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Abstract

3-month versus 6-month adjuvant chemotherapy for patients with high-risk stage II and III colorectal cancer: 3-year follow-up of the SCOT non-inferiority RCT

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Background: Oxaliplatin and fluoropyrimidine chemotherapy administered over 6 months is the standard adjuvant regimen for patients with high-risk stage II or III colorectal cancer. However, the regimen is associated with cumulative toxicity, characterised by chronic and often irreversible neuropathy.

Objectives: To assess the efficacy of 3-month versus 6-month adjuvant chemotherapy for colorectal cancer and to compare the toxicity, health-related quality of life and cost-effectiveness of the durations.

Design: An international, randomised, open-label, non-inferiority, Phase III, parallel-group trial.

Setting: A total of 244 oncology clinics from six countries: UK (England, Scotland, Wales and Northern Ireland), Denmark, Spain, Sweden, Australia and New Zealand.

Participants: Adults aged ≥ 18 years who had undergone curative resection for high-risk stage II or III adenocarcinoma of the colon or rectum.

Interventions: The adjuvant treatment regimen was either oxaliplatin and 5-fluorouracil or oxaliplatin and capecitabine, randomised to be administered over 3 or 6 months.

Main outcome measures: The primary outcome was disease-free survival. Overall survival, adverse events, neuropathy and health-related quality of life were also assessed. The main cost categories were chemotherapy treatment and hospitalisation. Cost-effectiveness was assessed through incremental cost comparisons and quality-adjusted life-year gains between the options and was reported as net monetary benefit using a willingness-to-pay threshold of £30,000 per quality-adjusted life-year per patient.

Results: Recruitment is closed. In total, 6088 patients were randomised (3044 per group) between 27 March 2008 and 29 November 2013, with 6065 included in the intention-to-treat analyses (3-month analysis, $n = 3035$; 6-month analysis, $n = 3030$). Follow-up for the primary analysis is complete. The 3-year disease-free survival rate in the 3-month treatment group was 76.7% (standard error 0.8%) and in the 6-month treatment group was 77.1% (standard error 0.8%), equating to a hazard ratio of 1.006 (95% confidence interval 0.909 to 1.114; p-value for non-inferiority = 0.012), confirming non-inferiority for 3-month adjuvant chemotherapy. Frequent adverse events (alopecia, anaemia, anorexia, diarrhoea, fatigue, hand–foot syndrome, mucositis, sensory neuropathy, neutropenia, pain, rash, altered taste, thrombocytopenia and watery eye) showed a significant increase in grade with 6-month duration; the greatest difference was for sensory neuropathy (grade ≥ 3 was 4% for 3-month vs.16% for 6-month duration), for which a higher rate of neuropathy was seen for the 6-month treatment group from month 4 to ≥ 5 years ($p < 0.001$). Quality-of-life scores were better in the 3-month treatment group over months 4–6. A cost-effectiveness analysis showed 3-month treatment to cost £4881 less over the 8-year analysis period, with an incremental net monetary benefit of £7246 per patient.

Conclusions: The study achieved its primary end point, showing that 3-month oxaliplatin-containing adjuvant chemotherapy is non-inferior to 6 months of the same regimen; 3-month treatment showed a better safety profile and cost less. For future work, further follow-up will refine long-term estimates of the duration effect on disease-free survival and overall survival. The health economic analysis will be updated to include long-term extrapolation for subgroups. We expect these analyses to be available in 2019–20. The Short Course Oncology Therapy (SCOT) study translational samples may allow the identification of patients who would benefit from longer treatment based on the molecular characteristics of their disease.

Trial registration: Current Controlled Trials ISRCTN59757862 and EudraCT 2007-003957-10.

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Contents

List of tables

List of figures

List of abbreviations

5FU	5-fluorouracil
AE	adverse event
AUC	area under the curve
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CTCAE	common terminology criteria for adverse event
DFS	disease-free survival
DMC	Data Monitoring Committee
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
FACT/GOG-Ntx4	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity
HR	hazard ratio
HRQoL	health-related quality of life
IDEA	International Duration Evaluation of Adjuvant chemotherapy
IQR	interquartile range
ITT	intention to treat
i.v.	intravenous
NCI	National Cancer Institute
NIHR	National Institute for Health Research
NMB	net monetary benefit
p_{NI}	*p*-value for non-inferiority
PRO	patient-reported outcome
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SCOT	Short Course Oncology Therapy
SD	standard deviation
SE	standard error
ToT	time on treatment
ULN	upper limit of normal
WTP	willingness to pay

Plain English summary

Patients diagnosed with bowel cancer are likely to have surgery to remove the tumour. Patients diagnosed with a more advanced stage of the disease are then likely to be offered what is known as adjuvant chemotherapy – chemotherapy to kill any cancer cells that have already spread but cannot be seen. Adjuvant chemotherapy is usually given over 6 months using two medicines known as oxaliplatin and fluoropyrimidine. This chemotherapy has side effects of diarrhoea, nausea and vomiting, and it reduces the numbers of cells in the blood. It can also damage nerves, which causes discomfort, numbness and tingling; in some cases, this can go on for years. These side effects are more likely to develop with longer treatment. This study looked at whether or not shortening the time over which patients were given oxaliplatin and fluoropyrimidine chemotherapy reduced its effectiveness.

In this large study of over 6000 patients, half of the patients were allocated by chance to be treated for 3 months and the other half to be treated for 6 months. Reducing the time that patients had chemotherapy from 6 months to 3 months did not make the treatment less effective. When patients treated with chemotherapy over 3 months were compared with those treated over 6 months, 77% of patients in both groups were well with no detectable disease 3 years after surgery. Patients were less likely to get side effects with 3-month chemotherapy. In particular, the chance of persistent long-term nerve damage was lower, resulting in patients with 3-month chemotherapy having better health-related quality of life.

Overall, the study showed that 3-month adjuvant chemotherapy for patients with bowel cancer is as effective as 6-month adjuvant chemotherapy and causes fewer side effects.

Scientific summary

Background

Patients with high-risk stage II or stage III colorectal cancer usually undergo surgical resection, followed by 6-month adjuvant chemotherapy. Administration of an oxaliplatin and fluoropyrimidine-based adjuvant chemotherapy regimen improves disease-free survival but is associated with a problematic toxicity profile; in particular, dose-dependent, cumulative peripheral neuropathy is a key toxicity that can persist long term despite the treatment for colorectal cancer having been curative. The toxicity of oxaliplatin and fluoropyrimidine regimens is cumulative, so reducing adjuvant treatment duration could ameliorate such effects; however, whether or not shortening the duration of adjuvant treatment could compromise its efficacy is debated.

The cost of colorectal cancer treatment in the year after diagnosis is considerably higher than that of treating other common cancers. Three-month adjuvant chemotherapy could be anticipated to be more cost-effective than the current standard 6-month treatment, provided that efficacy is maintained.

The Short Course Oncology Therapy (SCOT) study was designed to compare 3-month and 6-month oxaliplatin-based adjuvant chemotherapy in patients with colorectal cancer in terms of efficacy, toxicity, health-related quality of life and economic aspects.

Objectives

The objectives of the study were to assess the efficacy of 3-month versus 6-month adjuvant chemotherapy for colorectal cancer and to compare the associated toxicity and health-related quality of life. The primary end point of the study was disease-free survival, with the null hypothesis being that 3-month chemotherapy is inferior to 6-month chemotherapy with a hazard ratio of > 1.13. Secondary end points were overall survival, safety, health-related quality of life and cost-effectiveness parameters.

The economic evaluation explored the cost-effectiveness of 3-month versus 6-month adjuvant chemotherapy (in terms of incremental cost, quality-adjusted life-year gains and net monetary benefit with a willingness-to-pay threshold of £30,000/quality-adjusted life-year), using trial data on treatment and hospitalisation costs, health-related quality of life, and survival outcomes within the timeframe of the SCOT clinical trial.

Methods

The SCOT trial was an international, randomised (1 : 1), open-label (non-blinded), non-inferiority, Phase III, parallel-group trial comparing 3 months with 6 months of oxaliplatin plus fluoropyrimidine adjuvant chemotherapy in patients with high-risk stage II or stage III colorectal cancer. The study was conducted in 244 oncology clinics in six countries (the UK, Denmark, Spain, Sweden, Australia and New Zealand). Eligible patients were adults aged ≥ 18 years who had undergone curative resection for high-risk stage II (having one or more of the following risk features: T4 disease, tumour obstruction and/or perforation of the primary tumour, < 10 lymph nodes harvested, poorly differentiated histology, perineural invasion or extramural venous/lymphatic vascular invasion) or stage III adenocarcinoma of the colon or the rectum.

Patients were randomised (one to one) to receive either 3 months or 6 months of treatment using a minimisation algorithm incorporating a random component. Minimisation factors were study centre, treatment regimen, sex, disease site (colon or rectum), N stage (X, 0, 1 or 2), T stage (X, 0, 1, 2, 3 or 4), and capecitabine starting dose (for those receiving oxaliplatin and capecitabine). The adjuvant treatment regimen used could be oxaliplatin with 5-fluorouracil or oxaliplatin with capecitabine, with the treatment selected on an individual-patient basis to reflect the choice of the patient and/or physician.

Disease-free survival was defined as the time from randomisation (or trial registration for those randomised after 3 months of therapy) to relapse, development of a new colorectal cancer, or death from any cause. Overall survival was defined as the time from randomisation (or registration for those randomised at 3 months) to death from any cause. Comparison of disease-free survival between treatment groups was based on a Cox regression model incorporating minimisation factors as covariates; the population selection was intention to treat.

Toxicity was assessed by the investigators after each cycle of chemotherapy, with adverse events graded using the National Cancer Institute common terminology criteria for adverse events (version 3). Patients were followed up for a minimum of 3 years to a maximum of 8 years. Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer questionnaires QLQ-C30 and QLQ-CR29, and using EuroQol-5 Dimensions, three-level version. Neuropathy was assessed with the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx4) questionnaire.

The economic analysis was undertaken from the perspective of the UK NHS and Personal Social Services for 2016. The effectiveness measure for the economic analysis was the discounted quality-adjusted life-year gain per patient. Overall survival data were partitioned into three health states, (1) time on treatment, (2) disease free and (3) recurrence, with Kaplan–Meier sample averages used to compute the quality-adjusted survival time in each health state over the 8-year within-trial period; a separate model estimated health-related quality of life for each health state. Costs associated with patient treatment were calculated by measuring and valuing resources used by patients during the treatment and follow-up periods. The total cost of treatment per patient was estimated as the Kaplan–Meier survival analysis, considering the main cost categories of chemotherapy treatment and hospitalisation. Bootstrapping was used to account for uncertainty of the results and probabilistic sensitivity analysis was reported through confidence intervals and cost-effectiveness acceptability curves.

Results

A total of 6088 patients from 244 centres were randomised into the trial between 27 March 2008 and 29 November 2013: 5244 patients were randomised at 164 study centres in the UK, 311 patients were randomised at 10 centres in Denmark, 237 patients were randomised at 19 centres in Spain, 197 patients were randomised at 32 centres in Australia, 83 patients were randomised at 14 centres in Sweden and 16 patients were randomised at five centres in New Zealand. Of these, 6065 patients were included in the intention-to-treat analysis population and 6022 patients started study treatment. Data cut-off point for the analyses was 1 December 2016, at which time patients in both treatment groups had reached a median follow-up of 37 months.

Baseline data identified approximately 60% of patients as male and 40% as female, with the median age being 65 years. Most patients (> 80%) had a diagnosis of colon cancer and approximately 80% had stage III disease. For about 67% of patients, the planned treatment comprised oxaliplatin and capecitabine, with the remaining 33% of patients planned to receive oxaliplatin and 5-fluorouracil. Baseline characteristics were comparable for the 3-month and 6-month treatment groups.

Overall, 83.3% of patients randomised to the 3-month treatment group received 3 months of treatment and 58.8% of those randomised to the 6-month treatment group received 6 months of treatment; 6.9% of patients randomised to the 6-month treatment group stopped treatment at 3 months. The most common reason for not completing 6 months of treatment was an inability to tolerate the associated toxicity. The median percentage of the full fluoropyrimidine dose delivered was 95.3% for the 3-month and 83.2% for the 6-month treatment group; the median percentage of the full oxaliplatin dose delivered was 96.6% for the 3-month and 70.2% for the 6-month treatment group.

By the time of analysis, there were 1482 disease-free survival events (740 in the 3-month treatment group and 742 in the 6-month treatment group). The 3-year disease-free survival rate was 76.7% (standard error 0.8%) for the 3-month treatment group and was 77.1% (standard error 0.8%) for the 6-month treatment group; this equated to a hazard ratio of 1.006 (95% confidence interval 0.909 to 1.114; *p*-value for non-inferiority = 0.012). The study, therefore, confirmed non-inferiority for 3-month versus 6-month oxaliplatin-based adjuvant chemotherapy. By the time of analysis, there were 787 deaths, with the 3-year overall survival rate for the 3-month treatment group being 90.0% (standard error 0.6%) and for the 6-month treatment group 89.6% (standard error 0.6%), equating to a hazard ratio of 0.994 (95% confidence interval 0.964 to 1.143; *p*-value for non-inferiority = 0.035).

Treatment safety/toxicity was assessed for 868 patients. The most common adverse events seen during the study were alopecia, anaemia, anorexia, diarrhoea, fatigue, hand–foot syndrome, mucositis, sensory neuropathy, neutropenia, pain, rash, altered taste, thrombocytopenia and watery eye; these adverse events showed a statistically significant increase in severity for the 6-month treatment group compared with the 3-month treatment group. Sensory neuropathy, diarrhoea, neutropenia, fatigue, pain, nausea and hand–foot syndrome were the most common grade ≥ 3 adverse events reported, with statistically significant differences observed between treatment groups for diarrhoea ($p = 0.033$), neutropenia ($p = 0.023$), pain ($p = 0.014$), hand–foot syndrome ($p = 0.031$) and sensory neuropathy ($p < 0.001$). The most marked increase in the proportion of patients with grade ≥ 3 with 6-month adjuvant chemotherapy was for sensory neuropathy (16.4% vs. 4.3% with 3-month treatment). Serious adverse reactions were reported for 421 patients in the 3-month treatment group and for 511 patients in the 6-month treatment group. Thirty-two patients died as a result of events attributed to treatment toxicity, with the events distributed equally between the randomised groups (16 patient deaths for both the 3-month and the 6-month treatment groups).

