose	Acquisition cost excl. VAT (*BNF* edition 49)
Capecitabine	Xeloda	Roche	1250 mg/m^2 administered twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose)	£44.47 for 60 tablets of 150 mg and £295.06 for 120 tablets of 500 mg
Oxaliplatin	Eloxatin	sanofi-aventis	85 mg/m^2 administered intravenously over 2–6 hours, prior to the administration of 5-FU/FA, and repeated every 2 weeks for 12 cycles (6 months)	£165.00 per 50 mg vial

3 The evidence

3.1 Clinical effectiveness

The marketing authorisation of oxaliplatin does not allow for combination with capecitabine as a substitute for intravenous 5-FU/FA. Because oxaliplatin is used in addition to 5-FU/FA, comparisons of clinical effectiveness between oxaliplatin in combination with 5-FU/FA and capecitabine monotherapy have not been included in the Assessment Report.

Capecitabine

One randomised, open label, active-controlled trial was identified that investigated the efficacy and safety of treatment with capecitabine in the postoperative adjuvant

setting in patients with stage III (Dukes' C) colon cancer: Xeloda - Adjuvant Chemotherapy Trial (X-ACT) (Table 3). Apart from the protocol-specified analyses, ad hoc analyses were carried out on the request of the US Food and Drug Administration (FDA).

Table 3 Randomised trial for capecitabine.

Name of trial	Number of participants	Stage	Comparison	Duration	Primary endpoint	Secondary endpoints	Note
X-ACT[a]	1987	III (100%)	Capecitabine versus 5-FU/FA[b] monotherapy (bolus - Mayo Clinic regimen)	Capecitabine: every 21 days for 8 cycles (24 weeks) 5-FU/FA: every 28 days for 6 cycles (24 weeks)	Disease-free survival (after 632 events = median 3.8 years follow-up)	Relapse-free survival Overall survival Safety Pharmaco-economics Quality of life	Additional analyses after all minimum 3 years (ongoing to 5 years)

[a] Xeloda - Adjuvant Chemotherapy Trial
[b] 5-fluorouracil in combination with folinic acid (parenteral)

The X-ACT study was designed to show that capecitabine was at least as equivalent to 5-FU/FA (Mayo Clinic regimen) in achieving the primary efficacy endpoint of disease-free survival when administered as adjuvant treatment following surgery for Dukes' C colon cancer. For the primary endpoint, the study was powered to establish at least equivalence if the upper limit of the 95% confidence interval (CI) for the hazard ratio (HR) was below 1.20. The median age of participants was 62 years in the capecitabine and 63 years in the 5-FU/FA (Mayo Clinic regimen) arms.

After a median follow-up of 3.8 years, 35% of patients in the capecitabine group had experienced disease recurrence (relapse or new occurrence of colon cancer) or died, compared with 39% in the 5-FU/FA group (p = 0.0528 – for superiority). The hazard ratio for recurrence was 0.87 (95% CI, 0.75–1.00). Updated analyses, not specified in the protocol, showed that with longer follow-up (minimum of 3 years and median 4.4 years) capecitabine remained at least as effective as 5-FU/FA.

Capecitabine therapy significantly improved relapse-free survival[3] at 3 years compared with 5-FU/FA, with a hazard ratio of 0.86 (95% CI, 0.74–0.99). 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 groups respectively.

As a result of toxicity, dose modifications were commonly required in both groups (57% and 52% in capecitabine and 5-FU/FA arms respectively). The adverse events that most commonly led to dose modifications were hand–foot syndrome (31%) and diarrhoea (15%) in the capecitabine group, and stomatitis (23%) and diarrhoea

[3] Relapse-free survival is a similar endpoint to disease-free survival but excludes deaths unrelated to disease progression or treatment.

(19%) in the 5-FU/FA group. Gastrointestinal toxicities and hair loss were significantly more common in the 5-FU/FA-treated participants. 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 event occurring more frequently with capecitabine than with 5-FU/FA was hand–foot syndrome ($p < 0.001$).

