

# NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

## Overview

### The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer (review of Technology Appraisal Guidance No. 33)

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.

#### Abbreviations used

ACRC	Advanced colorectal cancer	5-FU/FA	5-Fluorouracil in combination with folinic acid (parenteral)
AIC	Academic in confidence	HR	Hazard ratio
AG	Assessment Group	LY	Life year
AIO	Arbeitsgemeinschaft Internische Onkologie	PFLY	Progression-free life year
AR	Assessment Report	QoL	Quality of life
FOLFIRI	5-FU/FA (modified de Gramont regimen) in combination with irinotecan	QALY	Quality adjusted life year
FOLFOX	5-FU/FA (modified de Gramont regimen) in combination with oxaliplatin	RCT	Randomised controlled trial

**Academic in confidence information was removed from the text and tables.**

## **1 Background**

### **1.1 *The Appraisal***

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This overview relates to a review of the original guidance on irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.

### **1.2 *The condition***

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Colorectal cancer is a malignant neoplasm arising from the lining (mucosa) of the large intestine (colon and rectum). Colorectal cancer is defined as advanced if, at presentation or recurrence, it is either metastatic or so locally invasive that surgical resection is unlikely to be carried out with curative intent.

Colorectal cancer is the third most common cancer in the UK, with almost 30,000 new cases registered in England and Wales in 2001, representing over 12% of all new cancer cases. The incidence of colorectal cancer increases with age. In people between the ages of 45 and 55, the incidence is about 25 per 100,000. Among those aged over 75 the rate is over 300 per 100,000 per year.

The overall 5-year survival rate in England is 35%; however, large differences in survival exist according to the stage of disease. On average, patients survive for 3 years after diagnosis. About 20% of patients with colorectal cancer present with advanced disease, of which around 50% have liver metastases. The 5-year survival rate for advanced colorectal cancer is less than 5%. Median survival after diagnosis of metastatic disease is approximately 6–9 months (see Assessment Report [AR], page 17).

About 70% of patients diagnosed with colorectal cancer undergo surgery. Many have good outcomes following surgery (with adjuvant chemotherapy in some cases), but approximately 30% of those who have undergone surgery with apparently complete excision will eventually develop advanced disease and distant metastases (typically presenting within two years of initial diagnosis).

The most frequent site of metastatic disease is the liver, and for these patients surgery provides the only chance of a cure. Reported 5-year survival rates for resection of liver metastases range from 16 to 48%, considerably better than those for systemic chemotherapy; however, reported operative mortality rates range from 0 to 14%, and postoperative complications are common and often serious.

### **1.3 *Current management***

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Treatments following a diagnosis of advanced colorectal cancer are mainly palliative and aim to improve both the duration and quality of the patient's remaining life while controlling symptoms. Clinical outcomes such as overall survival, response and toxicity are important, but alternatives such as progression-free survival, quality of life (QoL), convenience, acceptability to patients and patient preferences have also gained importance.

Progression-free survival is considered a particularly important outcome measure in the treatment of advanced colorectal cancer because disease progression impairs both physical and emotional health. However, the relationship between progression-free survival obtained after drug treatment in clinical trials and overall survival is unclear, because differences in second-line or salvage therapies after failure may also have an influence. Tumour response does not necessarily correspond to subjective benefit in terms of quality of life. Also, there is some evidence that extended survival is not always associated with an overall improvement in QoL. Chemotherapy in advanced disease is palliative, and offers no possibility of cure. For this reason, information about health-related QoL particularly that associated with treatment-related toxicity has been given careful consideration.

The management of patients with advanced colorectal cancer involves a combination of specialist active treatment (palliative surgery, cytotoxic chemotherapy and radiation), symptom control and psychosocial support. Patients with advanced disease who are sufficiently fit can be treated with systemic chemotherapy as first- or second-line therapy, typically with an established 5-fluorouracil (5FU)-containing regimen. 5-FU inhibits thymidylate synthase, a key enzyme involved in pyrimidine biosynthesis, and folinic acid (FA) enhances thymidylate synthase inhibition by increasing the intracellular folate pool. 5-FU is usually administered intravenously. Oral analogues of 5-FU, capecitabine and tegafur with uracil, are also used in the treatment of colorectal cancer. Capecitabine and tegafur are prodrugs, that is, they are metabolised to the active drug (5-FU) in the body. Tegafur is given with uracil to increase 5-FU concentrations by inhibiting the enzyme responsible for its breakdown.

There is no universally accepted 5-FU/FA regimen. The different regimens are described in Table 4 of the AR (page 19). Infusional regimens are more complex to administer, requiring permanent vascular access technology or admission to hospital, and are more costly. However, they have been reported to be more effective in terms of progression-free survival, safety, toxicity and QoL compared to bolus regimens, although equivalent in terms of overall survival.

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

## **1.4 Current NICE guidance (2002)**

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### **Guidance**

- 1.1 On the balance of clinical and cost-effectiveness, neither irinotecan nor oxaliplatin in combination with 5-fluorouracil and folinic acid (5-FU/FA) are recommended for routine first-line therapy for advanced colorectal cancer.
- 1.2 Oxaliplatin should be considered for use as first-line therapy, in combination with 5-FU/FA, in advanced colorectal cancer in patients with

metastases that are confined solely to the liver and may become resectable ('downstaged') following treatment.

- 1.3 Irinotecan monotherapy is recommended in patients who have failed an established 5-fluorouracil containing treatment regimen.
- 1.4 On the balance of evidence relating to its clinical and cost effectiveness, raltitrexed is not recommended for the treatment of advanced colorectal cancer. Its use for this patient group should be confined to appropriately designed clinical studies.
- 1.5 It is likely that patients currently receiving irinotecan or oxaliplatin in combination with 5-FU/FA or raltitrexed could suffer loss of well being if their treatment is discontinued at a time they did not anticipate. Because of this, patients and their consultants may wish to continue therapy until they consider it is appropriate to stop.

### **Further research**

- 6.1 It is anticipated that the MRC CR08 (FOCUS) trial, due to report in 2004, will provide further clinical evidence on the clinical and cost effectiveness of first-line irinotecan and oxaliplatin combination therapies. Clinicians are encouraged to discuss enrolment in this study with their patients.
- 6.2 The collection and analysis of clinical and economic data for patients receiving oxaliplatin for the purposes of 'downstaging' will help to clarify the cost effectiveness of this approach for future appraisals, and it is strongly urged that these data are collected.
- 6.3 Further prospective or retrospective clinical studies are needed that compare raltitrexed with best supportive care or other treatments that do not contain 5-FU/FA.
- 6.4 Older patients, who represent the majority of individuals with advanced colorectal cancer, are consistently under-represented in clinical trials, which affects the generalisability of the results. Organisers of these trials are particularly encouraged, therefore, not to exclude these patients from studies on the basis of age alone.

### **Other relevant guidance**

Oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) has also been recommended by NICE (Technology Appraisal Guidance No. 61, May 2003) as an option for the first-line treatment of metastatic colorectal cancer.

## 2 The technologies

### 2.1 Irinotecan

Irinotecan hydrochloride (Campto, Aventis Pharma Ltd) inhibits topoisomerase I. This enzyme catalyses the unwinding of DNA and is essential for cell division.