Peripheral neuropathy was also assessed using the FACT/GOG-Ntx4 questionnaire, with data available for 2871 patients who were assessed for up to 7 years. The neurotoxicity standardised adjusted area under the curves for questionnaire scores differed markedly between treatment groups ($p < 0.001$), with a higher rate of neuropathy for the 6-month treatment group being apparent from 4 months and persisting to ≥ 5 years ($p < 0.001$).

Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer QLQ-C30 and CR29 ($n = 1829$) and EuroQol-5 Dimensions, three-level version ($n = 1828$) and the area under the curves was compared. European Organisation for Research and Treatment of Cancer QLQ-C30 global health status and functional and symptom scales demonstrated a statistically significant difference between treatment groups. Scores for the two groups mirrored each other for the first 3 months of treatment but subsequently showed functional improvement and decreased side effects in those who stopped treatment at 3 months. The largest difference between the treatment groups was seen at 6 months and, thereafter, mean values became more comparable as patients completed 6 months of treatment. For the European Organisation for Research and Treatment of Cancer QLQ-CR30, a subset of symptoms showed statistically significant differences, indicating fewer side effects in patients who received 3-month adjuvant chemotherapy (body image, $p = 0.037$; dry mouth, $p < 0.001$; hair loss, $p = 0.035$; taste alteration, $p < 0.0001$). The magnitude of the mean differences in functional and global health status scales between treatment groups was indicative of 'moderate' differences in global health status, role functioning and social function and 'a little' difference in physical, emotional and cognitive functions. Statistically significant

differences in area under the curves between the treatment groups were also seen for both the EuroQol-5 Dimensions self-rated visual analogue scale ($p = 0.00081$) and the EuroQol-5 Dimensions, three-level version health index ($p = 0.00081$), with differences apparent from months 4 to 6.

Adjuvant chemotherapy costs were higher for the 6-month treatment group ($p < 0.001$) and hospitalisation costs differed between treatment groups from 4 to 6 months after the start of treatment ($p < 0.001$). However, 6-month adjuvant chemotherapy was also associated with higher hospitalisation costs over the 7- to 12-month period ($p = 0.030$), possibly reflecting the persistence of treatment-related complications. No difference in cost was seen between the treatment groups after 12 months. Overall, the cost was significantly higher for the 6-month treatment group ($p < 0.001$), driven primarily by hospitalisation (–£2835) rather than the by cost of the adjuvant chemotherapy agents (–£1829). The 3-month treatment strategy was dominant, as it was cost saving and showed an improvement in quality-adjusted life-years, with an incremental net monetary benefit of £7246 per patient. Three-month adjuvant chemotherapy for colorectal cancer showed 99% probability of being cost-effective across the UK decision threshold range of £20,000–30,000 per quality-adjusted life-year.

Conclusions

The SCOT study showed that the efficacy of 3 months of oxaliplatin-containing adjuvant chemotherapy is non-inferior to 6 months of the same regimen; 6-month treatment was also associated with considerably higher levels of toxicity, particularly neurotoxicity, which can be chronic. Compared with traditional 6-month adjuvant chemotherapy, the 3-month treatment strategy costs significantly less and has no significant detrimental impact on patient outcomes (health-related quality of life and survival). Three-month oxaliplatin-based chemotherapy should, therefore, be considered as an option as adjuvant therapy for patients with high-risk stage II or stage III colorectal cancer, particularly when using oxaliplatin and capecitabine combination therapy.

Recommendations for research

The SCOT trial raised questions regarding whether 3-month treatment is applicable when using oxaliplatin and 5-fluorouracil as the adjuvant regimen or when treating patients with high-risk disease (T4 or N2 pathology). Further research should be conducted to identify any specific patient groups (e.g. patients with specific high-risk pathological features) for whom 6 months of adjuvant chemotherapy might be appropriate and if this is dependent on the regimen selected. The translational tissue samples from the SCOT study (3383 tumour samples and 3100 blood samples) and other similar studies should be used to build molecular predictors of which patients may benefit from a longer treatment duration. Some of this work is currently underway for the SCOT study.

Trial registration

This trial is registered as ISRCTN23516549 and EudraCT 2007-003957-10.

Funding

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Chapter 1 Introduction

Colorectal cancer is a common malignancy, with 1,360,000 cases annually, leading to 694,000 deaths each year. Colorectal cancer accounts for 12% of all new cancer cases each year in the UK, with approximately 41,265 cases estimated in 2014.[1] The initial treatment for patients presenting with colorectal cancer is usually surgical resection, which is potentially curative; however, 40–50% of patients subsequently relapse and die as a result of the disease becoming metastatic.[2] Postoperative adjuvant fluoropyrimidine-based chemotherapy was first shown to reduce the recurrence of colon cancer in 1990.[3] Initially, adjuvant treatment was given for 12 months, but a randomised study suggested equivalence for 6 months of treatment,[4] which is now accepted as the standard duration for adjuvant chemotherapy in patients with high-risk stage II or stage III colorectal cancer.[5]

High-risk stage II is defined as having one of the following risk features: T4 disease, tumour obstruction and/or perforation, < 10 lymph nodes harvested, poorly differentiated histology, perineural invasion or extramural venous/lymphatic vascular invasion.

The addition of oxaliplatin to a fluoropyrimidine-based regimen has been shown to improve 3-year disease-free survival (DFS) in patients with colorectal cancer.[6–8] The benefit seen in the MOSAIC[6] and NSABP C-07[7] studies was similar, despite the total oxaliplatin doses being different (1020 mg/m^2 and 765 mg/m^2, respectively).[6,7] These studies led to the adoption of oxaliplatin and fluoropyrimidine chemotherapy as the adjuvant treatment of choice for most patients with stage III disease who were aged < 70 years.[5,9] However, the administration of oxaliplatin with the fluoropyrimidine backbone results in additional toxicity, with increased neutropenia, thrombocytopenia, diarrhoea, nausea and vomiting.[6,7] There is also increased peripheral neuropathy, which is cumulative, dose-dependent and often irreversible, persisting long term despite the treatment of colorectal cancer having been curative. Neurotoxicity was measured using the National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) (version 1) in MOSAIC study,[6] and the NCI-Sanofi Neurosensory score in the NSABP C-07 study.[7] In the MOSAIC trial, 12.4% of patients experienced grade 3 sensory neuropathy, with 0.5% having residual problems at 18 months;[6] in the NSABP C-07 trial, 8.4% of patients had grade 3 or 4 neuropathy at the end of treatment, with 10% reporting some residual neuropathy beyond 2 years.[10]

As the toxicity of oxaliplatin and fluoropyrimidine regimens is cumulative, a reduction in the duration of adjuvant treatment could potentially ameliorate such effects;[11] however, whether or not short-duration adjuvant treatment could compromise efficacy is widely debated. Data for one study[12] are available in the literature, comparing 3 months with 6 months of adjuvant treatment with a fluoropyrimidine-based chemotherapy regimen; however, the study was conducted before the introduction of oxaliplatin-combination adjuvant treatment. Although the study was somewhat underpowered, reducing treatment duration did not appear to affect patient outcomes and was associated with reduced toxicity and improved health-related quality of life (HRQoL).

The cost of treatment for colorectal cancer in the first year after diagnosis is considerably higher than that of treating other common cancers and was estimated to cost the English health-care system £542M in 2010.[13] Three-month duration adjuvant chemotherapy for patients with colorectal cancer could be anticipated to be more cost-effective than the current standard 6-month duration, provided that efficacy is maintained. Benefits might be associated not only with lower treatment costs but also with reduced expenditure to manage problematic side effects and improvements in HRQoL.

The Short Course Oncology Therapy (SCOT) study was designed to compare 3-month and 6-month oxaliplatin-based adjuvant chemotherapy in patients with colorectal cancer in terms of efficacy, toxicity, HRQoL and economic aspects. At the time of starting this study, no published data were available on the effectiveness of short-duration treatment with adjuvant oxaliplatin and fluoropyrimidine regimens in patients with colorectal cancer. The main objective of the study was to identify whether or not 3-month adjuvant chemotherapy was inferior to 6-month treatment in terms of DFS rate. The trial also aimed to compare overall survival, toxicity and HRQoL in patients between the two treatment groups and to assess the cost-effectiveness of the two regimens. The SCOT study was designed as an international, stand-alone study of adjuvant oxaliplatin and fluoropyrimidine treatment conducted in patients with high-risk stage II or stage III colon or rectal cancers. Although stand-alone, the SCOT study was conducted in parallel with the International Duration Evaluation of Adjuvant chemotherapy (IDEA) collaborative initiative, which aimed to consolidate results from numerous worldwide trials that were attempting to clarify the importance of adjuvant treatment duration for colon cancer patients. The IDEA initiative was restricted to treatment of patients with stage III colon cancer; therefore, it was prospectively planned that patient data from the SCOT study would be pooled with those from six other studies (TOSCA, IDEA France, CALGB/SWOG 80702, ACHIEVE and HORG).[14]

Chapter 2 Methods

Study design

The SCOT study was an international, randomised (1 : 1), open-label (non-blinded), non-inferiority, Phase III, parallel-group trial comparing 6 months with 3 months of oxaliplatin plus fluoropyrimidine adjuvant chemotherapy in patients with high-risk stage II or stage III colorectal cancer.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines;[15] all aspects of the study received ethics approval from the ethics services in the participating countries. All participants provided written informed consent before enrolment.

Study participants

Parts of this section are taken from Iveson *et al.*[16]

Patients were recruited from 244 oncology clinics from six countries (the UK, Denmark, Spain, Sweden, Australia and New Zealand).

Eligible patients were adults aged ≥ 18 years who had undergone curative resection for high-risk stage II (having one or more of the following risk features: T4 disease, tumour obstruction and/or perforation of the primary tumour, < 10 lymph nodes harvested, poorly differentiated histology, perineural invasion or extramural venous/lymphatic vascular invasion) or stage III adenocarcinoma of the colon or rectum.

Patients were enrolled within 11 weeks of surgery and started treatment in their allocated treatment group within 2 weeks of randomisation. Other eligibility inclusion requirements included having a World Health Organization performance status of 0 or 1, having adequate organ function and having a life expectancy of > 5 years with reference to non-cancer-related disease, accepting that they may die earlier due to colorectal cancer. Patients were to have a normal computed tomography scan of the chest, abdomen and pelvis prior to study enrolment and a carcinoembryonic antigen level of < 1.2 times the local upper limit of normal (ULN) in the week prior to randomisation. Rectal cancer patients were to have undergone total mesorectal excision with negative resection margins (> 1 mm clearance).

Exclusion criteria included undergoing chemotherapy (except chemotherapy administered with curative intent that had been completed > 5 years previously with no residual complications); having undergone previous long-course chemoradiotherapy (preoperative short-course radiotherapy was allowed); having moderate or severe renal impairment (creatinine clearance rate of < 30 ml/minute using the Cockcroft–Gault equation); having a haemoglobin concentration of < 9 g/dl, an absolute neutrophil count of < 1.5×10^9 per litre, a platelet count of < 100×10^9 per litre, and aspartate aminotransferase or alanine aminotransferase levels of > 2.5 × ULN; having clinically significant cardiovascular disease; being pregnant or lactating; being of childbearing potential and not using or being unwilling to use medically approved contraception (postmenopausal women were to have been amenorrhoeic for ≥ 12 months to be considered of non-childbearing potential); having previous malignancy other than adequately treated in situ carcinoma of the uterine cervix or basal or squamous cell carcinoma of the skin (unless there was a disease-free interval of ≥ 5 years); and having known or suspected dihydropyrimidine dehydrogenase deficiency.

Public/patient involvement

The original SCOT study protocol was formally reviewed by consumers as part of the internal review and approval processes at the Glasgow Clinical Trials Unit. Patients were involved informally in the original concept of the trial, and they thought that whether or not shorter chemotherapy could reap the same benefit as longer chemotherapy was an exceptionally important question to define.

Patients at the clinics of the lead investigators were also asked about a proposal to extend study follow-up to increase the number of DFS events for analysis (application to the NIHR programme in 2014). As they felt that the question was exceptionally important, the view was that every effort should be made to extend the study to ensure that a thorough and accurate answer could be obtained for both patients with low-risk and patients with high-risk disease. The proposal to extend the study was also formally discussed and supported both by the main National Cancer Research Institute Colorectal Clinical Studies group and at the meeting of the Adjuvant and Advanced Disease subgroups. The public/patient representative at these meetings was fully supportive.

Study interventions

The adjuvant treatment regimen used was oxaliplatin with 5-fluorouracil (5FU) or oxaliplatin with capecitabine. Participating sites were able to select which treatment combination they wanted to use on an individual-patient basis, reflecting the choice of the patient and/or physician.

Oxaliplatin and 5-fluorouracil

For patients receiving oxaliplatin and 5FU, treatment was given every 2 weeks, the intention being to deliver six cycles to patients assigned 3 months of therapy and 12 cycles to patients assigned 6 months of therapy. On the first day of each cycle, 85 mg/m^2 of intravenous (i.v.) oxaliplatin was given over 2 hours, concurrently with 175 mg of L-folinic acid or 350 mg of folinic acid (also known as leucovorin). This was followed by a 400 mg/m^2 5FU i.v. bolus injection administered over 5 minutes, and then a continuous i.v. infusion of 2400 mg/m^2 of 5FU over 46 hours. At the investigator's discretion, patients who were aged > 70 years could start both 5FU infusions at 75% of the specified starting dose, if clinically indicated.

If a grade 1 adverse event (AE) occurred as a result of chemotherapy, treatment was to be continued at the full dose. For treatment-related AEs of grade ≥ 2, treatment was to be withheld until recovery to grade 1 and then restarted. If more than one delay or a delay of ≥ 2 weeks occurred, doses of oxaliplatin and infused 5FU were to be kept the same but the bolus 5FU dose was to be omitted; if further delays occurred as a result of myelotoxicity, the oxaliplatin and infusional 5FU doses were to be reduced by 25%. In addition, if after the first cycle the neutrophil count was $< 1.0 \times 10^9$ cells/l, the bolus 5FU dose was to be omitted and the oxaliplatin and infused 5FU doses were to be reduced by 25%. Wherever possible, the oxaliplatin dose was to be reduced rather than discontinued; if oxaliplatin dosing had to be discontinued, 5FU was to be continued where possible.