Quality of life (QoL) was assessed using the European Organisation 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. Although studies have clearly shown that patients prefer oral chemotherapy over intravenous treatment, this was not reflected in QoL outcomes. The Assessment Group (AG) reports the suggestion by some authors that the lack of improvement in QoL when giving capecitabine could be because patients who received the bolus Mayo Clinic regimen experienced adverse events during the middle of their cycle. However, they mostly recovered by the time they received their next course, and if the QoL questionnaire was administered at the beginning of each cycle and it referred only to the preceding week then it would be less likely to capture the effect of adverse events on QoL.

Oxaliplatin in combination with 5-FU/FA

Two phase III, randomised, active-controlled trials were identified by the AG: the Multicenter International Study of Oxaliplatin/5-Fluorouracil and Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial and the National Surgical Adjuvant Breast and Bowel Project (NSABP C-07) trial (Table 4). The MOSAIC trial was open label. The NSABP C-07 did not report whether the patients and investigators were blinded or not. Participants in both studies were chemotherapy-naïve and had undergone complete surgical resection of the primary tumour. The treatment was given within 7 weeks (MOSIAC) or 6 weeks (NSABP C-07) following surgery. In addition to the protocol-specified analyses, ad hoc analyses were carried out at the request of the FDA in the MOSAIC trial. In the MOSAIC trial median age 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.

Table 4 Randomised controlled trials for oxaliplatin.

	Number of participants	Stage	Comparison	Regimen (duration)	Primary efficacy	Secondary efficacy	Note
MOSAIC	2246	II/III (60% with stage III)	Oxaliplatin plus 5-FU/FA[a] (FOLFOX4)[b] versus 5-FU/FA monotherapy (de Gramont regimen)	Every 14 days for 12 cycles (6 months)	Disease-free survival (after 3 years follow-up)	Safety Overall survival	Additional analyses after all minimum 3 years (ongoing to 5 years)
NSABP C-07	2492	II/III (71% with stage III)	Oxaliplatin plus 5-FU/FA (FLOX) versus 5-FU/FA monotherapy (Roswell Park bolus regimen)	6 weekly treatments, followed by 2 weeks of rest, repeated for three cycles (24 weeks)	Disease-free survival (after 3 years follow-up)	Safety Overall survival	Not powered to detect differences in subgroups

[a] 5-Fluorouracil in combination with folinic acid (parenteral)
[b] 5-FU/FA (modified de Gramont regimen) in combination with oxaliplatin

In both trials the addition of oxaliplatin to 5-FU/FA, albeit administered in different regimens, led to a statistically significant reduction in risk of relapse when compared with 5-FU/FA monotherapy. Analysis of median disease-free survival at 3 years resulted in a hazard ratio for recurrence of 0.77 (95% CI, 0.65–0.91) in the MOSAIC trial (median follow-up 37.9 months, intention to treat analysis) and 0.79 (95% CI, 0.67–0.93) in the NSABP C-07 trial (median follow-up 34 months, according to protocol analysis). In the MOSAIC trial this hazard ratio represents an absolute risk reduction of 5% (26.1% and 21.1% relapsed or died in the 5-FU/FA and oxaliplatin plus 5-FU/FA groups respectively) or a number needed to treat of 18.2 (95% CI, 11.7–47.5) to produce one additional patient that remains alive and disease free at 3 years. Additional analyses on MOSAIC – requested by regulatory authorities – showed a 24% reduction in the risk of relapse at a median follow-up of 4 years (hazard for recurrence 0.76, 95% CI, 0.65–0.90).

Overall survival results for MOSAIC and NSABP C-07 are calculated at 6 and 5 years follow-up respectively. No mature data are available for MOSAIC at present but the 3- 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). However, the hazard ratio for death in the 4-year analysis favours the addition of oxaliplatin, although this was not statistically significant (HR 0.89, 95% CI, 0.72–1.09). The abstract of the NSABP C-07 trial did not report overall survival.

All these results relate to summary results of the whole study population (stage II and stage III). Only in the MOSAIC study were subgroups pre-specified according to stage of the disease and were results reported separately. For participants with stage III colon cancer the hazard ratio for recurrence was found to be 0.76 (95% CI, 0.62–0.92) at 3 years, and 0.75 (95% CI, 0.62–0.90) at 4 years (26.9% and 33.5% experiencing relapse or death in the oxaliplatin plus 5-FU/FA and the 5-FU/FA arms respectively). The hazard ratio for death for stage III patients in MOSAIC was 0.86 (95% CI, 0.66–1.11) at 3 years. It should be noted that 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. Furthermore, statistical tests for interaction indicated in both the MOSAIC and NSABP C-07 trials that oxaliplatin plus 5-FU/FA was of benefit for both stage II and stage III colorectal cancer..