In the UK, irinotecan is licensed for use in adults with advanced colorectal cancer:

- in combination with 5-FU/FA in patients with advanced disease without prior history of chemotherapy
- as a single agent in patients who have failed an established 5-FU based regimen.

Contraindications for irinotecan include chronic inflammatory bowel disease and bowel obstruction. In addition to dose-limiting myelosuppression, side-effects of irinotecan include acute cholinergic syndrome (with early diarrhoea), gastrointestinal effects (delayed diarrhoea requiring prompt treatment may follow irinotecan treatment), asthenia, alopecia and anorexia.

### 2.2 Oxaliplatin

Oxaliplatin (Eloxatin, Sanofi Synthelabo) is a water-soluble platinum-based cytotoxic compound that cross-links DNA, preventing replication and hence cell division.

At the time of the 2002 appraisal, oxaliplatin was licensed only for the first-line treatment of adults with advanced colorectal cancer in combination with 5-fluorouracil. In December 2003, the marketing authorisation was extended. Oxaliplatin is now licensed in the UK in combination with 5-FU and FA and is indicated for:

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

The *BNF* warns that oxaliplatin can lead to renal failure. It is contraindicated in peripheral neuropathy with functional impairment. Neurotoxic side-effects (including sensory peripheral neuropathy) are dose limiting. Other side-effects include gastrointestinal disturbances, ototoxicity and myelosuppression.

### 2.3 Raltitrexed

Raltitrexed (Tomudex, AstraZeneca UK Ltd) inhibits the enzyme thymidylate synthetase, which is involved in DNA synthesis. Raltitrexed has market authorisation in the UK for the 'palliative treatment of advanced colorectal cancer where 5-fluorouracil and folinic acid based regimens are either not tolerated or inappropriate'.

It is contraindicated in severe renal impairment. It is generally well tolerated, but can cause marked myelosuppression and gastrointestinal side-effects.

**Table 1 Summary of drugs included in this appraisal.**

Generic name	Proprietary name	Manufacturer (MA holder)	Dose	Acquisition cost excl. VAT (BNF edition 48)
Irinotecan	CRT-11, Campto	Pfizer Ltd (Sanofi-Aventis now markets the drug)	First line: 180mg/m <sup>2</sup> by i.v. 30–90 minutes infusion every 2 weeks, followed by 5-FU infusion Second line: 350mg/m <sup>2</sup> by 30–90 minutes i.v. infusion every 3 weeks	£53.00 per 2 ml vial (20 mg/ml) £130.00 per 4 ml vial (20mg/ml)
Oxaliplatin	L-OHP, Eloxatin	Sanofi-Aventis	85mg/m <sup>2</sup> by 2–6 hours i.v. infusion prior to the administration of 5-FU, every 2 weeks.	£165.00 per 50 mg vial
Raltitrexed	ZD 1694, Tomudex	AstraZeneca	3mg/m <sup>2</sup> by 15 minute i.v. infusion repeated every 3 weeks	£121.86 per 2 mg vial

**Table 2 Licensed indications.**

	First-line monotherapy	First-line combination therapy	Second-line monotherapy	Second-line combination therapy
5-FU i.v	✓	✓	✓	✓
Irinotecan	✗	✓	✓	✗
Oxaliplatin	✗	✓	✗	✓ <sup>b</sup>
Raltitrexed	✓ <sup>a</sup>	✗	✓	✗

<sup>a</sup>When fluorouracil and folinic acid cannot be used; <sup>b</sup>indication licensed after issue of original guidance.

## 3 The evidence

### 3.1 Clinical effectiveness

Advanced colorectal cancer is usually managed with sequences of therapies, either mono- or combination therapies. The frequent use of unplanned second- or third-line salvage chemotherapy after disease progression can compromise the internal validity of study outcomes such as overall survival. This means that for all first-line or individual therapies, the outcome overall survival is of limited value. The AR has therefore also evaluated the clinical effectiveness of treatment sequences by examining studies with planned crossover treatments, which minimise the potential for bias.

Overall survival and progression-free survival data for the individual treatments and treatment sequences analysed in the AR are summarised in Table 3. In the following sections, the clinical evidence base will be discussed in more detail. The evidence base used in the original appraisal and any resulting research recommendations are also mentioned. Additionally, the evidence for the use of oxaliplatin and irinotecan in downstaging is shown (Section 3.1.8).

### 3.1.1. Irinotecan in first-line therapy in combination with 5-FU/FA

#### ***Evidence considered in original appraisal:***

*Two studies reported increases in overall survival of 2–3 months (four more trials had not completely reported at the time).*

#### **Updated evidence:**

Four new randomised controlled trials (RCTs) were identified (one of which was submitted in confidence) and one of the previously unfinished studies was now fully available, so seven RCTS were identified in total. In four studies, irinotecan in combination with 5-FU/FA was compared with oxaliplatin with 5-FU/FA, and in four irinotecan with 5-FU/FA was compared with 5-FU/FA alone. The RCTs were judged to be well designed and conducted.

#### **Results:**

The addition of irinotecan to first-line 5-FU/FA resulted in significantly improved median overall survival (by 2.2 to 3.3 months), median progression-free survival (by 2.1 to 2.7 months) (see Table 3). The response rates were 18–23% better in the irinotecan + 5-FU/FA arms.

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**Table 3 Summary of overall survival and progression-free survival (adapted from AR).**

Comparison	Studies (in meta-analysis, if appropriate)	Study participants	Overall survival	First-line progression- free survival	
Overview Section			HR (95% CI unless indicated otherwise)		
<b>Individual therapies:</b>					
Irinotecan + 5-FU/FA vs 5-FU/FA	3.1.1	4	2340	0.84 (0.76–0.93)	0.76 (0.70-0.82)
Irinotecan + 5-FU/FA vs oxaliplatin + 5-FU/FA	3.1.1	4	1740	1.12 (1.00–1.25)	1.10 (1.01-1.19)
Second-line irinotecan vs 5-FU/FA	3.1.2	1	267	0.70 (p = 0.035)	0.78 (p=0.03)
Second-line irinotecan vs best supportive care	3.1.2	1	279	0.54 (p = 0.0001)	Not reported
Oxaliplatin + 5-FU/FA vs 5-FU/FA	3.1.3	4	2651	0.93 <sup>a</sup> (0.83–1.03)	0.75 (0.69-0.82)
Second-line oxaliplatin + 5-FU/FA vs 5-FU/FA	3.1.4	1	542	0.84 (n.s.)	0.60 (p=0.0001)
Raltitrexed vs 5-FU/FA	3.1.5	4	1538	1.10 (0.97–1.25)	1.19 (1.06-1.34)
Infusional vs bolus 5-FU/FA regimens	3.1.6	4	938	0.89 (0.88–1.03)	0.78 (0.66-0.91)
<b>Treatment sequences</b>					
[5-FU then irinotecan + 5-FU] vs [5-FU then irinotecan] (FOCUS trial, B <sup>b</sup> vs A)	3.1.7	1	1066	<u>academic/commercial inconfidence information removed</u>	Not relevant
[irinotecan + 5-FU] vs [5-FU then irinotecan] (FOCUS trial, C vs A)	3.1.7	1	1066	<u>academic/commercial inconfidence information removed</u>	
[5-FU then oxaliplatin + 5-FU] vs [5-FU then irinotecan] (FOCUS trial, D vs A)	3.1.7	1	1066	<u>academic/commercial inconfidence information removed</u>	Not relevant
[Oxaliplatin + 5-FU] vs [5-FU then irinotecan] (FOCUS trial, E vs A)	3.1.7	1	1067	<u>academic/commercial inconfidence information removed</u>	
[Irinotecan + 5-FU] vs [5-FU then irinotecan + 5-FU] (FOCUS trial, C vs B <sup>b</sup> )	3.1.7	1	712		
[Oxaliplatin + 5-FU] vs [5-FU then oxaliplatin + 5-FU] (FOCUS trial, E vs D)	3.1.7	1	713		
[Irinotecan + 5-FU then oxaliplatin + 5-FU] vs [oxaliplatin + 5-FU then irinotecan + 5-FU]	3.1.7	1	226	NR	NR