Oxaliplatin and capecitabine

For patients receiving oxaliplatin and capecitabine, treatment was given every 3 weeks, the intention being to deliver four cycles to patients assigned 3 months of therapy and eight cycles to patients assigned 6 months of therapy. On the first day of each cycle, 130 mg/m^2 of i.v. oxaliplatin was given over 2 hours. Oral capecitabine 1000 mg/m^2 was taken twice per day for the first 14 days of each cycle. Patients with a creatinine clearance rate of 30–50 ml/minute were to start capecitabine treatment at 75% of the specified dose. Patients aged > 70 years could be considered for treatment with capecitabine at 75% of the full dose, with the decision to reduce dose being made at the discretion of the investigator depending on the fitness of the individual patient. If the investigator considered that any patient required dose reduction

because of any other comorbidity, the patient could receive a minimum starting dose of oral capecitabine of 800 mg/m^2 twice per day.

If a grade 1 AE occurred as a result of chemotherapy, treatment was to be continued at the full dose. For treatment-related AEs of grade ≥ 2, treatment was to be withheld until recovery to grade 1 and then restarted. For AEs related to oxaliplatin and capecitabine, if more than one delay or a delay of ≥ 2 weeks occurred, capecitabine and oxaliplatin doses were to be reduced by 25%; if further delays occurred as a result of myelotoxicity, further dose reductions were allowed at the investigator's discretion.

Objectives

The objective of the SCOT study was to assess the efficacy of 3-month versus 6-month adjuvant chemotherapy for colorectal cancer and to compare the associated toxicity and HRQoL. The study also provided data for an economic analysis of the cost-effectiveness of the two regimens. The primary end point of the study was DFS, the null hypothesis being that 3-month chemotherapy is inferior to 6-month chemotherapy with a hazard ratio (HR) of > 1.13. Secondary end points were overall survival, safety, HRQoL and cost-effectiveness parameters.

The aim of the economic evaluation was to explore the cost-effectiveness of 3-month versus 6-month adjuvant chemotherapy [in terms of incremental cost per quality-adjusted life-year (QALY) gains and net monetary benefit (NMB)], using trial data on treatment and hospitalisations costs, HRQoL and survival outcomes within the timeframe of the SCOT clinical trial.

Outcomes

Disease-free survival was defined as the time from randomisation (or from trial registration for those randomised after 3 months of therapy) to relapse, development of a new colorectal cancer, or death from any cause. Overall survival was defined as the time from randomisation (or registration for those randomised at 3 months) to death from any cause. Toxicity was assessed by the investigators after each cycle of chemotherapy with AEs graded using NCI CTCAE version 3.

Patients were followed up for a minimum of 3 years to a maximum of 8 years, with full blood count, urea and electrolyte levels, liver function and carcinoembryonic antigen all being tested at 9, 12, 18, 24 and 36 months, and then annually. Computed tomography of the chest, abdomen and pelvis was conducted at 6, 12, 18, 24 and 36 months.

Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) questionnaires QLQ-C30[17] and QLQ-CR29,[18] and using the EuroQol-5 Dimensions, three-level version (EQ-5D-3L) (with both the visual analogue scale and the health index),[19] with UK value sets.[20] Neuropathy was assessed using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx4) questionnaire.[21] Questionnaires were administered at baseline and before each treatment cycle. Additionally, HRQoL was assessed each month in the first 3 months after treatment for the 3-month treatment group. Subsequent assessments were conducted at 9 and 12 months for the EORTC questionnaires; 9, 12, 18 and 24 months and then annually for the EQ-5D-3L; and up to 12 months for the FACT/GOG-Ntx4.

Sample size

In the previous MOSAIC trial, 3-year DFS in the oxaliplatin and 5FU treatment group was 78% compared with 73% for 5FU plus leucovorin.[6] To be able to conclude that the 3-month treatment group in the SCOT study was non-inferior, it was assumed that at least half of this benefit should be retained.

The SCOT study was designed as a randomised (1 : 1) non-inferiority trial aiming to reliably determine whether or not there was < 2.5% decrease in the 3-year DFS for patients in the 3-month treatment group (from 78% in the 6-month treatment group), which corresponds to excluding a HR of > 1.13 with 90% power at the 2.5%, one-sided level of significance. Assuming that the study would recruit over a period of 5 years with a subsequent minimum follow-up of 2 years, this design required 8600 patients to undergo randomisation and 2750 events (relapses, deaths or new colorectal cancers) to be observed; to allow for loss to follow-up, the recruitment target was 9500 patients.

From the outset, it was recognised that detecting meaningful differences based on safety and HRQoL data would not require information from all of the 9500 planned patients. For safety outcomes, 700 patients (350 in each group) were deemed sufficient to detect (80% power and a 2-sided significance level of 5%) a halving in the proportion of patients with grade 3 or 4 toxic effects from 12% to 6% (12% being the rate at which grade 3 or 4 paraesthesia, the most common non-haematological grade 3 or 4 toxic effect, occurred in the oxaliplatin treatment group in the MOSAIC trial).[6] This sample size would allow small changes in global HRQoL to be detected (assuming a difference of magnitude of 7.53[22] and a standard deviation of 23.4)[17] with 95% power at the 1% significance level. This more stringent level of significance was used to allow for multiple testing across various health-related quality-of-life scales. It should be noted that the power and sample size calculations for safety and health-related quality-of-life outcomes are based on a superiority comparisons, not on non-equivalence.

All sample size calculations were made in EAST 5.3.0.0 (Cytel Corporation, Cambridge, MA, USA).

Information on toxicity and health-related quality-of-life end points was collected from recruited patients until the number required was exceeded and the decision to stop was endorsed by the independent data monitoring committee (DMC) and trial steering committee. An administrative delay in notifying sites about the end of collection of detailed toxicity information resulted in data being collected from 868 patients. The DMC had access to summary plots of EORTC HRQoL data, EuroQol-5 Dimensions (EQ-5D) health status data and FACT/GOG-Ntx4 neuropathy data. In May 2010 (based on interim data from 1047 randomised patients), the committee recommended that the collection of HRQoL data and FACT/GOG-Ntx4 data should be continued because they were concerned that the number of missing data might undermine comparison at later time points. They also recommended that collection of FACT/GOG-Ntx4 data should be extended beyond 12 months for new patients and, where possible, for patients already participating in the study. In November 2010, the DMC recommended that the collection of these data should stop once 1800 patients had been recruited; delays in the amendment of the protocol led to patient recruitment beyond this recommendation. These extensions to data collection were made to compensate for missing data and were not based on formal power calculations.

Randomisation

The adjuvant treatment (oxaliplatin and 5FU or oxaliplatin and capecitabine) that was administered was selected on an individual-patient basis and was not randomised. Patients were randomised (1 : 1) centrally to receive either 3 months or 6 months of treatment using a minimisation algorithm incorporating a random component (80% probability of allocation to the 'minimum' group; 1 : 1 randomisation if no preferred group). Minimisation factors were study centre, treatment regimen, sex, disease site (colon or rectum), N stage (X, 0, 1 or 2), T stage (X, 0, 1, 2, 3 or 4) and capecitabine starting dose (from February 2010 for those receiving oxaliplatin and capecitabine). Centralised randomisation was conducted by the Cancer Research UK Clinical Trials Unit (Glasgow, UK). The computerised randomisation system allocated every patient a unique identification number and determined their treatment duration.

Initially, some participating centres were randomly allocated such that patients would be registered in the study prior to starting treatment but then be randomised after completing the first 3 months of treatment (delayed randomisation) to either receive a further 3 months of treatment or stop treatment. The remaining centres randomised patients to 3 months or 6 months of treatment prior to starting treatment. This delayed randomisation approach was discontinued because of a poorer randomisation rate [median 4.09, interquartile range (IQR) 1.29–7.09; $n = 41$, patients/centre/year] than in centres that randomised patients before the start of treatment (median 5.21, IQR 3.56–11.55; $n = 36$).[24]

The study was open-label for patients, clinicians, and those conducting data analysis.

Statistical analyses

Efficacy and safety analyses

The efficacy analyses of DFS and overall survival included, as far as possible, all randomly assigned patients [the intention-to-treat (ITT) population] and were plotted using Kaplan–Meier techniques. Analysis of treatment delivery and safety was based on patients who started the study treatment. The analysis time was prespecified in the study protocol. Statistical analyses used SPSS version 22 (IBM Corporation, Armonk, NY, USA) and R version 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria). The data cut-off point for this analysis was 1 December 2016.

Comparison of disease-free and overall survival between treatment groups was based on a Cox regression model incorporating minimisation factors as covariates; this approach was also used to derive the HR and associated 95% confidence intervals (CIs). The *p*-value for testing the null hypothesis, that the HR comparing 3 months with 6 months of adjuvant treatment was ≥ 1.13, was derived from this model by comparing the log-likelihood of the fitted model with the log-likelihood of a model where the HR between groups was set to 1.13 using a likelihood-ratio test. The proportional hazards assumption implicit in these analyses was examined graphically using a log-minus log plot of survival function against log time and using a test of the interaction between treatment group and time (logged) obtained from a Cox model incorporating an appropriate time-varying covariate.

The components of the forest plot (estimated hazard for the comparison between groups and associated 95% CI) were derived from a Cox model that included separate terms for the effect of duration in each category of the relevant stratification factor or other factors being examined. The *p*-value for heterogeneity was derived from comparison of the log-likelihoods of a model with separate terms for the effect of duration in each category compared with the model with a single overall term. The aim of this analysis was to establish whether or not the impact of treatment duration varied across important patient subgroups.

Multiple imputation analysis[25] was used to fill in missing data for questionnaires in the HRQoL and neuropathy scales. Five multiple imputation sets were produced for each HRQoL or neuropathy scale and the area under the curve (AUC)[26] was calculated with imputed data, as prespecified in the statistical analysis plan. The AUC was then adjusted by dividing by the follow-up period and subtracting the baseline value for each patient to produce a standardised-adjusted AUC. The standardised-adjusted AUC was calculated for the five imputed data sets and compared between the randomised treatment groups via a generalised linear model (with treatment group as an independent factor and study minimisation factors as covariates). The test statistics associated with treatment group from each of the five imputations were finally combined to provide an overall *p*-value that took into account the extent of missing data. To allow for the number of scales being examined, an adjustment for multiple comparisons (separately for the EORTC and the EQ-5D questionnaires) was made using the sharpened Hochberg procedure;[27] the *p*-value

threshold for statistical significance was 5% after adjustment. Comparison of these scales at individual time points also made use of multiple imputation and generalised linear models.

The Mann–Whitney *U*-test was used to compare ordered categorical variables for toxicity grade. Fisher's exact test was used to compare the incidence of grade 3–5 toxicity and logistic regression was used to estimate the odds ratio and associated CI for the incidence of grade 3–5 toxicity.

Study data were reviewed by the DMC approximately once a year to assess safety and efficacy issues from an ethics viewpoint. Conditional power methods[28] were used to aid the committee in reaching decisions about study continuation, but no formal stopping rules were set. The conditional power for DFS was presented at the fifth (June 2012), sixth (January 2013) and seventh (October 2013) meetings of the DMC; the DMC requested the analysis because of apparent differences in DFS curves. The results were discussed by the DMC in the context of the limited follow-up of patients and available survival data. The DMC concluded that no action was required.

Changes to the study protocol

The approach of randomising patients to a treatment group was changed after the trial had been running for 1 year; after this time all patients were randomised as they started adjuvant therapy (rather than some being randomised after 3 months of adjuvant chemotherapy), as this approach proved to have a higher randomisation rate and a lower dropout rate.

From March 2012, the requirement for the neuropathy questionnaire to be completed was extended to follow-up visits at 18 and 24 months; from December 2012 the neuropathy questionnaire was to be completed at follow-up visits to a maximum of 8 years. These extensions to data collection were made to compensate for missing data and to monitor long-term change in neuropathy.

The planned duration of patient follow-up for the primary analysis was extended so that (1) patients with stage III disease were to be followed up until the end November 2014 or for a minimum of 3 years (if they did not have $\geq$ 3 years of follow-up at the end of November 2014) and (2) all patients with stage II disease were to be followed up until the end of November 2016. Follow-up was extended to increase the number of events for the primary study analysis.

Chapter 3 Results

Participant recruitment and flow

The data cut-off point for the analyses presented here was 1 December 2016, at which time patients in both treatment groups had undergone median follow-up of 37 months (IQR 36–49 months, as calculated using the reverse Kaplan–Meier approach). A total of 88% of patients were followed up for a minimum of 3 years, which allowed for a 2-month window around the follow-up time. A total of 787 patients had died by the time of analysis. Study patients are still undergoing follow-up to support further DFS and overall survival analyses.

A total of 6088 patients were randomised to the trial between 27 March 2008 and 29 November 2013 from 244 centres: 5244 patients were randomised at 164 study centres in the UK, 311 patients at 10 centres in Denmark, 237 patients at 19 centres in Spain, 197 patients at 32 centres in Australia, 83 patients at 14 centres in Sweden, and 16 patients at five centres in New Zealand. The study did not meet its target of 9500 patients as a result of slow recruitment; despite extending the planned enrolment period by 6 months, the target was not reached and recruitment was stopped to allow adequate follow-up of ongoing randomised patients within the budget for the trial. This allowed the minimum follow-up period to be extended to 3 years. A total of 1482 DFS events were observed, which gave the study 66% power rather than the planned 90% power for rejecting the null hypothesis.

A total of 6065 patients were included in the ITT analysis population, 6022 of whom started study treatment. Treatment safety/toxicity was assessed after each chemotherapy cycle for 868 patients. HRQoL was assessed using EORTC QLQ-C30 and CR29 ($n = 1829$) and EQ-5D-3L ($n = 1828$) and neuropathy were assessed using FACT/GOG-Ntx4 ($n = 2871$).

The Consolidated Standards of Reporting Trials (CONSORT) flow diagram (*Figure 1*) shows patients who entered and progressed through the trial and provided data for the different assessment parameters. Of the 6088 patients entering the trial, 3044 were randomised into each treatment group (3-month and 6-month duration). Of these 3044 patients, 3035 (99.7% of 3044 randomised to this group) in the 3-month treatment group were included in the ITT analyses, with 3009 patients receiving the study drug, and 3030 (99.5% of 3044 randomised to this group) in the 6-month treatment group were included in the ITT analyses, with 3013 patients receiving the study drug. The reasons patients were not included in the ITT analysis and did not start study treatment are also detailed in *Figure 1*.