In the MOSAIC study 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. Other more frequent grade 3 and 4 adverse events in the oxaliplatin plus infusional 5-FU/FA group were diarrhoea and vomiting. Participants in the NSABP C-07 trial showed a similar pattern of adverse events for oxaliplatin plus bolus 5-FU/FA, but the AG noted that the incidence of grade 3/4 diarrhoea in the combination arm was approximately 40%, which is much higher than the 11% rate observed in MOSAIC.

Infusional versus bolus regimens for 5-FU/FA

Evidence emerging from adjuvant studies conducted in the 1990s showed that 5-FU and low dose FA (20 mg/m^2) is equivalent to 5-FU and high-dose FA (200–500 mg/m^2); 5-FU given for 6 months is as effective as when given for 12 months and there is no significant difference between the two most commonly used bolus 5-FU/FA regimens (Mayo Clinic and Roswell Park). It also showed that levamisole as a modulating agent makes no difference in overall survival.

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 expense of infusional treatment. Although local variations on the original Mayo Clinic 5-FU/FA regimen have emerged, one of the most important deviations from the original Mayo Clinic regimen is that the 30 chemotherapy doses were delivered over 30 weeks, on one day each week, instead of 24 weeks. This amended regimen has never been compared with the original schedule in a randomised trial.

Other evidence from consultee submissions

‘When given a choice, most cancer patients prefer oral instead of intravenous therapy but only if treatment is equally effective. Patients cite increased convenience, less distress over repeated intravenous access and more control over their own treatment as major factors.’ [Royal College of Nursing]

‘Oxaliplatin causes a unique cold related peripheral neuropathy affecting over 90% of patients during treatment with symptoms still present to a greater or lesser degree 18 months after completing treatment in 24% of patients. Given the preliminary nature of the MOSAIC trial results and the concern surrounding neurotoxicity we

would not recommend oxaliplatin based chemotherapy as adjuvant treatment for all Dukes' C colorectal cancer however it should be an option for high risk patients e.g. more than 3 positive nodes, or T4 lesions.' [Royal College of Physicians/Royal College of Radiologists/Association of Cancer Physicians/Joint Collegiate Council for Oncology]

'Eighteen months following completion of treatment 3.9% of patients had persistent debilitating Grade 2/3 symptoms. While **routine** use of combination oxaliplatin/5-FU/FA in the adjuvant setting might not be safe or practical, there is nonetheless a subgroup of high-risk Dukes' C patients who would probably benefit from having more aggressive combination treatment as opposed to the current standard. Clearly the risks and benefits of a more toxic regimen and the requirement to place a central venous catheter would have to be assessed in each individual patient.' [Royal College of Nursing]

'However, although 92.1% of patients with oxaliplatin experienced peripheral neuropathy during their treatment, half of these episodes were of grade 1. Of the 137 patients (12.4%) who experienced grade 3 peripheral neuropathy, 8 patients still had symptoms at the 6-month follow up and in 5 patients at the 1-year follow-up visit. Overall, 11 out of 1018 patients (1.1%) who were assessed one year after end of treatment continued to have grade 3 peripheral neurosensory symptoms. This number dropped to 5 patients (0.5%) at 18 and 24 months.' [sanofi-aventis]

Summary of clinical effectiveness evidence

Capecitabine is shown in the one study performed to date to be of at least equivalent efficacy compared with bolus 5-FU/FA in the adjuvant treatment of patients with stage III (Dukes' C) colon cancer. The only treatment-related adverse event occurring more frequently with capecitabine was hand–foot syndrome. No statistical significant differences in quality of life were found. Although there is evidence to suggest that patients have a preference for oral rather than intravenous chemotherapy the potential for poor patient concordance, and subsequent treatment failure, needs to be considered with oral therapy.