<sup>a</sup>Unplanned second-line therapies (oxaliplatin in control arm); <sup>b</sup>not licensed indication



When irinotecan + 5-FU/FA in first-line therapy was compared with oxaliplatin + 5-FU/FA, there was no significant difference in overall survival. Progression-free survival showed a difference in favour of oxaliplatin + 5-FU/FA. However this could have been due to the inclusion of studies using bolus regimens (and in particular one study that included bolus in the irinotecan arm and infusion in the oxaliplatin arm). Similarly, response rates only showed a difference in favour of oxaliplatin arms when bolus regimens were used.

Differences in toxicity between the study arms were not always statistically significant. Overall, gastrointestinal toxicities (vomiting, nausea, diarrhoea, stomatitis and mucositis) were seen more often in the irinotecan + 5-FU/FA groups than with 5-FU/FA alone or oxaliplatin+5-FU/FA. Generally, haematological or neurological toxicities were seen less often in the irinotecan + 5-FU/FA groups than in the 5-FU/FA alone or oxaliplatin+5-FU/FA groups.

QoL was reported in two RCTs only, and no statistically significant difference was found between treatment arms, although one identified that deterioration in QoL and performance status occurred significantly later in the irinotecan + 5-FU/FA arm.

### 3.1.2. Irinotecan in second-line monotherapy

#### ***Evidence considered in original appraisal:***

*Seven trials; only one of which compared irinotecan with best supportive care. An increase in overall survival of 2.7 months was reported.*

#### **Updated evidence:**

No new evidence was identified. Only two of the seven RCTs identified in the previous AR were included (the remaining five used second-line combination therapy or the study was stopped early), one of which compared irinotecan with best supportive care and the other compared it with 5-FU/FA. The RCTs were judged to be well designed and conducted. However, the treatment arm populations in one trial appear to be unbalanced, with unknown consequences for the estimation of treatment effect.

#### **Results:**

In the comparison with second-line 5-FU/FA, irinotecan significantly improved median overall survival by 2.3 months, median progression-free survival by 1.3 months but with more toxicities. Response rate was improved with irinotecan.

In the comparison with best supportive care, irinotecan improved median overall survival by 2.7 months. Progression-free survival and response rate were not reported.

Serious gastrointestinal and haematological toxicities were observed more often with irinotecan monotherapy than with best supportive care, but fewer neurological problems, such as asthenia and pain, were seen.

QoL was reported in both RCTs. There was no evidence for a significant difference in QoL between second-line irinotecan and 5-FU/FA. Compared with best supportive care, irinotecan, despite causing additional toxicity, maintained baseline QoL longer.

### 3.1.3. Oxaliplatin as first-line combination therapy

#### ***Evidence considered in original appraisal:***

*Seven trials were included; a number of different regimens were used and there was no statistically significant effect on overall survival, possibly because of the small size of the RCTs. The addition of oxaliplatin to 5-FU/FA increased progression-free survival (by 2–3 months) and the response rate.*

#### **Updated evidence:**

One new RCT was identified (in confidence) and one of the previously unfinished studies was now fully available. Two of the previously identified RCTs were also included, so four RCTs were included in total. The RCTs included were judged to be relatively well-designed and conducted. There were issues with baseline comparability in two trials.

#### **Results:**

The addition of oxaliplatin to first-line 5-FU/FA was not shown to significantly improve median overall survival but it significantly improved median progression-free survival (by 2.5–2.8 months). Response rates were 27–38% higher in the oxaliplatin arm. Outcomes may have been confounded by over half of trial participants in three trials receiving unplanned second-line therapy, that is, those on 5-FU/FA monotherapy receiving second-line oxaliplatin.

Gastrointestinal, haematological and neurological toxicities were generally more frequent in the group receiving oxaliplatin + 5-FU/FA. Pain and alopecia were more frequent in 5-FU/FA group.

Data on QoL was only available for one RCT which showed that time to deterioration in global health status was prolonged in the oxaliplatin + 5-FU/FA arm, but there was no significant difference between study arms in overall QoL.

### 3.1.4. Oxaliplatin – second-line combination therapy

#### ***Evidence considered in original appraisal:***

*This indication was not licensed when the previous guidance was issued, but the AG mentioned abstract information from three RCTs, which only reported response rates. In two of these combination therapy with oxaliplatin increased response rates compared with either 5-FU/FA alone, or irinotecan alone or irinotecan + 5-FU/FA combination.*

**Updated evidence:**

This is now a licensed indication for oxaliplatin. One new RCT was identified, which was available in abstract form only but formed the basis of the analysis. No assessment of the design and conduct of the RCT was possible.

**Results:**

Oxaliplatin+ 5-FU/FA improved median overall survival by 1.1 months (HR 0.84, not statistically significant) compared with 5-FU/FA alone Median progression-free survival was significantly improved by 2.1 months, and response rates were significantly higher in the oxaliplatin + 5-FU/FA treatment arm relative to 5-FU/FA alone.

Gastrointestinal, haematological and neurological toxicities (including asthenia and pain) were higher in the oxaliplatin arm. QoL results were not presented.

**3.1.5. Raltitrexed in first- and second-line therapy*****Evidence considered in original appraisal:***

*Four RCTs comparing raltitrexed with 5-FU/FA. Raltitrexed was associated with a shorter time to progression and shorter overall survival than 5-FU/FA, and possibly more treatment-related deaths. It was noted that further studies are needed that compare raltitrexed with best supportive care or other treatments that do not contain 5-FU/FA.*

**Updated evidence:**

No new evidence was identified. Three of the four existing RCTs were relatively well designed and conducted, but there was too little information about the fourth to make an informed judgement. The populations in two trials contained imbalances and a third had a large quantity of withdrawals.

**Results:**

Raltitrexed did not improve overall survival or progression-free survival when compared with 5-FU/FA, and no RCT reported a significant improvement in response rates using raltitrexed.

The toxicity profiles of raltitrexed and 5-FU/FA were different and results varied across trials. Raltitrexed was associated with more vomiting and nausea, but less diarrhoea and mucositis.

One study reported consistent, statistically significant differences in QoL outcomes between arms, the direction of which favoured 5-FU/FA.