Baseline data

Baseline data (recorded at the time of randomisation) identified approximately 60% of patients as male and 40% as female, with the median age being 65 years. Most patients (> 80%) had a diagnosis of colon cancer and approximately 80% had stage III disease. For about 67% of patients, the planned treatment was oxaliplatin and capecitabine, with the remaining 33% planned to receive oxaliplatin and 5FU. Baseline characteristics were comparable for the 3-month and 6-month treatment groups for the overall patient population (*Table 1*) and for the other analysis sets considering toxicity and HRQoL (see *Appendix 1*).

Exposure to study medication

The duration of adjuvant chemotherapy, based on the number of treatment cycles delivered, is presented in *Table 2*; for the purpose of this analysis, one cycle of oxaliplatin and 5FU equated to 2 weeks of

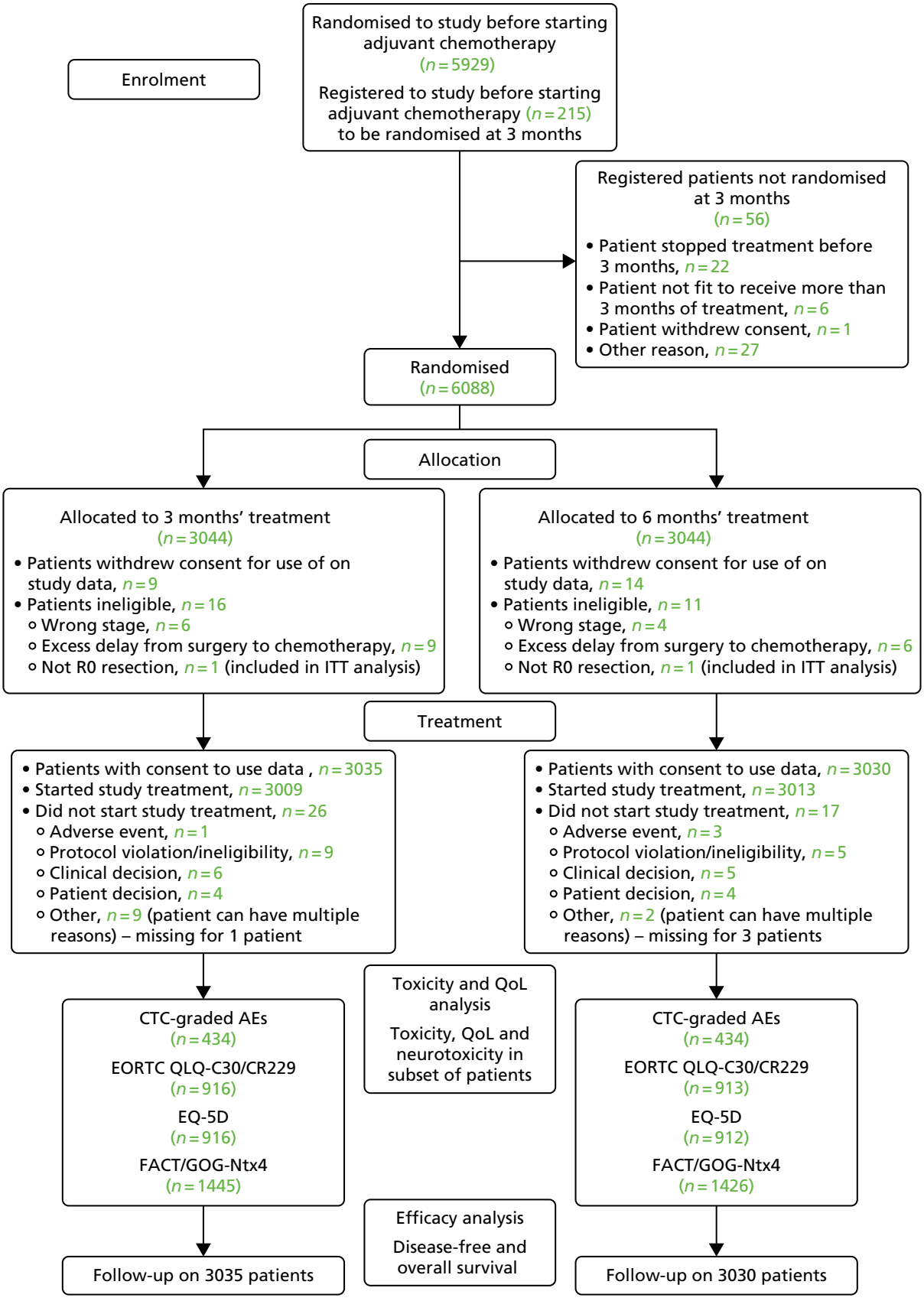


FIGURE 1 The CONSORT flow diagram of patient progression through the SCOT trial. Reproduced from Iveson *et al.*[16] © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

TABLE 1 Baseline patient characteristics as recorded at randomisation, by treatment group

Characteristic	Randomised treatment group	
	3 months of treatment ($N = 3044$)	6 months of treatment ($N = 3044$)
Gender,* n *(%)		
Female	1201 (39.5)	1200 (39.4)
Male	1843 (60.5)	1844 (60.6)
Total	3044 (100.0)	3044 (100.0)
Age (years)		
Median	65	65
IQR	58–70	58–70
Range	23–84	20–85
Total	3044	3044
Performance status at randomisation,* n *(%)		
0	2190 (71.9)	2144 (70.4)
1	854 (28.1)	900 (29.6)
Total	3044 (100.0)	3044 (100.0)
Disease site,* n *(%)		
Colon	2492 (81.9)	2495 (82.0)
Rectum	552 (18.1)	549 (18.0)
Total	3044 (100.0)	3044 (100.0)
T stage,* n *(%)		
0	1 (0.0)	3 (0.1)
1	92 (3.0)	95 (3.1)
2	284 (9.3)	283 (9.3)
3	1749 (57.5)	1748 (57.4)
4	917 (30.1)	915 (30.1)
X	1(0.0)	0 (0.0)
Total	3044 (100.0)	3044 (100.0)
N stage,* n *(%)		
0	559 (18.4)	557 (18.3)
1	1731 (56.9)	1732 (56.9)
2	754 (24.8)	755 (24.8)
Total	3044 (100.0)	3044 (100.0)
Planned treatment,* n *(%)		
FOLFOX	993 (32.6)	988 (32.5)
CAPOX	2051 (67.4)	2056 (67.5)
Total	3044 (100.0)	3044 (100.0)
If CAPOX planned, starting dose of capecitabine,* n *(%)		
750 mg/m^2	348 (19.5)	349 (19.4)
800 mg/m^2	72 (4.0)	78 (4.3)
1000 mg/m^2	1369 (76.5)	1370 (76.2)
Total	1789 (100.0)	1797 (100.0)

continued

TABLE 1 Baseline patient characteristics as recorded at randomisation, by treatment group (*continued*)

Characteristic	Randomised treatment group	
	3 months of treatment (*N* = 3044)	6 months of treatment (*N* = 3044)
High-risk stage II,* n *(%)		
No	2493 (81.9)	2499 (82.1)
Yes	551 (18.1)	545 (17.9)
Total	3044 (100.0)	3044 (100.0)
Randomisation time point,* n *(%)		
Baseline	2964 (97.4)	2965 (97.4)
3 months	80 (2.6)	79 (2.6)
Total	3044 (100.0)	3044 (100.0)

CAPOX, oxaliplatin and capecitabine; FOLFOX, oxaliplatin and 5FU.

TABLE 2 Treatment duration by treatment group

Treatment	Duration of treatment (based on the number of cycles) (weeks)	3-month treatment (*N* = 3044), *n* (%)	6-month treatment (*N* = 3044), *n* (%)
FOLFOX	< 12	116 (11.8)	107 (10.9)
	12	845 (86.2)	55 (5.6)
	> 12, ≤ 16	18 (1.8)	64 (6.5)
	> 16, ≤ 20	0 (0.0)	88 (8.9)
	> 20, ≤ 24	1 (0.1)	74 (7.5)
	24	0 (0.0)	586 (59.5)
	> 24	0 (0.0)	11 (1.1)
	Total	980 (100.0)	985 (100.0)
CAPOX	< 12	310 (15.2)	310 (15.3)
	12	1675 (81.9)	154 (7.6)
	> 12, ≤ 16	59 (2.9)	75 (3.7)
	> 16, ≤ 20	0 (0.0)	124 (6.1)
	> 20, ≤ 24	0 (0.0)	141 (7.0)
	24	0 (0.0)	1187 (58.5)
	> 24	0 (0.0)	37 (1.8)
	Total	2044 (100.0)	2028 (100.0)
All patients	< 12	426 (14.1)	417 (13.8)
	12	2520 (83.3)	209 (6.9)
	> 12, ≤ 16	77 (2.5)	139 (4.6)
	> 16, ≤ 20	0 (0.0)	212 (7.0)
	> 20, ≤ 24	1 (0.0)	215 (7.1)
	24	0 (0.0)	1773 (58.8)
	> 24	0 (0.0)	48 (1.6)
	Total	3024[a] (100.0)	3013[b] (100.0)

CAPOX, oxaliplatin and capecitabine; FOLFOX, oxaliplatin and 5FU.
a Missing for 20 patients: 9 withdrew consent for use of information, 11 had data missing.
b Missing for 31 patients: 14 withdrew consent for use of information, 17 had data missing.

treatment and one cycle of oxaliplatin and capecitabine equated to 3 weeks of treatment. Overall, 83.3% of patients randomised to the 3-month treatment group received 3 months of treatment: the frequency was slightly higher for those receiving oxaliplatin and 5FU (86.2% of patients vs. 81.9% of those receiving oxaliplatin and capecitabine). Overall, 58.8% of those randomised to the 6-month treatment group received 6 months of treatment, with the proportion being similar for those receiving oxaliplatin and 5FU (59.5%) and for those receiving oxaliplatin and capecitabine (58.5%); 6.9% of patients randomised to 6 months of treatment stopped treatment at 3 months. A total of 13.8% of patients stopped treatment before 3 months, with the proportion being similar for those randomised to receive 3 months of treatment (14.1%) and for those randomised to receive 6 months of treatment (13.8%).

The overall median treatment duration based on actual start and end dates was 11.3 weeks (IQR 10.1–12.6 weeks) for the 3-month treatment group and 23.1 weeks (IQR 17.0–25.3 weeks) for the 6-month treatment group. A higher proportion of patients receiving oxaliplatin and 5FU had at least one delayed cycle in both the 3-month (65.0% vs. 45.2% with oxaliplatin and capecitabine) and the 6-month (83.0% vs. 66.3%) treatment groups.

The median percentage of the full fluoropyrimidine dose delivered was 95.3% (IQR 83.1–99.8%) in the 3-month and 83.2% (IQR 56.7–95.7%) in the 6-month treatment groups. The median percentage of the full oxaliplatin dose delivered was 96.6% (IQR 82.3% to 99.7%) in the 3-month and 70.2% (IQR 44.3% to 87.1%) in the 6-month treatment groups. These values were similar irrespective of the fluoropyrimidine backbone (*Figure 2*).

A total of 788 patients (26.2%) underwent 5FU or capecitabine dose reduction in the 3-month treatment group compared with 1286 patients (42.7%) in the 6-month treatment group; 906 patients (30.1%) underwent oxaliplatin dose reduction in the 3-month treatment group compared with 1869 patients (62.0%) in the 6-month treatment group.

As patients receiving oxaliplatin and 5FU require insertion of a line, this could potentially delay the start of their treatment. However, the difference in mean time from surgery to the start of adjuvant chemotherapy was negligible when comparing patients treated with oxaliplatin and 5FU [mean 58 days, standard deviation (SD) 16 days)] and those treated with oxaliplatin and capecitabine (mean 56 days, SD 14 days).

Comparison of efficacy for 3-month versus 6-month adjuvant chemotherapy

Disease-free survival

By the time of analysis there had been 1482 DFS events (740 in the 3-month treatment group and 742 in the 6-month treatment group). In the 3-month treatment group, 658 patients (21.7%) experienced disease recurrence, 71 patients (2.1%) died without disease recurrence or a new primary colorectal lesion, and 11 patients (0.4%) had a new primary colorectal cancer lesion; in the 6-month treatment group, 654 patients (21.6%) experienced disease recurrence, 76 patients (2.6%) died without disease recurrence or new primary colorectal lesion, and 12 patients (0.4%) had a new primary colorectal cancer lesion. The 3-year DFS rate in the 3-month treatment group was 76.7% [standard error (SE) 0.8%] and in the 6-month treatment group was 77.1% (SE 0.8%); this equated to a HR of 1.006 [95% CI 0.909 to 1.114; *p*-value for non-inferiority (p_{NI}) = 0.012] and therefore met the criteria confirming non-inferiority for 3-month compared with 6-month adjuvant chemotherapy (*Figure 3*).