Evidence for the clinical efficacy of oxaliplatin plus 5-FU/FA is restricted to the outcomes of two randomised clinical trials and to the intermediate endpoint of disease-free survival. Mature data for overall survival data were not available and the 3- and 4-year analyses reported no statistically significant differences. The adverse event data for oxaliplatin in the adjuvant setting are broadly in line with those reported earlier; neurotoxicity consists of a rapid-onset acute sensory neuropathy and a late-onset cumulative sensory neuropathy that occurs after several cycles of therapy, and is reported to be reversible in about three quarters of patients affected, with a median time to recovery of 13 weeks after treatment discontinuation. The effect of oxaliplatin plus 5-FU/FA was shown to be statistically significantly different from 5-FU/FA in the subgroup of patients with stage III (Dukes' C) but not in those with stage II colon cancer, and no statistical tests for interaction were reported.

Concerns about catheter-associated complications and patients' inconvenience should be taken into account when considering the equivalent efficacy but less

toxicity of infusional 5-FU based chemotherapy when compared with bolus regimens of 5-FU/FA in the adjuvant treatment of colorectal cancer.

3.2 Cost effectiveness

Introduction

The AG reviewed three published economic evaluations, two of which were submitted by manufacturers, and also presented its own 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.

Capecitabine

The manufacturer's submission was an updated version of an economic analysis that had been presented at a conference in 2004. There were no other published economic analyses involving capecitabine. The AG developed an independent economic assessment. See Table 6 in Appendix B for a detailed comparison of the economic analyses for capecitabine included in the Assessment Report.

Manufacturer's submission

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 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 respectively.

Primarily as a result of reduced drug administration costs associated with capecitabine (long-term costs assumed to be approximately equal), the manufacturer's submission concluded that capecitabine dominates 5-FU/FA (Mayo Clinic regimen), costing on average £3653 less per patient than the 5-FU/FA arm, with a gain of 0.749 quality adjusted life years (QALYs).

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. Probabilistic sensitivity analysis was not performed. A threshold analysis revealed that the single most important uncertain parameter is the cost per intravenous drug administration visit; that would have to fall below £40 (from £169) for capecitabine to not be cost saving anymore. Scenario analyses on the regimen used for 5-FU/FA indicate that capecitabine remains cost saving whichever regimen is used.

Assessment Group's model

Total cost savings from the use of capecitabine compared with the Mayo Clinic 5-FU/FA regimen resulting from the AG model (£3320) are slightly less than those reported in the manufacturer's submission. This is primarily due to the differences

between the two models in the costs associated with relapse. The higher QALY gain of capecitabine in the AG model (0.98 QALYs) is suggested to be attributable to the different methods used to estimate survival. In all the one-way sensitivity analyses capecitabine remains cost saving when compared with 5-FU/FA in the Mayo Clinic regimen. At a threshold of £30,000, the probability of capecitabine being cost effective is 99.78%, compared with 99.86% at a threshold of £20,000.

Oxaliplatin in combination with 5-FU/FA

Two published economic analyses were included in the Assessment Report for oxaliplatin plus 5-FU/FA in the adjuvant setting. One of these analyses was conducted from the perspective of an Austrian provider institution. It used survival estimates from trials of oxaliplatin plus 5-FU/FA in advanced cancer that are unlikely to be representative of survival outcomes for patients receiving adjuvant chemotherapy. Further analysis by the AG 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 an economic analysis was presented at ASCO 2005 and updated to form the basis of the manufacturer's submission to the appraisal. The cost per life year gained associated with FOLFOX4 (5-FU/FA (modified de Gramont [regimen] in combination with oxaliplatin)[4] in this study was estimated to be US$27,300.

The AG developed an independent economic assessment because of the flaws in the method in the published evidence. See Table 7 in Appendix B for a detailed comparison of the economic analyses for oxaliplatin included in the Assessment Report.

Manufacturer's submission and addendum

The submission reports a base-case cost per QALY gained (CQG) of £4805 for FOLFOX4 versus 5-FU/FA (de Gramont), calculated over a 50-year time horizon. This CQG estimate consists of a discounted difference in costs of £3267 and in benefits of 0.680 QALYs. When in a one-way sensitivity analysis benefits and costs were limited to those within trial data the CQG increased to £56,780. No other one-way sensitivity analysis resulted in a very different estimate from that of the base case – not even a doubling of the disutility for relapse (from 0.2 to 0.4). The probabilistic sensitivity analysis resulted in a 96.7% probability of FOLFOX4 having a cost effectiveness that is better than 5-FU/FA at a threshold of £30,000 per QALY and 94.7% at £20,000. 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 (see above) is probably due to the lower drug acquisition costs of oxaliplatin in the UK compared with the US.