### 3.1.6. Infusional vs bolus regimens for 5-FU/FA

**Evidence considered in original appraisal:**

*Any differences between bolus and infusional regimens, or between different infusional regimens were not explored; however infusional regimens appear to have become standard clinical practice in the UK because of their improved tolerability.*

**Evidence and results:**

Three RCTs were meta-analysed and showed no significant difference in terms of overall survival but infusional regimens were better in terms of progression-free survival. Response rates were significantly higher with infusional regimens than with bolus administration in two out of three studies (in the third the same trend was seen, but it was not significant). All grade 3–4 toxicities were significantly less frequent with infusional than with bolus administration in the study where this outcome was reported.

The results for overall survival show the same direction and size of effect as those presented in another published meta-analysis which included, in addition to the studies included here, a number of studies of poorer quality. A further Phase III RCT found no significant difference between two different infusional regimens (Lokich and De Gramont), in terms of either overall survival or progression-free survival.

### 3.1.7. Sequencing of treatment

**Evidence considered in original appraisal:**

*(same evidence as described in Section 3.1.2)*

**New evidence:**

Two RCTs that investigated the effect of treatment sequences were identified: GERCOR and FOCUS (the results of the latter being supplied in confidence). These RCTs, included among other outcomes, overall survival and progression-free survival, and included treatment arms as described below:

GERCOR (Tournigand et al), 226 patients, follow up 44 months, this study did not allow third-line salvage therapy:

- A. irinotecan + 5-FU/FA followed by oxaliplatin + 5-FU/FA at progression
- B. oxaliplatin + 5-FU/FA followed by irinotecan + 5-FU/FA at progression.

FOCUS (Seymour et al), 2135 patients, follow up academic/commercial inconfidence information removed, this study allowed third-line salvage therapy:

- A. 5-FU/FA alone followed by irinotecan alone at progression (current NICE guidance)
- B. 5-FU/FA alone followed by irinotecan + 5-FU/FA at progression

- C. irinotecan + 5-FU/FA
- D. 5-FU alone followed by oxaliplatin + 5-FU/FA at progression
- E. oxaliplatin + 5-FU/FA.

FOCUS also included third-line salvage therapy where clinicians deemed it necessary.

It is important to emphasise that there is no published comparison between three active chemotherapies (as in GERCOR) and only two over a planned sequence (as in FOCUS). A direct comparison of the GERCOR and FOCUS data is therefore difficult. It is also not certain if the baseline characteristics of all trial participants in these two RCTs are homogeneous. The FOCUS trial outcomes could be confounded to an unknown extent by allowing salvage with a third chemotherapy.

**Results:**

In the FOCUS trial, the treatment sequence of first-line 5-FU/FA followed by irinotecan (current NICE recommendation) was inferior to any other sequence, although differences in overall survival were small and not statistically significant (Table 3), particularly when calculated on the basis of mean overall survival or by Weibull modelling (see below in Section 3.2). academic/commercial inconfidence information removed

Second-line combination treatment-sequences (5-FU, then irinotecan + 5-FU or oxaliplatin + 5-FU; note irinotecan is not licensed for second-line combination treatment) were as effective as first-line combination sequences, but there were significantly more first-line responders where 5-FU/FA was combined with either irinotecan or oxaliplatin.

In the GERCOR trial, there were no significant differences between the treatment sequences, but in second-line therapy there were significantly more responders to oxaliplatin + 5-FU/FA.

The FOCUS trial confirmed the higher toxicity profile of combination chemotherapies, and a similar lifetime probability of toxicity whether participants received combination chemotherapy in a first-line combination or staged approach.

The GERCOR trial reported that, in first-line therapy, irinotecan + 5-FU led to significantly fewer grade 3–4 toxicities, but significantly more serious adverse events than oxaliplatin + 5-FU. However the definition of a serious adverse event is not given. During second-line therapy, there were no significant differences between treatments in overall toxicity or the number of serious adverse event. It was also found that elderly patients did not experience worse toxicity than younger patients.

At the time of the AR, full QoL outcomes had not been published by either the GERCOR or the FOCUS studies.

### 3.1.8. Irinotecan/oxaliplatin in 'downstaging' otherwise unresectable liver metastases

#### **Evidence considered in original appraisal:**

*Two case series. It was recommended to collect data on clinical and economic data for patients receiving oxaliplatin for the purposes of 'downstaging'.*

#### **Updated evidence:**

In the three RCTs mentioned in Section 3.1.3 that reported the number of cancers which were rendered resectable by systemic therapy, survival outcomes were not reported separately. Six single-arm studies were identified for irinotecan + 5-FU/FA and two for oxaliplatin + 5-FU/FA (consisting of Phase II studies, prospective case series and/or other case series).

#### **Results:**

Where response rates were reported, these were around 50% for both irinotecan and oxaliplatin. Resection rates varied from 9% to 35% for irinotecan + 5-FU/FA and 7% to 51% for oxaliplatin + 5-FU/FA. In the one head-to-head study, significantly more resections occurred in the oxaliplatin + 5-FU/FA arm (22%) than with irinotecan + 5-FU/FA (9%). Complete resection was also reported to be more frequent with oxaliplatin + 5-FU/FA than with irinotecan + 5-FU/FA. However, in the one head-to-head study, the complete resection rate was not significantly different between arms.

### 3.1.9 Submissions

The majority of the clinical evidence presented in the manufacturers' submissions and the submissions received from patient or professional organisations was also included in the AR. However, the Aventis submission mentions several retrospective subgroup analyses of other included studies for elderly patients indicating that there are no differences in efficacy between fit elderly and younger age groups. The Sanofi submission and the submission received from the British Association for Surgical Oncology include a number of additional studies to show the effectiveness of oxaliplatin, which were not included in the AR because they were reported in abstract only, or were from non-randomised or Phase II studies. These studies were used as supporting evidence that there was no difference between oxaliplatin and irinotecan when used in combination with 5-FU/FA, that there was a survival benefit for oxaliplatin combined with 5-FU/FA compared with 5-FU/FA alone, and that oxaliplatin was beneficial for downstaging.

The submissions received from CancerBACUP and from the British Association for Surgical Oncology mention studies showing that patients with metastases at other sites than the liver may also benefit from treatment that shrinks the tumour to a size where surgical resection becomes a possibility.

Two further studies were highlighted by consultees:

- In the LIFE study first-line oxaliplatin + 5-FU/FA was compared with 5-FU/FA alone with second-line irinotecan in both arms. However, the results from this

study were also only available in abstract form, showing a difference in first-line progression-free survival of 2.5–3.2 months and 1.5–5.3 months for overall survival in favour of the oxaliplatin plan.

- Preliminary data from a further study suggest that a triple combination (5-FU/FA + oxaliplatin + irinotecan) could lead to increased survival over 5-FU/FA + irinotecan.

### 3.1.10 Summary of clinical effectiveness evidence

#### Individual therapies

- The addition of irinotecan or oxaliplatin to 5-FU/FA in first-line therapy is more effective in terms of progression-free survival than 5-FU/FA alone, but there is more toxicity.
- Upon progression on 5-FU/FA alone, a switch to irinotecan or addition of oxaliplatin to 5-FU/FA is more effective in terms of progression-free survival than staying on 5-FU/FA alone (for irinotecan also for overall survival).
- Raltitrexed is not more effective than 5-FU/FA.