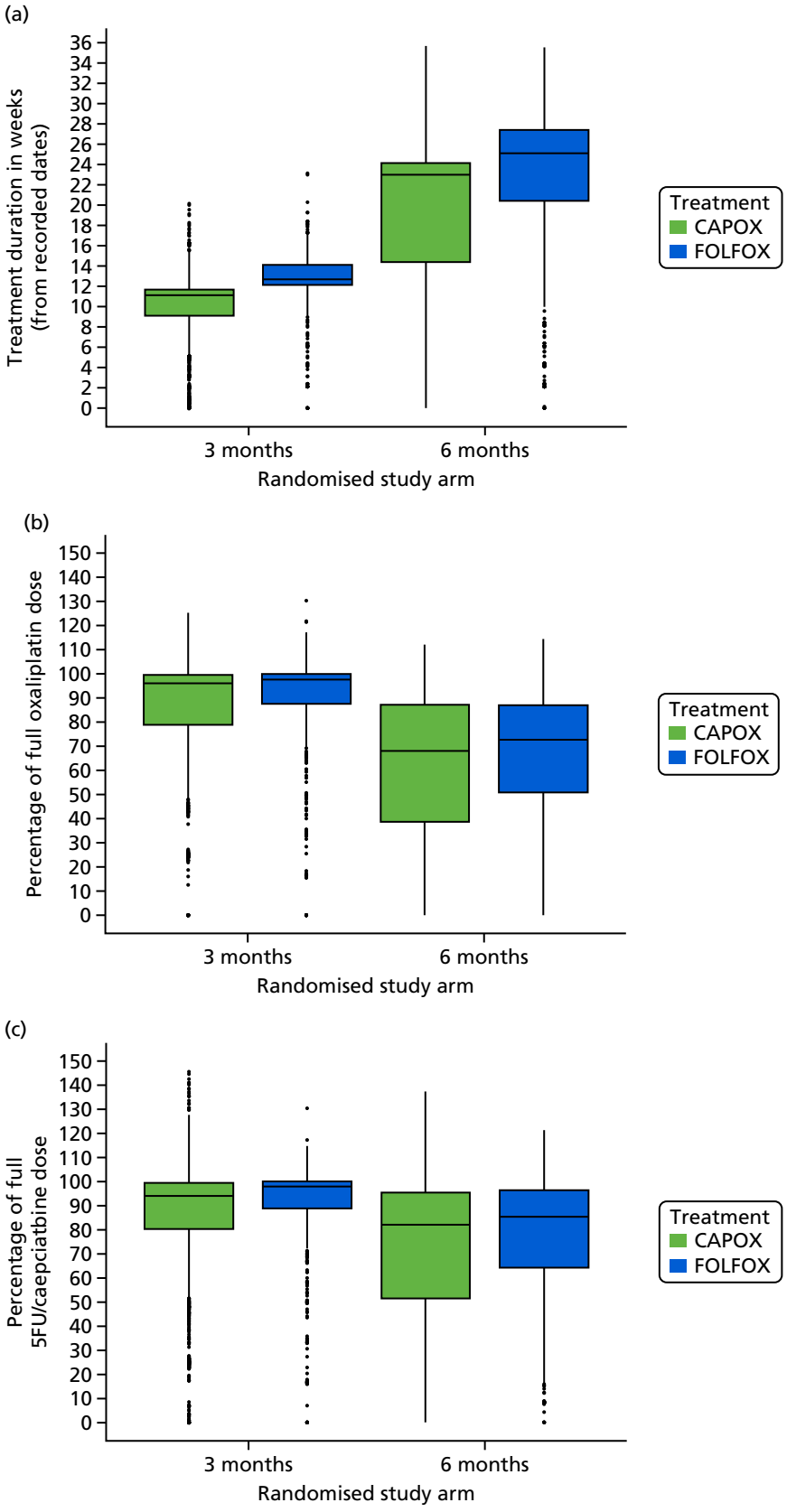


FIGURE 2 Treatment delivery by treatment group and adjuvant regimen. (a) Treatment duration; (b) percentage of intended oxaliplatin dose; and (c) percentage of intended 5FU/capecitabine dose. Boxes show median and IQR; whiskers show range; dots represent outliers. FOLFOX, oxaliplatin and 5FU. Adapted from Iveson *et al.*[16]

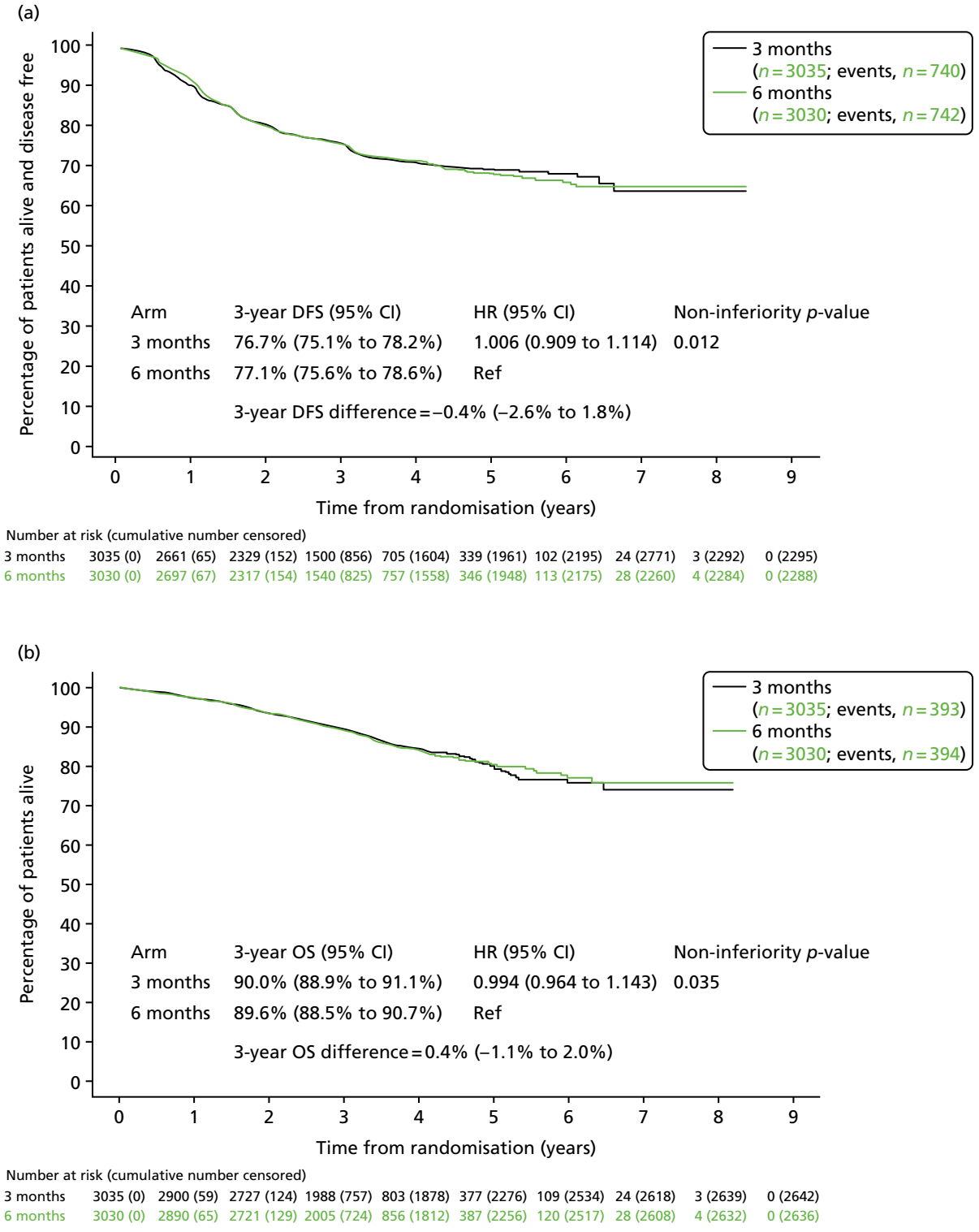


FIGURE 3 (a) Disease-free survival and (b) overall survival, by treatment group. Adapted from Iveson *et al.*[16]

Sensitivity analysis considered the difference between treatment groups based on the actual duration of treatment (*Figure 4*). For eligible patient who received 3 months (2513 patients; see *Table 2*) or 6 months (1771 patients; see *Table 2*) of adjuvant chemotherapy, the observed HR was 1.158 (95% CI 1.018, 1.317; $p = 0.641$) with non-inferiority not confirmed in any of these smaller, non-ITT populations.

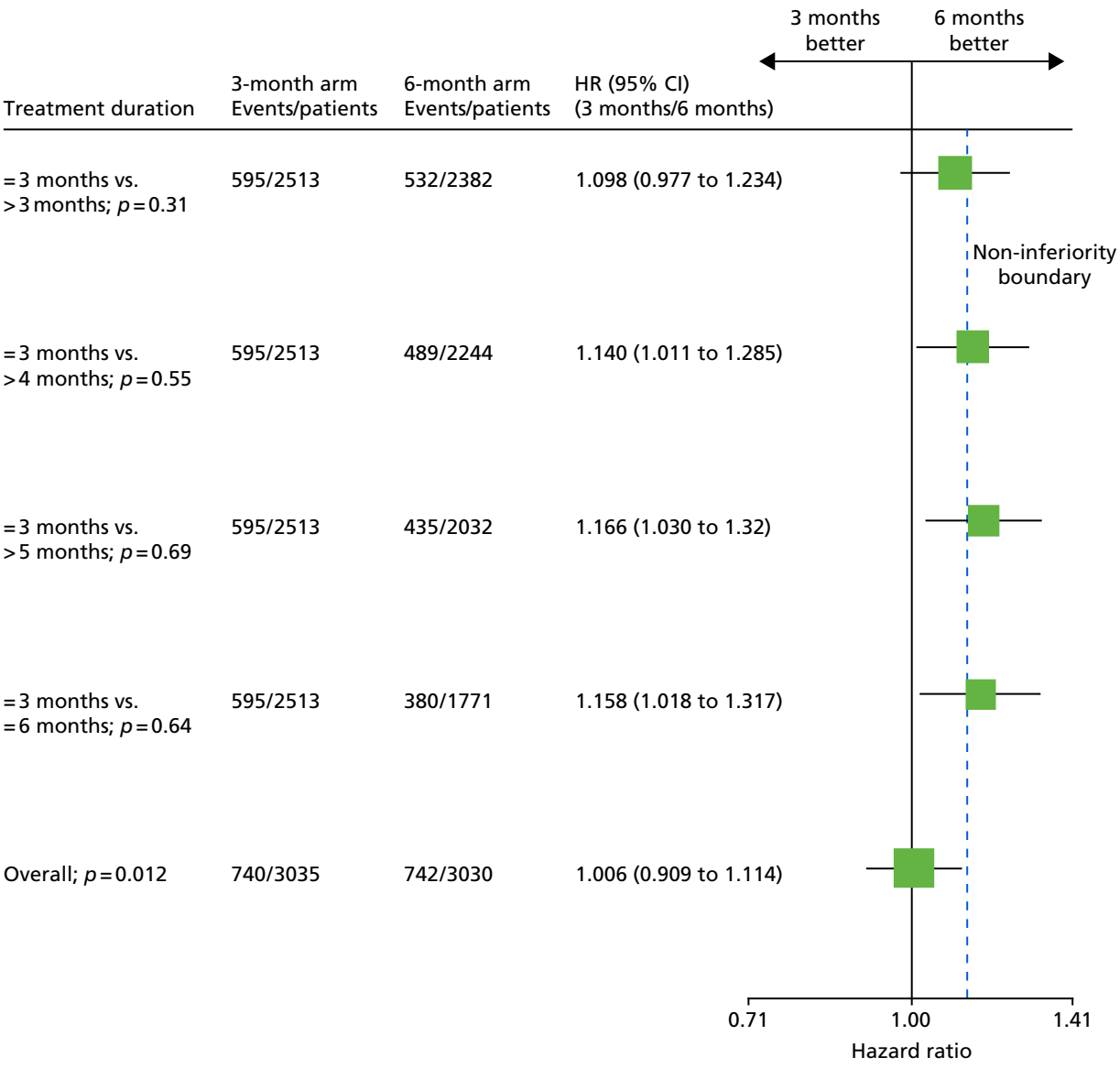
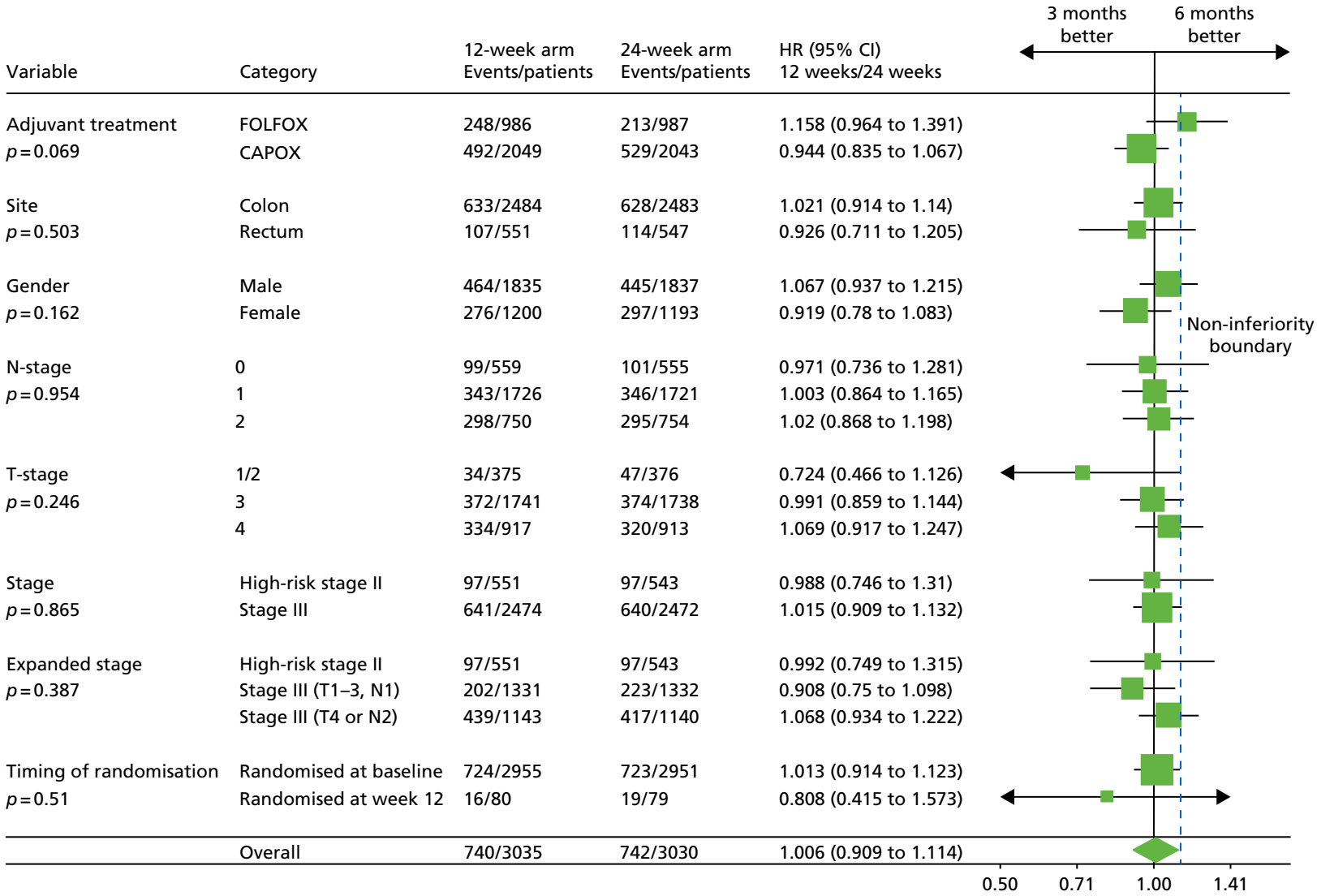


FIGURE 4 Plot of 3-month/6-month HR by actual treatment duration (analysis according to duration restricted to eligible patients who started treatment) with associated non-inferiority *p*-values. Reproduced from Iveson *et al.*[16]

Heterogeneity of the 3-month versus 6-month effect was assessed for the stratification factors used for randomisation and for the randomisation time-point. The resulting HRs, 95% CIs and *p*-values testing the heterogeneity of the treatment-duration effect for these subgroups are presented in *Figure 5*. The adjuvant treatment regimen selected at randomisation was associated with a trend towards heterogeneity in effect ($p = 0.069$).