[4] Several versions of FOLFOX, containing varying doses and schedules of leucovorin, fluorouracil and oxaliplatin, have been studied. FOLFOX 1, 2, 3, 4, 6 and 7 have all been used in the treatment of colorectal cancer. FOLFOX4 has been the most widely studied, and is the most commonly used FOLFOX regimen.

In an addendum to its submission the manufacturer presented a cost-effectiveness analysis based on the NSABP C-07 trial. Equivalent efficacy (0.680 QALYs gained) was assumed for oxaliplatin plus bolus 5-FU/FA (Mayo Clinic regimen) when compared with oxaliplatin plus 5-FU/FA (de Gramont), and data from X-ACT and MOSAIC were used to estimate probabilities of starting on the 5-FU/FA alone or on oxaliplatin plus 5-FU/FA respectively. When combined with a cost difference of £4246 between oxaliplatin plus bolus 5-FU/FA (Mayo) and 5-FU/FA alone (Mayo), the economic analysis resulted in a CQG estimate of £6244. No probabilistic sensitivity analyses were reported.

Assessment Group's model

Incremental benefits in the AG model were significantly larger than those of the manufacturer's submission (1.33 QALYs) when oxaliplatin plus 5-FU/FA (de Gramont) was compared with 5-FU/FA alone (de Gramont). Combined with a cost difference that was also greater than that in the manufacturer's submission (£3941) the AG model resulted in an estimated CQG of £2970. This cost difference between the models is explained by the AG to result from the use of differential costs of relapse for the 5-FU/FA and combination arm in the manufacturer's model, whereas the AG model uses costs of relapse unrelated to the intervention received in the adjuvant setting. No specific explanation is given for the QALY difference in the AG report, but differences in the method of fitting survival functions, the use of discounts for benefits, and utilities after relapse result in significant differences in QALYs gained.

By setting the model parameters to the 'worst-case' scenario the estimated CQG was increased to £7587. Probabilistic sensitivity analysis suggests a probability of 99.6% of oxaliplatin plus 5-FU/FA (de Gramont) being cost effective when compared with 5-FU/FA, rising to 99.9% at a threshold of £20,000 and £30,000 per QALY, respectively.

Indirect comparisons as modelled by the Assessment Group

Despite the absence of data from direct comparisons the AG found it worthwhile to include indirect comparisons of oxaliplatin plus 5-FU/FA (de Gramont) versus capecitabine and versus bolus 5-FU/FA in the adjuvant treatment of stage III colon cancer. For the first analysis two approaches were taken – using the absolute predicted long-term survival and cost data of the AG model and using 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 CQG for oxaliplatin plus 5-FU/FA (de Gramont) compared with capecitabine was £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 analysis, 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.

See Table 5 for a summary of the cost-effectiveness evidence.

Summary of cost effectiveness evidence

Table 5 Point estimates of cost effectiveness for capecitabine and oxaliplatin (cost per quality adjusted life year gained).

	Bolus 5-FU/FA[a]			**Infusional 5-FU/FA**				**Capecitabine**
	Roche	Assessment Group	sanofi-aventis	Paper 1	Paper 2	sanofi-aventis	Assessment Group	Assessment Group
Capecitabine	**Cost saving**	**Cost saving**						
Oxaliplatin + infusional 5-FU/FA		**£5777**		**£24,953**[b]	**$27,300**[b]	**£4805**	**£2970**	**£12,874** **£46,814**
Oxaliplatin + bolus 5-FU/FA			**£6244**					

[a] 5-fluorouracil in combination with folinic acid (parenteral)
[b] Per life-year gained

4 Issues for consideration

Clinical effectiveness

- Overall survival data for X-ACT and MOSAIC were not yet mature at the time of the primary (specified) and secondary (ad hoc) analysis. Does disease-free survival at 3 years in these trials accurately predict overall survival after 5 years? Are the survival benefits observed in the X-ACT and MOSAIC trials generalisable to patients with stage III (Dukes' C) colon cancer in England and Wales?