#### Therapy sequences

- Sequences using three active chemotherapies appear to lead to the longest median overall survival, but no direct comparison of plans using three with plans using two active chemotherapies exist.
- Staged combination plans are no different from first-line combination plans in terms of overall survival.
- First-line combination therapy is more effective in terms of first-line progression-free survival than the therapy plan involving 5-FU/FA followed by irinotecan on progression (current NICE recommendation). However there is no statistically significant difference for overall survival, which is prolonged by approximately one months or less when mean survival is used.

#### Other aspects

- Infusional regimens are more effective than bolus regimens.
- Irinotecan and oxaliplatin are effective in downstaging of liver metastasis for resection.

## 3.2 *Cost effectiveness*

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### 3.2.1 General

The Assessment Group (AG) identified four new published economic evaluations relevant to the review. Two manufacturers submitted economic analyses, and the AG developed an economic model. The AG model was issued as an addendum to the Assessment Report and incorporates academic in confidence (AIC) data from the GERCOR study (Tournigand et al.) and from the FOCUS study (MRC CR 08, Seymour et al).

Survival can be estimated in several ways. Estimates of median survival have often been used in economic analyses. While improvements in median survival have the clear benefit of avoiding assumptions regarding survival distributions, this may not reflect the actual survival difference between treatments. The true survival benefit of one intervention compared to another relates to the area between two survival curves – the mean survival difference. Survival curves are typically incomplete (right censored) because trials are not able to follow all patients to death. Curve-fitting techniques (e.g. Weibull) are used to extrapolate the final portion of the survival curve. A degree of error is inevitable.

The biggest problem in interpreting survival data from existing trials concerns the uncertainty in the number of patients who crossover to alternative chemotherapies following disease progression or treatment failure. It is generally accepted that overall survival can best be evaluated as an outcome of sequences of chemotherapy regimens. Only in the GERCOR trial was sequencing planned; and the FOCUS trial incorporated a protocol change that allowed for the full benefit of sequences to be assessed.

Health-related QoL has been evaluated using cancer-specific questionnaires but no preference-scaling method exists through which to translate scores on this scale into a utility score. Indirect estimates of utility have been used but are not considered to be ideal. Instead, the AG was able to use EQ-5D estimates of utility derived from FOCUS. The AG noted that there is evidence from some trials that censoring of QoL data is not random, an effect known as 'informative censoring'. This means that completion rates are not independent of the quality of life of the patient, and quality of life data for the very ill patients may not be represented within the results of the study.

Estimates of the costs of treatment depend on assumptions concerning time on treatment, and time until progression following cessation of treatment. The only consistent treatment duration specified in all trials is the median. For costing purposes it is the mean that is required. The economic analyses described below (Table 4) generally used estimates from the literature or were based on the following costing scenarios.

- Scenario 1: Median treatment duration for chemotherapy and low estimate of other costs (all costs other than drug acquisition and administration).
- Scenario 2: Mean time to progression is used as treatment duration. This is seen to be the absolute maximum for people to be on treatment. High estimates of other costs were also used.
- Scenario 3 (base case): where mean treatment duration was available this was used. Otherwise an average of the median and the mean time to progression was used. Both in combination with the mean of the high and low estimate for other costs.



Instead of using these scenarios, the current AG model was able to use empirical data on the number of cycles of chemotherapy used, sourced from the same trials in which clinical effectiveness was established (see Section 3.2.9).

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Table 4. Summary of available cost-effectiveness estimates (see also Table 56 [AR page 118]; references refer to AR)

Author	Economic comparison(s)		Central estimate of cost-effectiveness			
	First-line	Second-line	Per LY gained	Per first-line PFLY gained	Per first-line QA-PFLY gained	Per QALY gained
Cunningham et al <sup>126</sup>	Irinotecan + 5-FU/FA <sup>a</sup> vs 5-FU/FA <sup>a</sup>		£14,794			
Industrial submission from Aventis <sup>52</sup>	a) Irinotecan + 5-FU/FA <sup>a</sup> vs 5-FU/FA <sup>a</sup> b) Oxaliplatin + 5-FU/FA <sup>a</sup> vs 5-FU/FA <sup>a</sup>			a) £43,712 b) £24,961		
Lloyd-Jones et al <sup>1</sup>	a) Oxaliplatin + 5-FU/FA <sup>a</sup> vs 5-FU/FA <sup>a</sup> b) Irinotecan + 5-FU/FA <sup>a</sup> vs 5-FU/FA <sup>a</sup>	c) Irinotecan vs 5-FU/FA <sup>a</sup>		a) £23,047 b) £58,424 c) Dominating		
Levy-Piedbois et al <sup>128</sup>		Irinotecan vs 5-FU/FA <sup>b</sup>	\$9,344 to \$10,137			
Iveson <sup>31</sup>		Irinotecan vs 5-FU/FA <sup>b</sup>	£7,965 to £11,974			
Poston et al <sup>125</sup>	Oxaliplatin + 5-FU/FA <sup>a</sup> vs 5-FU/FA <sup>a</sup> (patients with initially unresectable liver metastases)		£11,985			
Nicholls et al <sup>130</sup>	a) Oxaliplatin + 5-FU/FA <sup>a</sup> vs 5-FU/FA <sup>a</sup> b) Irinotecan + 5-FU/FA <sup>a</sup> vs 5-FU/FA <sup>a</sup>			a) £26,655 b) £30,171		
Nicholls et al <sup>129</sup>	Oxaliplatin + 5-FU/FA <sup>a</sup> vs 5-FU/FA <sup>a</sup>			£25,600		
Industrial submission from Sanofi-synthelabo <sup>119</sup>	a) Oxaliplatin + 5-FU/FA <sup>c</sup> vs 5-FU/FA <sup>c</sup> ; b) Oxaliplatin + 5-FU/FA <sup>c</sup> vs 5-FU/FA <sup>c</sup> (both followed on progression by second-line irinotecan)	c) Oxaliplatin + 5-FU/FA <sup>c</sup> vs irinotecan (both after first-line 5-FU/FA)		a) £22,576	a) £25,951	b) £22,302 c) dominating
Assessment Report	c) Irinotecan + 5-FU/FA <sup>c</sup> followed by best-supportive care vs a) e) Oxaliplatin + 5-FU/FA <sup>c</sup> followed by best-supportive care vs a) [salvage therapy in c is oxaliplatin + capecitabine or 5-FU/FA; in e irinotecan + capecitabine or 5-FU/FA] f) FOLFIRI followed by FOLFOX g) FOLFOX followed by FOLFIRI	a) second-line irinotecan (after 5-FU/FA) b) second-line irinotecan + 5-FU/FA <sup>c</sup> (after 5-FU/FA) vs a) d) second-line oxaliplatin + 5-FU/FA <sup>c</sup> (after 5-FU/FA) vs a) [salvage therapy in b is oxaliplatin + capecitabine or 5-FU/FA; in d irinotecan + capecitabine or 5-FU/FA]	b) £13,174 c) £12,418 d) £23,786 e) £43,531 f) £12,761 g) £16,776	b) n.a. c) £45,407 d) n.a. e) £40,002 f) £95,653 g) £63,468		b) £10,338 c) £13,630 d) £31,556 e) £67,662 f) £16,663 g) £21,845

<sup>a</sup>5-FU/FA in de Gramont regimen; <sup>b</sup>5-FU/FA in three regimens (de Gramont, Lokich and AIO); <sup>c</sup>5-FU/FA in modified de Gramont regimen

### 3.2.2 Published economic evaluations and manufacturer submissions

Common features of published and submitted economic analyses are listed here. The sections below, dealing with individual analyses, describe deviations from these common features. The base case results are presented in Table 4 above. The Assessment Group's model is considered separately in Section 3.2.9.