Further (post hoc) analysis of DFS for patients receiving 3-month or 6-month duration adjuvant chemotherapy was conducted separately for patients who received oxaliplatin and 5FU and for patients who received oxaliplatin and capecitabine (*Figure 6*). For patients receiving oxaliplatin and capecitabine, the 3-year DFS rate for the 3-month treatment group was 76.9% (SE 1.0%) and for the 6-month treatment group was 76.1% (SE 1.0%), resulting in a HR of 0.944 (95% CI 0.835 to 1.067; $p_{NI} = 0.002$), which met the criteria for non-inferiority. However, for patients receiving oxaliplatin and 5FU, the 3-year DFS for the 3-month treatment group was 76.3% (SE 1.4%) and for the 6-month treatment group was 79.2% (SE 1.3%), resulting in a HR of 1.158 (95% CI 0.964 to 1.391; $p_{NI} = 0.591$), which did not meet the non-inferiority criteria.



Variable	Category	12-week arm Events/patients	24-week arm Events/patients	HR (95% CI) 12 weeks/24 weeks
Adjuvant treatment	FOLFOX	248/986	213/987	1.158 (0.964 to 1.391)
$p = 0.069$	CAPOX	492/2049	529/2043	0.944 (0.835 to 1.067)
Site	Colon	633/2484	628/2483	1.021 (0.914 to 1.14)
$p = 0.503$	Rectum	107/551	114/547	0.926 (0.711 to 1.205)
Gender	Male	464/1835	445/1837	1.067 (0.937 to 1.215)
$p = 0.162$	Female	276/1200	297/1193	0.919 (0.78 to 1.083)
N-stage	0	99/559	101/555	0.971 (0.736 to 1.281)
$p = 0.954$	1	343/1726	346/1721	1.003 (0.864 to 1.165)
	2	298/750	295/754	1.02 (0.868 to 1.198)
T-stage	1/2	34/375	47/376	0.724 (0.466 to 1.126)
$p = 0.246$	3	372/1741	374/1738	0.991 (0.859 to 1.144)
	4	334/917	320/913	1.069 (0.917 to 1.247)
Stage	High-risk stage II	97/551	97/543	0.988 (0.746 to 1.31)
$p = 0.865$	Stage III	641/2474	640/2472	1.015 (0.909 to 1.132)
Expanded stage	High-risk stage II	97/551	97/543	0.992 (0.749 to 1.315)
$p = 0.387$	Stage III (T1–3, N1)	202/1331	223/1332	0.908 (0.75 to 1.098)
	Stage III (T4 or N2)	439/1143	417/1140	1.068 (0.934 to 1.222)
Timing of randomisation	Randomised at baseline	724/2955	723/2951	1.013 (0.914 to 1.123)
$p = 0.51$	Randomised at week 12	16/80	19/79	0.808 (0.415 to 1.573)
	Overall	740/3035	742/3030	1.006 (0.909 to 1.114)

FIGURE 5 Disease-free survival and heterogeneity in subgroups by minimisation variables. Categories are listed as recorded at randomisation; 10 patients in the 3-month treatment group and 15 patients in the 6-month treatment group could not be allocated to high-risk stage II or stage III based on T/N data recorded at randomisation. CAPOX, oxaliplatin and capecitabine; FOLFOX, oxaliplatin and 5FU. Adapted from Iveson *et al.*[16]

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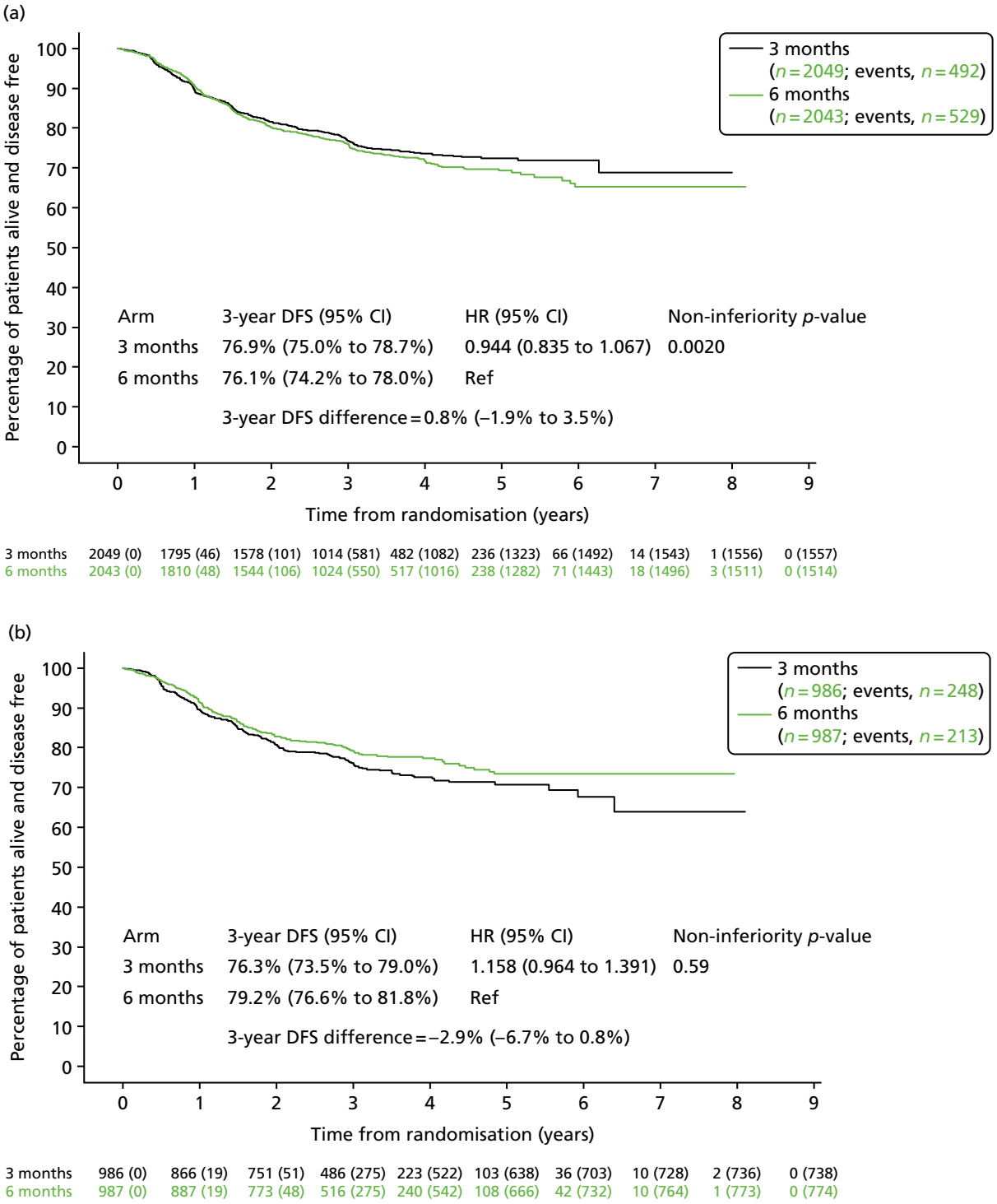

FIGURE 6 Disease-free survival by treatment group and adjuvant chemotherapy regimen. (a) CAPOX; and (b) FOLFOX. CAPOX, oxaliplatin and capecitabine; FOLFOX, oxaliplatin and 5FU. Adapted with minor corrections from Iveson *et al.*[16]

Previous clinical trials in patients with colorectal cancer have shown a marked difference in the risk of relapse between patients with T1–3, N1 disease and those with T4 or N2 disease.[29] Post hoc analyses were therefore conducted to assess whether or not disease stage affected DFS rate for patients with differing adjuvant treatment durations. Kaplan–Meier curves (*Figure 7*) showed that 3-year DFS for patients with T1–3, N1 primary disease in the 3-month treatment group reached 85.3% (SE 1.0%) and for the 6-month treatment group reached 84.0% (SE 1.0%), giving a HR of 0.907 (95% CI 0.749 to 1.097; $p_{NI} = 0.011$).

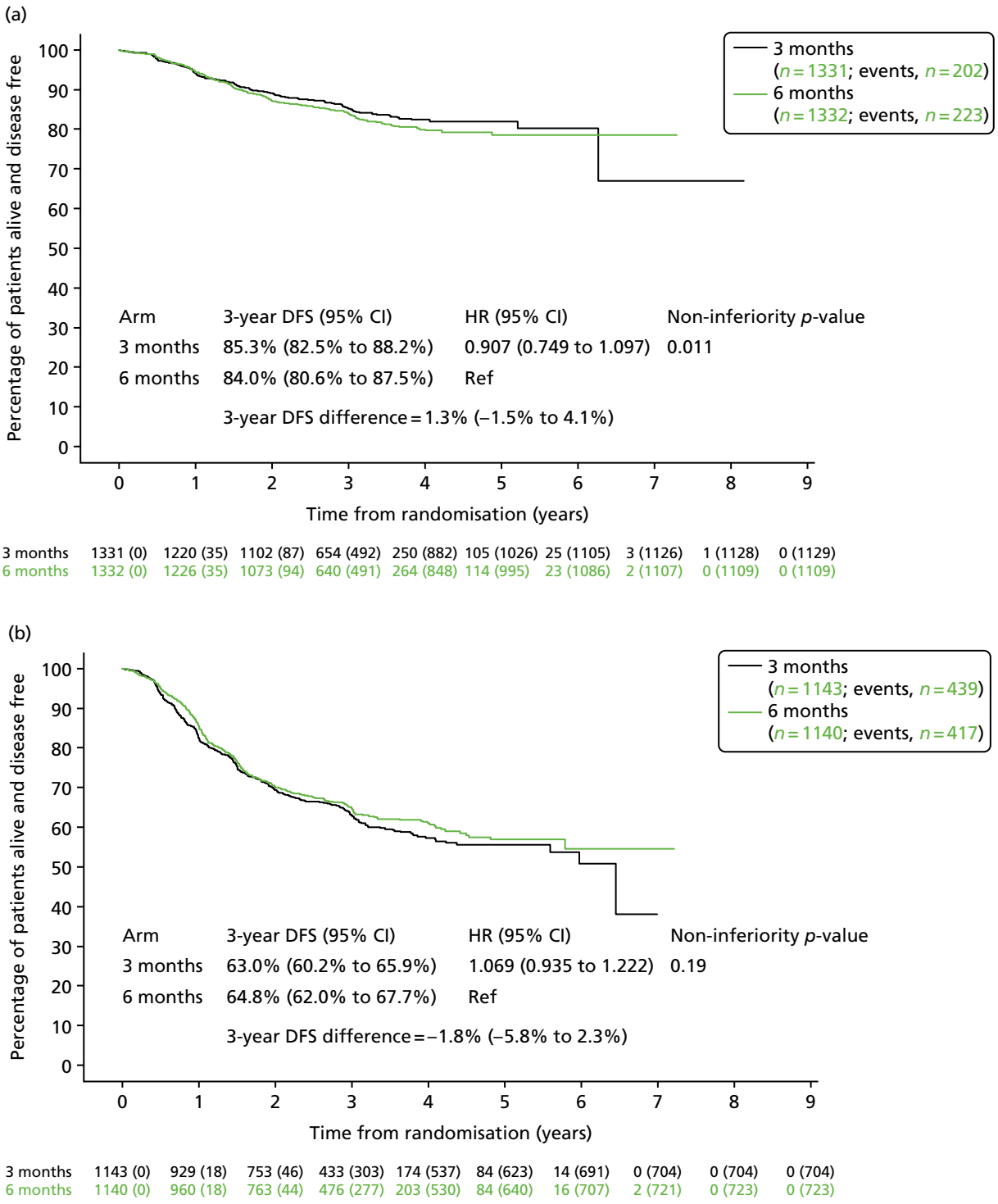

FIGURE 7 Disease-free survival by treatment group and disease stage. (a) T1–3 or N1; and (b) T4 or N2. Adapted with minor corrections from Iveson *et al.*[16] © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

For patients with T1–3, N1 disease non-inferiority was, therefore, demonstrated when comparing 3-month with 6-month chemotherapy. For stage III colorectal cancer patients with T4 and/or N2 pathology, 3-year DFS for the 3-month treatment group was 63.0% (SE 1.5%) and for the 6-month treatment group was 64.8% (SE 1.4%), giving a HR of 1.069 (95% CI 0.935 to 1.222; $p_{NI} = 0.19$), which did not meet the non-inferiority criteria.

Analysis of these prognostic groups according to the chemotherapy regimen they received (*Figure 8*) showed that Kaplan–Meier DFS curves suggest that 3 months of treatment with oxaliplatin and oxaliplatin (CAPOX) may be adequate both for T1–3, N1 and for T4 and/or N2 patients (most reliably for T1–3, N1), but this is not as clear for oxaliplatin and 5FU (FOLFOX), particularly for T4 and/or N2.