- The NSABP C-07 study that compared oxaliplatin plus bolus 5-FU/FA with bolus 5-FU/FA was only reported in abstract form.

- Are the infusional (de Gramont) and bolus (Mayo Clinic regimen) routes of administrating 5-FU/FA interchangeable in the treatment of adjuvant colon cancer?

Cost effectiveness

- Most published economic analyses used estimates of median (disease-free or overall) survival, whereas mean estimates are more suitable because they take into account the shape of the survival curve. Curve fitting was used to estimate the mean in most economic analyses but differences in the methods used led to inconsistent (capecitabine – crossing relapse-free survival and overall survival curves) or very different (oxaliplatin – AG model double the QALY benefit compared with manufacturer submission) results. The long-term survival of people without a relapse may have been overestimated in assumptions used for economic analyses.

- 'The Kaplan Meier estimate of overall survival conditional on relapse (i.e. survival from time of relapse to death) is likely to provide a biased estimate of the life expectancy after relapse. And, the absence of statistically significant difference in overall survival between the two treatment groups at 48 months raises the question whether that absence of difference is consistent with a difference in overall survival on a longer time-horizon. The trial [MOSAIC] shows that there is a significantly greater probability of death without antecedent relapse in the FOLFOX arm, which could offset to some extent the benefit stemming from greater disease-free survival. Although we acknowledge that this offset might be non-negligible, the hypothesis proposed here is that due to the delay between relapse and death, the difference in mortality between treatments becomes more evident on a longer time-horizon.' [sanofi-aventis]

- The median age in clinical trials is 10–15 years younger than that of newly diagnosed people in clinical practice. This could have an impact in two ways: the clinical effectiveness of chemotherapy in the adjuvant treatment of older people might be very different from that in younger people, and utility values used for the long-term section of the model for people in remission are different for the general public at a median age of 60 (0.80 for men and 0.76 for women) when compared with an median age of 75+ (0.76 for men and 0.71 for women). The latter consideration is important for the economic analysis submitted by the oxaliplatin manufacturer. Note that the AG uses an estimate of utility for people in remission that is unrelated to age – namely, 0.92.

- A potential weakness in the AG analysis and that of sanofi-aventis is the extent to which the adverse effects (experience) of infusional administration of oxaliplatin plus 5-FU/FA have been adequately included in the economic analyses. Furthermore, the AG attempted no economic analysis of the use of oxaliplatin plus bolus 5-FU/FA versus bolus 5-FU/FA alone.

- 'Patients receiving oral chemotherapy such as capecitabine will need access to nursing support and care to ensure concordance and safety.' [CancerBACUP.] The AG analysis and Roche model appear not to have accounted for these extra costs.

- The costs of relapse used in the AG model are probably an underestimate of the true costs of chemotherapy for advanced colorectal cancer because little was known about the costs of salvage therapy used in the trials for advanced colorectal cancer. However, if the true costs of relapse are higher this would lead to more favourable cost effectiveness of chemotherapy for adjuvant treatment, other things being equal.

- The validity of the indirect comparisons between oxaliplatin plus 5-FU/FA (de Gramont) and capecitabine, and bolus 5-FU/FA (Mayo Clinic regimen), as reported by the AG.

- The patent for oxaliplatin is due to expire in 2006/7.

5 Current research

- COLON-OXALAD – does the addition of oxaliplatin to 5-FU/FA prolong disease-free and overall survival in very-high-risk patients with stage III colon cancer?

6 Authors

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September 2005

Appendix A. Sources of evidence considered in the preparation of the overview

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

- Pandor et al. The use of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer. September 2005

B Submissions from the following organisations:

I Manufacturer/sponsors:

sanofi-aventis
Roche

II Professional/specialist and patient/carer groups:

- British Oncology Pharmacy Association
- CancerBACUP
- Colon Cancer Concern
- Royal College of Nursing
- Royal College of Physicians }
- Royal College of Radiologists } These groups submitted
- Association of Cancer Physicians } their responses jointly
- Joint Collegiate Council for Oncology }

III Commentator organisations (without the right of appeal):

None received

Appendix B. Detailed comparisons of economic analyses

Table 6 Economic analyses for capecitabine in the adjuvant setting for colon cancer.