- UK – NHS perspective.
- Time horizon – until death.
- Data on effectiveness are taken from a clinical trial (Douillard or de Gramont).
- The de Gramont regimen is used for administration of 5-FU/FA (alone and in combination therapy).
- Mean and median time on treatment was estimated using Kaplan-Meier survival curves from individual trials or taken from the literature.
- Costs of drug acquisition and administration, as well as costs incurred as a result of complications due to treatment were included.
- Utility estimates were taken from a study in which specialist nurses were asked to rate QoL benefits of stabilisation in ACRC (Petrou).
- Only simple sensitivity analyses were used to explore uncertainty in the economic analyses.

### 3.2.3 Irinotecan combined with 5-FU/FA in first-line therapy

***Evidence considered in original appraisal:***

*In the original Assessment Report one economic evaluation was identified from the literature but only an abstract was available for analysis and the manufacturer submitted an economic model. A revised cost per additional PFLY gained of £37,000, relative to 5-FU/FA alone excluding the costs of second-line care and disregarding the figure from the manufacturer's meta-analysis, was accepted as a reasonable estimate. The Committee found it not reasonable to conclude that the extra 2.6 months survival that were used to estimate a cost per additional LY gained of £29,000, were purely attributable to irinotecan (or oxaliplatin) in combination with 5-FU/FA.*

**Updated evidence:**

The original AG's analysis (Lloyd-Jones) and the full paper of the abstract (Cunningham) were reviewed in the current Assessment Report, as well as an additional published economic analysis (Nicholls). The manufacturer submission updated the Lloyd-Jones analysis with results from three new trials and with new treatment times and unit costs.

In three analyses a first-line progression-free survival difference of 2.3 months was used to calculate base case costs per additional progression-free life year (PFLY) gained that ranged from £30,000 to £58,000 relative to 5-FU/FA alone. One analysis used overall survival to calculate a cost per additional LY gained of £15,000.

Two analyses (Lloyd-Jones and the manufacturer submission) used the cost scenarios described in 3.2.1, page 16 to calculate a range of cost effectiveness estimates. Inclusion of these scenarios resulted in costs per additional PFLY gained that increased from £44,000 (base case) to £71,000 in the manufacturer submission and from £48,000 to £95,000 in the Lloyd-Jones analysis (base case £58,000).

Apart from the common cost elements mentioned above, two analyses (Lloyd-Jones and the manufacturer submission) also included costs of hospital tests, primary care and pharmacy. Fixed costs such as line insertion were included for analysis of out-patients only. A key limitation of these analyses is that the adverse event profiles of the different treatment regimens were assumed to be identical.

Adjustments for QoL were explored in the Lloyd-Jones analysis but the authors stated that the results were too uncertain to draw conclusions from these.

The manufacturer submission also described cost effectiveness estimates of combinations of irinotecan with different regimens of 5-FU/FA compared with 5-FU/FA alone in those regimens. Most were associated with lower incremental costs and similar or lower incremental efficacy and thus lower costs per additional PFLY gained. academic/commercial inconfidence information removed

Furthermore, the submission included an analysis of oxaliplatin in first-line therapy combination with two regimens of 5-FU/FA (de Gramont and chronomodulated) that resulted in costs per additional PFLY gained of £25,000 and £27,000. A sensitivity analysis was undertaken that assumed all patients to be treated as in-patients or out-patients. The cost per additional PFLY gained was more favourable if all patients were treated on an out-patient basis (£40,000).

The relevance of the analysis of sequences that was included in the manufacturer submission can be questioned because data used from FOCUS were restricted to combined treatment arms and limited evidence was available on the amount of chemotherapy that was given in both the study by Tournigand et al. (GERCOR) and FOCUS. As the AG model was able to use evidence related to all five arms of FOCUS, and to incorporate more complete resource data from both trials the manufacturer submission could be seen to be outdated.

### 3.2.4 Irinotecan in second-line therapy

#### ***Evidence considered in original appraisal:***

*The original assessment report included two published economic evaluations of*

*irinotecan in second-line treatment. One resource-use study for irinotecan as second-line therapy was also identified. Best estimates for the cost per additional LY gained in second-line monotherapy were found to be probably between £17,000 and £28,000.*

**Updated evidence:**

The marginal second-line progression-free survival used in the Lloyd-Jones analysis was 1 month. Depending on the costing scenario used (see section 3.2.1, page 16), the resulting costs per additional PFLY gained were estimated to be between dominating and £26,000. The two published economic evaluations included in the original NICE guidance used a median survival estimate of 2.3 months.

No details were provided in the manufacturer submission on the cost effectiveness of irinotecan for second-line treatment of advanced colorectal cancer.

### 3.2.5 Oxaliplatin in combination with 5-FU/FA as first-line therapy

***Evidence considered in original appraisal:***

*The original Assessment Report included no published economic evaluations of oxaliplatin for the treatment of advanced colorectal cancer. The Committee considered that although RCTs demonstrated no statistically significant survival advantage for therapy with oxaliplatin in combination with 5-FU/FA, the gain in progression-free survival was similar to that demonstrated by combination irinotecan therapy (approximately 2–3 months). It was difficult to distinguish between irinotecan and oxaliplatin combination therapy when considering likely treatment benefits.*

**Updated evidence:**

Apart from the Lloyd-Jones analysis, four additional economic analyses of oxaliplatin in first-line treatment were included in the current Assessment Report; one of which is the manufacturer submission (Sanofi-Synthelabo) and another relates to an analysis of patients with unresectable liver metastases.

In three analyses, progression-free survival estimates for oxaliplatin were 2.8 months; slightly higher than those for irinotecan. The manufacturer submission used a much larger estimate of 4.5 months. The extra 2 months appear to be the result of including results from the study by Douillard and Salz in the combined estimate (with de Gramont) of progression-free survival on 5-FU/FA. Another explanation could be that Weibull curves were fitted in order to extrapolate outcomes beyond the observation periods of the trials which seem to result in longer progression-free survival. It is also noteworthy that two clinical trials from the clinical effectiveness section of the submission (Giachetti and Grothey) were not included in their economic model. Moreover, the Goldberg 2004 trial that informed the progression-free survival estimate for oxaliplatin in the model did not include 5-FU/FA as a comparator.

Only drug costs were included in one analysis by Nicholls while in the other analysis by the same author, other costs were included, but the cost of chemotherapy administration was excluded as it was assumed that they would not differ between the combination and single-agent regimen. The AG asserts that this assumption may bias the estimate of total costs in favour of the combination therapy with oxaliplatin.