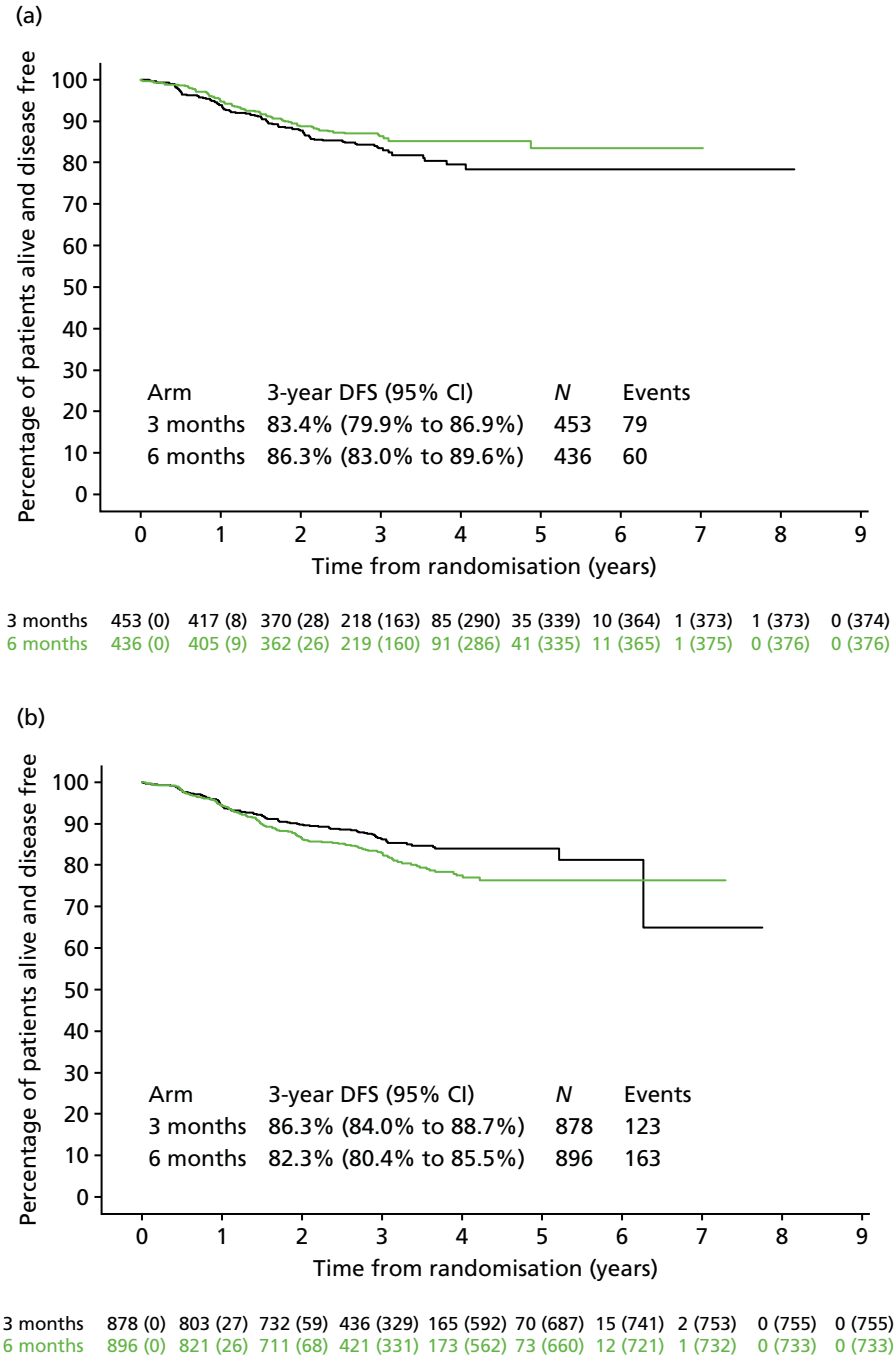

FIGURE 8 Disease-free survival by treatment group, disease stage, and adjuvant chemotherapy regimen. (a) Low-risk stage III (T1–3, N1)/FOLFOX; (b) low-risk stage III (T1–3, N1)/CAPOX; (c) high-risk stage III (T4 or N2)/FOLFOX; and (d) high-risk stage III (T4 or N2)/CAPOX. CAPOX, oxaliplatin and capecitabine; FOLFOX, oxaliplatin and 5FU. Adapted from Iveson *et al.*[16] (*continued*)

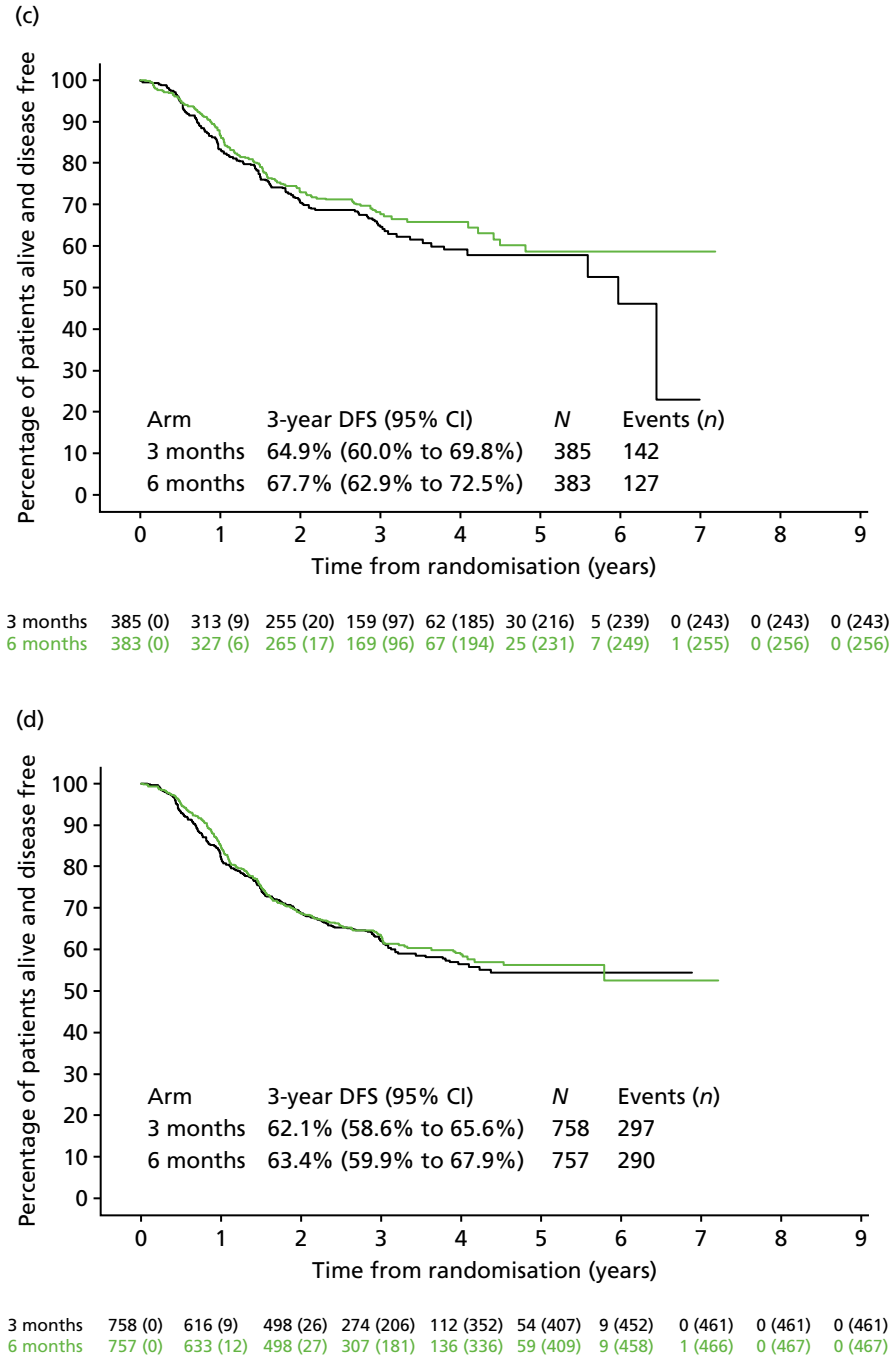

FIGURE 8 Disease-free survival by treatment group, disease stage, and adjuvant chemotherapy regimen. (a) Low-risk stage III (T1–3, N1)/FOLFOX; (b) low-risk stage III (T1–3, N1)/CAPOX; (c) high-risk stage III (T4 or N2)/FOLFOX; and (d) high-risk stage III (T4 or N2)/CAPOX. CAPOX, oxaliplatin and capecitabine; FOLFOX, oxaliplatin and 5FU. Adapted from Iveson *et al.*[16] © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

Note that although curves in some of the subgroups in *Figures 7* and *8* cross, there is no suggestion in any case that the proportional-hazards assumption is violated (minimum *p*-value testing for non-proportionality, $p = 0.226$).

Overall survival

By the time of analysis, 787 participants in the 3-month treatment group had died [393 (12.9% of 3035 in the efficacy analysis) and 394 participants in the 6-month treatment group had died (13.0% of the 3030 in the efficacy analysis). The 3-year overall survival rate for the 3-month treatment group was 90.0% (SE 0.6%) and for the 6-month treatment group was 89.6% (SE 0.6%), equating to a HR of 0.994 (95% CI 0.964 to 1.143; $p_{NI} = 0.035$; see *Figure 3b*). Sixteen deaths in each treatment group were considered related to study medication.

Safety

The occurrence of AEs was analysed for a total of 868 patients, comprising 434 patients in each treatment group. *Table 3* shows the maximum NCI CTCAE grade recorded per patient for AEs with an incidence of ≥ 10% in either treatment group. Most of these events (alopecia, anaemia, anorexia, diarrhoea, fatigue, hand–foot syndrome, mucositis, sensory neuropathy, neutropenia, pain, rash, altered taste, thrombocytopenia and watery eye) showed a statistically significant increase in grade for the 6-month treatment group compared with the 3-month treatment group.

The overall frequency of grade ≥ 3 toxicity was 59.4% for 6-month duration adjuvant chemotherapy and 35.7% for 3-month adjuvant chemotherapy ($p < 0.001$). Sensory neuropathy, diarrhoea, neutropenia, fatigue, pain, nausea and hand–foot syndrome were the most common grade ≥ 3 AEs reported. The difference in frequency between treatment groups was statistically significant for diarrhoea ($p = 0.033$), neutropenia ($p = 0.023$), pain ($p = 0.014$), hand–foot syndrome ($p = 0.031$) and sensory neuropathy ($p < 0.001$). The AE for which there was the most marked increase in the proportion of patients with grade ≥ 3 with 6-month adjuvant chemotherapy was sensory neuropathy (16.4% vs. 4.3% with 3-month treatment).

The proportion of those with febrile neutropenia was 1.6% of patients for the 3-month treatment group and 1.2% for the 6-month treatment group. *Figure 9* shows that diarrhoea and hand–foot syndrome were more common in patients receiving oxaliplatin and capecitabine and that neutropenia was more common in those receiving oxaliplatin and 5FU.

A total of 244 patients in the 3-month treatment group and 576 patients in the 6-month treatment group cited AEs as the reason for stopping treatment early. The most frequently cited AEs leading to treatment discontinuation were diarrhoea ($n = 90$ patients) for the 3-month treatment group, and diarrhoea ($n = 150$ patients) and peripheral neuropathy ($n = 156$ patients) for the 6-month treatment group.

Serious adverse reactions were reported for 421 patients in the 3-month treatment group and for 511 patients in the 6-month treatment group. Gastrointestinal SAEs were most common and occurred in similar proportions of patients in both groups. Thirty-two patients died owing to events attributed to treatment toxicity, with the events distributed equally between the groups (16 patients died in each group); 27 of these deaths occurred during the first 3 months of treatment. A total of 21 patients of the 4108 who received oxaliplatin and capecitabine (0.51%) and 11 patients of the 1980 who received oxaliplatin and 5FU (0.56%) were reported to have died from toxicity.

Peripheral neuropathy was also assessed using a patient-reported outcome (PRO) FACT/GOG-Ntx4 questionnaire. Data were available for 2871 patients who were assessed for up to 7 years. The mean FACT/GOG-Ntx4 questionnaire neuropathy scores for patients receiving 3-month and 6-month adjuvant chemotherapy are shown in *Figure 10*. The neurotoxicity standardised-adjusted AUC differed markedly between the groups ($p < 0.001$), with a higher rate of neuropathy for the 6-month treatment group being clearly apparent from 4 months and persisting to ≥ 5 years ($p < 0.001$). Peak neuropathy occurred at 6 months for the 3-month treatment group and at 9 months for the 6-month treatment group.

TABLE 3 Maximum NCI CTCAE grade of toxicity recorded during treatment by randomised treatment group (for toxicities with an incidence of ≥ 10%)