	Published abstract and submission	Assessment Group (AG)	AG notes on manufacturer's submission
Population	Stage III (Dukes' C) colon cancer	Stage III (Dukes' C) colon cancer	
Comparators	5-FU/FA[a] (Mayo Clinic) Other regimens in sensitivity analyses	5-FU/FA (Mayo Clinic) Indirect comparison with FOLFOX4[b]	
Perspective	NHS (separate analysis with societal costs included)	NHS/PSS	
Effectiveness – extrapolation	Relapse-free survival and overall survival: life-time period – 'best fit' (least squares regression) X-ACT[c] data (3 years) = log-normal and extrapolation (40 years)	Disease-free survival: 5-year post randomisation – fitted Weibull survival functions to the empirical X-ACT data (hazard ratios from the clinical effectiveness review) Overall survival-relapse: fitted Weibull functions to the FOCUS/GERCOR data and extrapolated Overall survival-non-relapse: age-matched without previous colon cancer * Survival after relapse independent of time of relapse and equivalent people with advanced CRC that had not received adjuvant chemotherapy * All relapses occur within 5 years following resection of the primary tumour	• Incidence relapse > 5 years unlikely • Illogical relapse-free survival > overall survival after 18 years • Overestimates relapse-free survival and overall survival – considering 60.4 years old population • Objective X-ACT was to prove equivalence
Model	State-transition: health states (utility) - during chemotherapy (0.80) - stable-remission	Markov: health states (utility) - alive without relapse o on chemotherapy without adverse events (0.70) o on chemotherapy with adverse events (0.63)	• Unclear from submission how the 0.80 was derived • Assumption that utilities are the same for both groups and include

	(0.86) - the relapse period (0.59) - post-relapse (0.59) - 12 months before death (0.59) - death (0)	o remission (0.92) - alive post relapse (0.24) - dead (0)	adverse events is favourable to the 5-FU/FA arm
Costs	Resource use from X-ACT Acquisition and administration - 7.35 visits for both Relapse = £25,000 (Alballea 2005 – abstract) Death = £10,000 No pharmacy costs included Adverse events costs included	Acquisition, administration and consultation/monitoring - 8 visits for capecitabine and 6 for 5-FU/FA Relapse = **academic in confidence information removed** Pharmacy costs included Adverse events costs included * Patients receiving 5-FU/FA via the de Gramont regimen are assumed to receive their treatment on an outpatient basis	• 7.35 visits for administration of 5-FU/FA slightly overestimates real costs • Unclear where the costs for relapse are sourced from and no breakdown is given • Not including pharmacy costs does not favour capecitabine
Sensitivity analyses	One way: - Cost estimates: mean chemotherapy cost per patient/cost per drug administration visit/total costs of adverse events - Proportion of patients requiring hospital transport - Survival increment of capecitabine over 5-FU/FA + alternative projection - Utilities +/- 20% - Discount rates both	One way: - Alternative treatment options in case of relapse – FOCUS/GERCOR - Assumptions of no relapse relaxed to after 7.5 and after 10 years - Discount rates both costs and benefits at 3.5% Probabilistic: (survival estimates, number of cycles, proportion receiving inpatient chemotherapy, utilities, cost parameters)	

	costs and benefits at 3.5% Extreme: all to worst-case		
Scenario analyses	5-FU/FA regimens: QUASAR, (modified) de Gramont (survival estimates assumed equal to X-ACT) Societal costs included – patient time and travel costs	Indirect comparison with FOLFOX4	
[a] 5-Fluorouracil in combination with folinic acid (parenteral) [b] 5-FU/FA (modified de Gramont regimen) in combination with oxaliplatin [c] Xeloda - Adjuvant Chemotherapy Trial			

Table 7 Economic analyses for oxaliplatin in the adjuvant setting for colon cancer.