The manufacturer submission included a new Markov-based economic model. The state transition approach was adopted to simulate chemotherapy sequences using data from both first-line and second-line clinical trials in an attempt to remove confounding from treatment crossover and mixed salvage treatment. However, the AG noted that the Markov approach to modelling does not overcome the problem of confounding that arises from patients' crossing over to other chemotherapy regimens following disease progression. Furthermore, the manufacturer acknowledged that the assumption in the model that all patients who progress on first-line therapy would subsequently get second-line therapy may overestimate the total benefit of treatment because in practice not all patients will be able to have, or will choose to have, second-line therapy.

Generally, simple sensitivity analyses were used to explore uncertainty. The manufacturer submission instead used probabilistic sensitivity analysis using Monte Carlo simulation. However, no parametric distributions were assigned to any of the uncertain parameters so the AG concluded that the probabilistic sensitivity analysis is theoretically incorrect and should be ignored. This is especially relevant since a weighted combination of median values of progression-free survival and overall survival from multiple studies are used to inform probabilities of transition between states.

Cost per PFLY gained in the economic evaluations of first-line oxaliplatin plus 5-FU/FA compared with 5-FU/FA alone ranged from £23,000 to £68,000.

### 3.2.6 Oxaliplatin in patients with unresectable liver metastases

#### ***Evidence considered in original appraisal:***

*Evidence on clinical effectiveness from two retrospective studies persuaded the Committee that significant survival benefit could be expected from oxaliplatin a proportion of patients, extending possibly to a cure. On this basis the Committee considered the estimate of cost effectiveness for oxaliplatin in this group of patients to be acceptable.*

**Updated evidence:** A published economic analysis was included in the AR. In the analysis by Poston, which led to £12,000 per LY gained, resectability rates of 11.4% and 4.1% were taken from the clinical trial data (de Gramont) and applied to two hypothetical cohorts of a 1000 patients. Kaplan-Meier survival curves were obtained from a retrospective study (Giacchetti) of patients with initially unresectable liver metastases who had been treated with oxaliplatin plus 5-FU/FA to reduce tumour size. Mean overall survival was 9.0 years for patients undergoing resection and 1.7 years for those considered unsuitable for resection.

The AG in their analysis of the trial notes that these figures include patients still alive at the end of the follow-up period, whose survival is assumed to be equal to that of the age-matched normal population (21.6 years), which may represent an overestimate given the likelihood of recurrent disease.

### 3.2.7 Oxaliplatin in second-line therapy

***Evidence considered in original appraisal:***

*The original Assessment Report included no published economic evaluations of oxaliplatin for the treatment of advanced colorectal cancer. This indication was not licensed when the original appraisal was carried out.*

**Updated evidence:**

No published economic evaluations for oxaliplatin in second-line treatment were included in the Assessment Report. Only the manufacturer submission presented an economic evaluation of second-line chemotherapy.

### 3.2.8 Raltitrexed

***Evidence considered in original appraisal:***

*Three economic analyses were included for raltitrexed in the original Assessment Report. The AG deemed it not to be appropriate to include raltitrexed in the original economic evaluation because no clinical benefit was established compared to 5-FU/FA.*

**Updated evidence:**

No new published economic analyses were included in the current Assessment Report and no submission was received by the manufacturer.

### 3.2.9 Assessment Group model

The AG's economic evaluation of irinotecan- and oxaliplatin-containing regimens aimed to determine the cost effectiveness of using:

- combination therapy in first-line
- combination therapy reserved for second-line management following progression on first-line single agent, and
- sequential combination therapy in first- and second-line.

All treatment options were compared with single agent first-line (5-FU/FA and second-line irinotecan), as recommended within current NICE guidance. Best supportive care was given in second-line to those who use combination therapy in first-line only. academic/commercial inconfidence information removed

Raltitrexed was not included in the economic evaluation.

Most of the common features described in Section 3.2.2 apply to the AG's analysis. Exceptions are:

- Data on effectiveness were obtained from the trial reported by Tournigand et al. (GERCOR) and from unpublished data for the individual arms in the FOCUS trial made available by the MRC (in confidence).
- In order to take account of correlations between effectiveness of regimens and sequences of chemotherapy regimens, survival curves and first-line progression-free survival curves for the six regimens were estimated using the Weibull survivor function for the common comparator regimen together with a log-rank hazard ratio describing the survival difference between the experimental and comparator curve. As the log-rank hazard ratios comparing regimens with the comparator were not available from GERCOR, an implied relative risk was estimated using the least-squares approach.
- An explicit assumption was made that the hazard of death at any given time for an individual within the GERCOR trial is proportional to the hazard of death at that time for a similar individual in the FOCUS trial.
- The modified de Gramont regimen was used for administration of 5-FU/FA (alone and in combination therapy).
- Additional costs that were included in the Lloyd-Jones analysis were also included here, and updated. Data on mean number of cycles and mean dosage were made available by the authors for the GERCOR and FOCUS studies. The data from FOCUS were obtained from an unpublished ad hoc analysis of a subset of 1200 patients. 18% of patients are assumed to receive treatment on inpatient basis.
- Utility estimates from the FOCUS study using EQ-5D were made available by the MRC/Centre for Health Economics, York. Straight lines were assumed between data points and beyond 48 weeks a utility score was taken equivalent to the mean of each treatment sequence utility profile.  
academic/commercial inconfidence information removed

As expected, higher estimates for overall survival were found when using the mean (AUC) compared with the median, and even higher when using the Weibull curve fitting to account for the missing portion of the curve. Importantly, this difference was not shown to be equal for all regimens. More specifically, when the adjusted mean was used instead of the median, the incremental difference in overall survival compared with the currently recommended regimen decreased significantly for first-line combinations in FOCUS but not for the planned second-line combinations. To complicate matters, the marginal difference of the sequential regimens of GERCOR with that recommended regimen increased. And the adjusted mean progression-



free survival estimates for all regimens were lower than those based on the median; except for one of the GERCOR regimens. See Table 5 below.

**Table 5 Comparison of median survival and mean survival estimated using Weibull regression analysis (from Addendum AG report – Table 9 page 18 with additions in *italic* by the authors of this overview).**

	FOCUS					GERCOR	
	Plan A: MdG then Ir	Plan B: MdG then IrMdG	Plan C: IrMdG	Plan D: MdG then OxMdG	Plan E: OxMdG	FOLFOX 6 then FOLFIRI <sup>1</sup>	FOLFIRI then FOLFOX6
<b>Overall survival (months)</b>							
Median	<u>academic/commercial inconfidence information removed</u>					20.6	21.5
<i>Versus comparator (A)</i>		<u>academic/commercial inconfidence information removed</u>				6.9	7.8
Weibull model	<u>academic/commercial inconfidence information removed</u>					25.7	27.3
<i>Versus comparator (A)</i>		<u>academic/commercial inconfidence information removed</u>				9.1	10.7
<b>Progression-free survival during first-line therapy (months)</b>							
Median	<u>academic/commercial inconfidence information removed</u>					8.0	8.5
<i>Versus comparator (A)</i>		<u>academic/commercial inconfidence information removed</u>				1.7	2.2
Weibull model	<u>academic/commercial inconfidence information removed</u>					10.2	9.0
<i>Versus comparator (A)</i>		<u>academic/commercial inconfidence information removed</u>				2.2	1.0
<b>Time to failure of first two drugs (months)<sup>a</sup></b>							
Median	<u>academic/commercial inconfidence information removed</u>					-	-