	Published abstract and submission	**Assessment Group (AG)**	**AG notes on manufacturer's submission**
Population	Stage III (Dukes' C) colon cancer	Stage III (Dukes' C) colon cancer	• MOSAIC included both stage II and III
Comparators	5-FU/FA[a] (de Gramont) Other regimens in sensitivity analyses – including oral	5-FU/FA (de Gramont) Indirect comparison with capecitabine	
Perspective	NHS	NHS/PSS[b]	
Effectiveness – extrapolation	DFS[c]: 4-year data – Kaplan Meier of MOSAIC[d] data DFS: extrapolation 5 years Weibull survival function fitted to tail of DFS curve (year 3–4) DFS: 5 years to life (50 years) – UK life table OS: resection to 4 years – Kaplan Meier OS: 4 years to life – extrapolated DFS and	DFS: 5-year post randomisation – fitted Weibull survival functions to the empirical MOSAIC data (hazard ratios from the clinical effectiveness review) OS[e]-relapse: fitted Weibull functions to the FOCUS/GERCOR[f] data and extrapolated OS-non relapse: age-matched without previous colon cancer * Survival after relapse independent of time of relapse and equivalent people with advanced colorectal cancer that had not received	• Potential flaw is the extrapolation of the DFS curve between 48 and 60 months, which does not use all of the previous DFS data • Manufacturer notes 'simple' method for estimating overall survival impact, considering the absence of statistically

	Weibull model fitted to survival after relapse	adjuvant chemotherapy * All relapses occur within 5 years following resection of the primary tumour	significant differences between the two groups at 48 months in the MOSAIC trial
Model	Clinical trial: 'health states' (utility) - disease-free (0.85 – first 5 years of model; afterwards as per general population) - relapse (disutility 0.2 = 0.65) - toxicities (proportional utility decrements - e.g. neutropenia grade 3 and 4 = -45% with, and -23% without hospitalisation) Benefits discounted at 3.5%	Markov: health states (utility) - alive without relapse o on chemotherapy without adverse events (0.70) o on chemotherapy with adverse events (0.63) o remission (0.92) - alive post relapse (0.24) - dead (0)	
Costs	Resource use from MOSAIC Acquisition, administration, pharmacy and monitoring Cost of 'replacement' chemotherapy (not for relapse but in case of toxicity) Costs associated with non-serious toxicities Costs for serious adverse events Costs of disease monitoring during chemotherapy and afterwards Costs of relapses	Acquisition, administration, pharmacy and consultation/monitoring - 8 visits for capecitabine and 6 for 5-FU/FA Relapse = **academic in confidence information removed** Adverse events costs included * Patients receiving 5-FU/FA via the de Gramont regimen are assumed to receive their treatment on an outpatient basis	• Irinotecan in second-line combination is not a licensed indication

	(local-, liver-, lung metastasis, or other type: average weighted by occurrence = £10,725) • all receive first-line chemotherapy, most in line with NICE / 55% receive second-line, all of these receive irinotecan plus 5-FU/FA (MdG)[g] • costs of surgical interventions after relapse Costs discounted at 3.5%		
Sensitivity analyses	One way: - Benefits and costs limited to short term 'within trial' and 5 year - Cost of 5-FU/FA replaced by bolus regimen used in X-ACT, and by capecitabine - Alter utility values associated with SAE[h] by +20% and -20%, disutility with relapse and disutility with hospitalisation - Higher cost of relapse ('Post NICE guidance') - Include people with stage II from MOSAIC - Discount rates 0% for benefits and 6% for costs Probabilistic sensitivity	One way: - Alternative treatment options in case of relapse – FOCUS/GERCOR - Assumptions of no relapse relaxed to after 7.5 and after 10 years - Discount rates at 3.5% Probabilistic: (survival estimates, number of cycles, proportion receiving inpatient chemotherapy, utilities, cost parameters)	

	analysis		
Scenario analyses		Indirect comparison with FOLFOX4[i]	

[a] 5-Fluorouracil in combination with folinic acid (parenteral)
[b] Personal Social Services
[c] Disease-free survival
[d] Multicenter International Study of Oxaliplatin/5-Fluorouracil and Leucovorin in the Adjuvant Treatment of Colon Cancer
[e] Overall survival
[f] Modified de Gramont
[g] Xeloda - Adjuvant Chemotherapy Trial
[h] Severe adverse events
[i] 5-FU/FA (modified de Gramont regimen) in combination with oxaliplatin