<sup>a</sup>Failure of planned treatment sequence, i.e. for plan C and E failure of first-line combination. The base case analysis of the AG used adjusted mean survival (Weibull model) to calculate marginal costs per LY gained. These ranged from £12,000 for irinotecan plus 5-FU/FA in first-line combination to £44,000 for oxaliplatin

<sup>1</sup> FOLFOX6 refers to oxaliplatin in combination with 5-FU/FA (modified de Gramont); FOLFIRI refers to irinotecan in combination with 5-FUFA.

plus 5-FU/FA in first-line combination. Cost-utility estimates ranged from £10,000 per additional QALY for irinotecan combination in second-line combination after single-agent therapy in first-line to £68,000 per additional QALY for the oxaliplatin first-line combination (see Table 4). Despite assuming large standard errors to the hazard ratios from the GERCOR study, the probabilistic sensitivity analysis resulted in the expectation that the regimens used in the GERCOR study<sup>2</sup> will always result in improved overall survival compared with the treatment sequences recommended by the current NICE guidance. FOCUS regimens instead had a distinct possibility of being less effective than the comparator. The cost effectiveness acceptability curve, combining all seven regimens, suggested that for thresholds less than £10,000, the comparator regimen is expected to be optimal while at a threshold of £30,000 the probability that FOLFIRI followed by FOLFOX is the optimal sequence is 70%. At that threshold all other regimens had a lower probability of being cost effective.

When interpreting the results of the economic evaluation, the AG suggests that it should be borne in mind that clinical and economic evidence from GERCOR and FOCUS were combined. Although the inclusion criteria of both studies were broadly similar, it is possible that the substantial differences in overall survival were not solely due to the chemotherapy received. Furthermore, the data on utility had not been subject to full checking and validation, nor had the data been adjusted for the effects of either informative or uninformative censoring within the trial. And, since salvage chemotherapy was available to a substantial percentage of people, the costs estimates for drug acquisition are likely to be underestimated. The degree to which the costs are underestimated would be greatest for the first-line combinations as they did not receive second-line treatment. Finally, because of limited evidence differential costs of hospitalisations between treatment arms were held constant; therefore uncertainty in the cost of regimens and sequences may be underestimated.

### 3.2.10 Summary of cost effectiveness evidence

Evidence from published economic evaluations, manufacturer submissions and the AG model suggests that combination of irinotecan or oxaliplatin with 5-FU/FA leads to costs per PFLY gained that are above £25,000. In most of these economic evaluations estimates of costs and benefits were accompanied with considerable uncertainty. Only the AG model calculated costs per QALY for combination therapies and sequences. This analysis suggests that first-line 5-FU/FA followed on progression by second-line irinotecan+5-FU/FA, first-line irinotecan+5-FU/FA, and first-line 5-FU/FA followed by second-line oxaliplatin+5-FU/FA have a cost effectiveness profile that is favourable. Whilst the FOCUS treatment costs are clear

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<sup>2</sup> irinotecan + 5-FU/FA followed by oxaliplatin + 5-FU/FA at progression or oxaliplatin + 5-FU/FA followed by irinotecan + 5-FU/FA at progression.

underestimates, the estimate of costs for two GERCOR treatment sequences are not. Despite this, both GERCOR sequences remain economically attractive in comparison to the FOCUS baseline.

## 4 Issues for consideration

### Clinical effectiveness

- It was recommended in the current guidance that organisers of trials are particularly encouraged not to exclude older patients, as these felt to be underrepresented in the existing studies. However, in many RCTs identified in the AR analysis, the populations are relatively young and fit by comparison with the majority of people in the UK who will receive second-line chemotherapy for advanced colorectal cancer, which also means that treatment effects are not necessarily transferable to clinical practice.
- It is unknown to what extent outcomes for overall survival are affected by the fact that in over half of studies included in the AG analysis, participants received unplanned third-line therapy.
- Overall survival differences are very small, particularly for 2 year overall survival

### Cost effectiveness

- Recommendations in the original NICE guidance did not specify the regimen to be used for 5-FU/FA. Most published economic analyses used de Gramont while the AG analysis based on FOCUS and GERCOR used modified de Gramont.
- Most published economic analyses used estimates of median (progression-free) survival while mean estimates are more suitable as they take into account the shape of the survival curve. The AG analysis showed that estimates for median and mean (Weibull) overall survival can differ substantially. Moreover, the magnitude and direction of the incremental difference in overall survival (versus current NICE guidance) varied per regimen or group of regimens.
- As it is often unclear what percentage of patients receives second-line chemotherapy, the use of progression-free survival was deemed to be appropriate as an outcome. However, in the current AG model based on FOCUS, the mean first-line progression-free survival of the 5-FU/FA regimen used as a comparator is much higher than the median in that analysis, and the median in published analyses and submissions. This is important because mean first-line progression-free survival of the combinations in the AG model does not show a similar magnitude of difference from the median. Even more so, this median progression-free survival is comparable to the published and submitted economic evaluations. This all results in the first-line progression-free survival benefit in the AG model being halved compared with other analyses, with significant impact on the cost effectiveness if calculated on first-line progression-free survival. Only

cost effectiveness estimates based on overall survival within the AG analysis would fall within an acceptable range.

- Clinical and economic evidence from GERCOR and FOCUS were combined in the AG model. However, although the inclusion criteria for both studies were similar, the substantial difference in survival between could also be explained by factors other than the chemotherapy received.
- Utility estimates used in most published economic analyses are sourced from one study only. Instead, the AG's analysis was able to use utility estimates directly from the FOCUS trial. These should be treated with caution though as they had not been subject to full checking and validation.
- Estimates of time on treatment are important for the calculation of drugs acquisition costs. Published economic analysis and submissions use median time on treatment from a trial, averages from a number of trials and scenario approaches, while the AG used data unpublished data from the GERCOR and FOCUS trials.
- The patent for oxaliplatin is due to expire in 2006/7.

#### **Current research**

- FOCUS 2/OPTIMOX (different treatment regimens)
- FOCUS 2 /SICOG/Grothey / Cassidy/CAPOX/XELIRI/Munoz (oral 5-FU/FA combined with irinotecan or oxaliplatin)
- COIN (new drugs – cetuximab and bevacizumab)
- LIFE (three active treatments)
- FOLFIRINOX (triple combination therapy for downstaging)
- Genetics and response (Weston Park Hospital Cancer Appeal)

## **5 AUTHORS**

Meindert Boysen, Elisabeth George (Health Technology Analysts)  
Janet Robertson (Technical Adviser)  
NICE Appraisal Team  
February 2005

## 6 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:

- Hind et al. The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation (review of Technology Appraisal Guidance No. 33), January 2005
- Hind et al. Addendum: Economic evaluation of irinotecan and oxaliplatin for the treatment of advanced colorectal cancer, January 2005.

B Submissions from the following organisations:

I Manufacturer/sponsors:

- Aventis/ Pfizer
- Sanofi-Synthelabo

II Professional/specialist and patient/carer groups:

- Association of Cancer Physicians
- Beating Bowel Cancer
- CancerBACUP
- Colon Cancer Concern
- Royal College of Nursing
- Royal College of Physicians/ Association of Cancer Physicians
- British Association of Surgical Oncology

III Commentator organisations (without the right of appeal):

- None received