	Randomised treatment group, *n* (%)													
	3 months of treatment (*N* = 434)					6 months of treatment (*N* = 434)						*p*-value (comparison of ordered categories)	*p*-value (comparison of percentage of grade 3/4/5 adverse events)	Odds ratio for incidence of grade 3/4/5 toxicities (6 months/3 months) from logistic regression (CI)
Adverse event	0	1–2	3	4	Missing	0	1–2	3	4	5	Missing			
Alopecia	345 (83.3)	69 (16.7)	0 (0.0)	0 (0.0)	20 (–)	309 (76.1)	97 (23.9)	0 (0.0)	0 (0.0)	0 (0.0)	28 (–)	0.0094	–	Not estimable
Anaemia	270 (64.7)	143 (34.3)	2 (0.5)	2 (0.5)	17 (–)	212 (52.2)	190 (46.8)	3 (0.7)	1 (0.2)	0 (0.0)	28 (–)	0.00013	1.00	1.027 (0.255–0.4.136)
Anorexia	312 (75.9)	92 (22.4)	7 (1.7)	0 (0.0)	23 (–)	262 (64.7)	140 (34.6)	3 (0.7)	0 (0.0)	0 (0.0)	29 (–)	0.00043	0.34	0.431 (0.111–1.677)
Constipation	289 (69.8)	122 (29.5)	2 (0.5)	1 (0.2)	20 (–)	268 (66.0)	135 (33.3)	3 (0.7)	0 (0.0)	0 (0.0)	28 (–)	0.28	1.00	1.010 (0.205–5.083)
Diarrhoea	128 (30.7)	243 (58.3)	44 (10.6)	2 (0.5)	17 (–)	99 (24.4)	241 (59.4)	63 (15.5)	2 (0.5)	1 (0.2)	28 (–)	0.0079	0.033	1.566 (1.045–2.345)
Fatigue	58 (14.0)	320 (77.1)	35 (8.4)	2 (0.5)	19 (–)	41 (10.1)	333 (82.0)	32 (7.9)	0 (0.0)	0 (0.0)	28 (–)	0.022	0.62	0.874 (0.533–1.433)
Hand–foot syndrome	277 (66.9)	129 (31.2)	8 (1.9)	0 (0.0)	20 (–)	218 (53.7)	169 (41.6)	18 (4.4)	1 (0.2)	0 (0.0)	28 (–)	<0.0001	0.031	2.492 (1.078–5.758)
Mucositis (clinical exam)	355 (86.0)	56 (13.6)	2 (0.5)	0 (0.0)	21 (–)	320 (79.0)	83 (20.5)	1 (0.2)	0 (0.0)	1 (0.2)	29 (–)	0.013	1.00	1.020 (0.143–7.275)
Mucositis (functional/ symptomatic)	283 (68.4)	127 (30.7)	4 (1.0)	0 (0.0)	20 (–)	242 (59.6)	159 (39.2)	4 (1.0)	0 (0.0)	1 (0.2)	28 (–)	0.0066	0.75	1.278 (0.341–4.794)
Nausea	147 (35.3)	249 (59.9)	20 (4.8)	0 (0.0)	18 (–)	120 (29.6)	277 (68.2)	9 (2.2)	0 (0.0)	0 (0.0)	28 (–)	0.26	0.057	0.449 (0.202–0.998)
Neuropathy: sensory	37 (8.8)	365 (86.9)	18 (4.3)	0 (0.0)	14 (–)	28 (6.8)	314 (76.8)	65 (15.9)	2 (0.5)	0 (0.0)	25 (–)	<0.0001	<0.0001	4.375 (2.550–7.508)
Neutropenia	287 (69.0)	90 (21.6)	23 (5.5)	16 (3.8)	18 (–)	221 (54.4)	127 (31.3)	43 (10.6)	14 (3.4)	1 (0.2)	28 (–)	<0.0001	0.031	1.611 (1.046–2.480)
Pain: other (specify)	311 (74.0)	99 (23.6)	10 (2.4)	0 (0.0)	14 (–)	278 (68.0)	107 (26.2)	24 (5.9)	0 (0.0)	0 (0.0)	25 (–)	0.026	0.014	2.556 (1.206–5.415)
Rash	359 (86.9)	52 (12.6)	2 (0.5)	0 (0.0)	21 (–)	320 (79.0)	84 (20.7)	1 (0.2)	0 (0.0)	0 (0.0)	29 (–)	0.00061	1.00	0.509 (0.046–5.632)
Taste alteration	231 (56.1)	180 (43.7)	1 (0.2)	0 (0.0)	22 (–)	179 (44.4)	222 (55.1)	2 (0.5)	0 (0.0)	0 (0.0)	31 (–)	0.0021	0.57	2.050 (0.185–22.696)
Thrombocytopenia	290 (69.7)	117 (28.1)	5 (1.2)	4 (1.0)	18 (–)	253 (62.3)	145 (35.7)	5 (1.2)	2 (0.5)	1 (0.2)	28 (–)	0.020	1.00	0.909 (0.347–2.380)
Vomiting	304 (73.1)	98 (23.6)	14 (3.4)	0 (0.0)	18 (–)	270 (66.5)	126 (31.0)	10 (2.5)	0 (0.0)	0 (0.0)	28 (–)	0.056	0.54	0.725 (0.318–1.652)
Watery eye	339 (82.7)	71 (17.3)	0 (0.0)	0 (0.0)	24 (–)	310 (76.7)	92 (22.8)	2 (0.5)	0 (0.0)	0 (0.0)	30 (–)	0.028	0.25	Not estimable

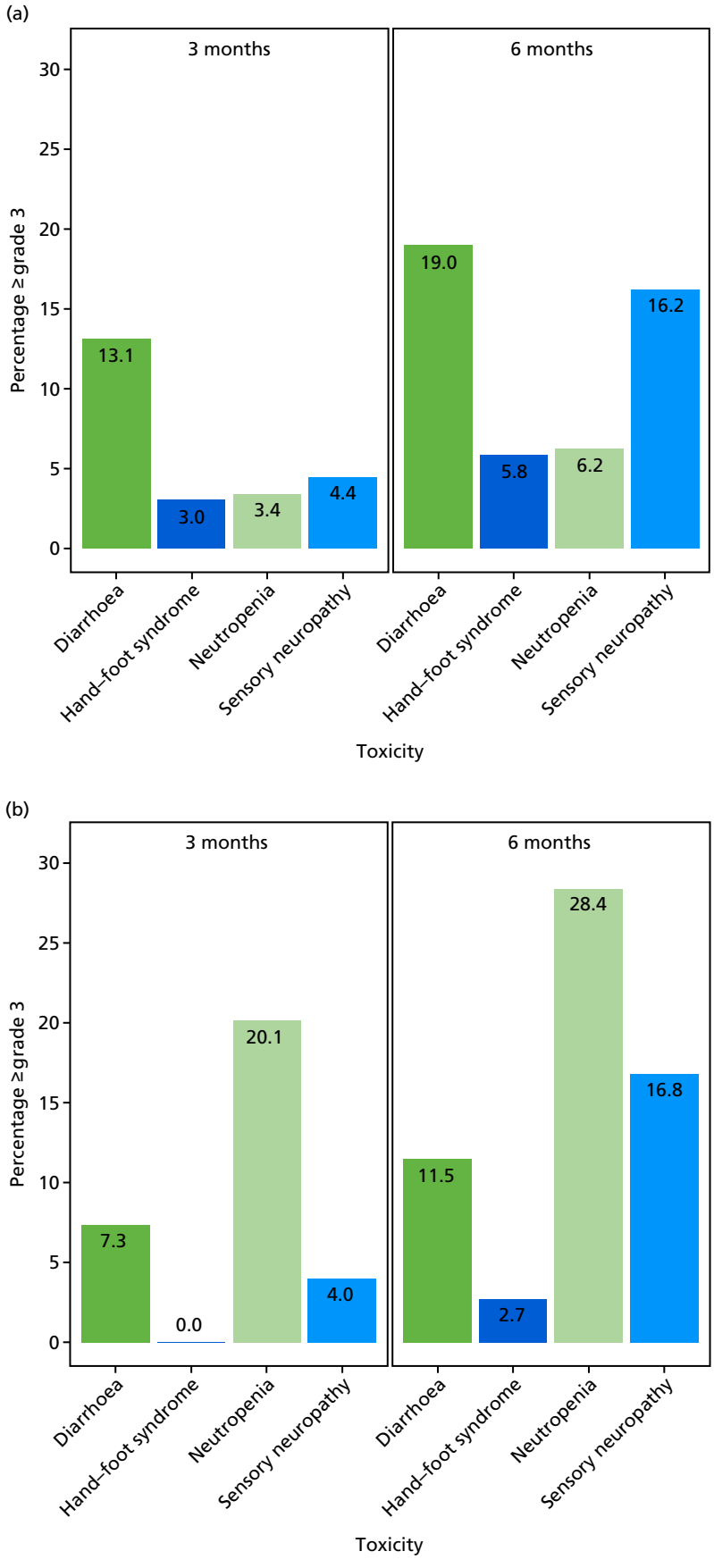

FIGURE 9 Frequency of patients with selected grade ≥ 3 toxicities, by treatment group and treatment regimen. (a) CAPOX 3 months; (b) CAPOX 6 months; (c) FOLFOX 3 months; and (d) FOLFOX 3 months. CAPOX, oxaliplatin and capecitabine; FOLFOX, oxaliplatin and 5FU.

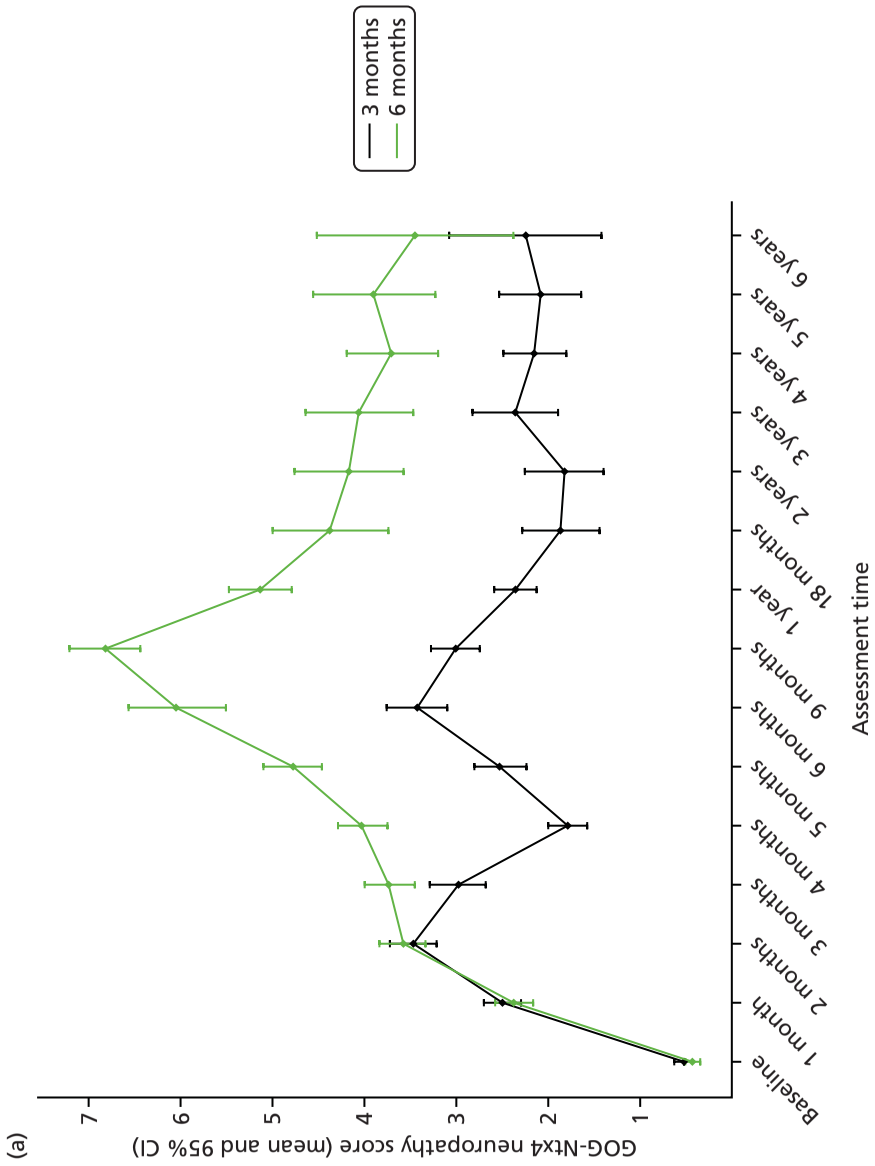

FIGURE 10 Peripheral neuropathy score, by treatment group. Data beyond year 6 were omitted because of small numbers. Error bars show 95% CIs. a, Low completion rate at these time points reflect the fact that neurotoxicity data were initially collected only up to 12 months; b, low return rate because patients were assessed at the start of the last cycle rather than at 6 months. Adapted from Iveson *et al.*[16] © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/). (*continued*)

(b)

		Number of patients completing questionnaire														
		Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Year 1	Month 18[a]	Year 2[a]	Year 3[a]	Year 4	Year 5	Year 6
3 months of treatment	Completed (*n*)	859	817	782	527	639	638	606	733	721	172	169	198	286	193	54
	Expected (*n*)	1445	1433	1426	1421	1416	1413	1400	1386	1366	1312	1202	887	590	313	84
	Expected (%)	59	57	55	37	45	45	43	53	53	13	14	22	49	62	64
6 months of treatment	Completed (*n*)	865	796	782	701	679	624	298	665	721	182	174	199	257	170	54
	Expected (*n*)	1426	1406	1395	1389	1384	1382	1375	1366	1346	1308	1195	887	610	317	85
	Expected (%)	61	57	56	51	49	45	20[b]	49	54	13	15	22	42	54	64

FIGURE 10 Peripheral neuropathy score, by treatment group. Data beyond year 6 were omitted because of small numbers. Error bars show 95% CIs. a, Low completion rate at these time points reflect the fact that neurotoxicity data were initially collected only up to 12 months; b, low return rate because patients were assessed at the start of the last cycle rather than at 6 months. Adapted from Iveson *et al.*[16]

Health-related quality of life

A total of 1829 patients provided data on the EORTC questionnaires. Global health status and all functional and symptom scales of the EORTC QLQ-C30 showed statistically significant differences in terms of standardised-adjusted AUC, indicating better functioning and fewer side effects in patients receiving 3-month adjuvant chemotherapy. Scores for the two groups mirrored each other over the first 3 months of treatment but subsequently improved from months 4 to 6 for patients in the 3-month treatment group, indicative of functional improvement and decreased side effects in those who stopped treatment at 3 months (*Figure 11*). For the EORTC QLQ-CR29, statistically significant differences were apparent for body image ($p = 0.037$), dry mouth ($p < 0.0001$), hair loss ($p = 0.035$) and taste ($p < 0.0001$) scales. The magnitudes of the mean differences in functional and global health status scales between treatment groups were indicative of 'moderate' differences for global health status, role functioning, and social function and 'a little' difference for physical, emotional and cognitive functions.[22]

A total of 1828 patients provided data on the EQ-5D. Statistically significant differences in standardised-adjusted AUC were seen for both the EQ-5D self-rated visual analogue scale ($p = 0.00081$) and the EQ-5D-3L health index ($p = 0.00081$). Differences between the two treatment groups were apparent from months 4 to 6 (*Figure 12*), consistent with the time when those in the 6-month treatment group were still receiving treatment but those in the 3-month treatment group had finished. From 9 months to the 7-year follow-up, there were no clinically relevant differences[23] between the treatment groups.

Given the notable number of missing data for HRQoL assessments (FACT/GOG-Ntx4, EORTC and EQ-5D), the reasons for missing questionnaires were analysed and are presented in *Appendix 2*. Missing questionnaire data were generally related to various errors. Patients who did complete questionnaires were shown to be representative of the overall study population, with no indication that missing data were associated with any particular baseline characteristic. Sensitivity analyses comparing the primary results with those based on just observed data or using data imputed only for patients who completed baseline questionnaires showed similar results.

Exploratory analysis considered differences in HRQoL scales when comparing patients with 'quite a bit'/'very much' numbness or tingling or discomfort in hands or feet on the FACT/GOG-Ntx4 toxicity questionnaire with those who rated these symptoms as 'somewhat'/'a little bit'/'not at all'. The proportion of patients recording neuropathy symptoms as being present 'quite a bit' or 'very much' was higher for patients in the 6-month treatment group at 1 year (34% vs. 14% of patients in the 3-month treatment group), 3 years (32% vs. 17%) and 5 years (29% vs. 16%). This analysis consistently demonstrated statistically significantly poorer HRQoL across the different scales for patients who had 'quite a bit' or 'very much' recorded for neuropathy symptoms, at all time points ($p < 0.001$; *Figure 13*).

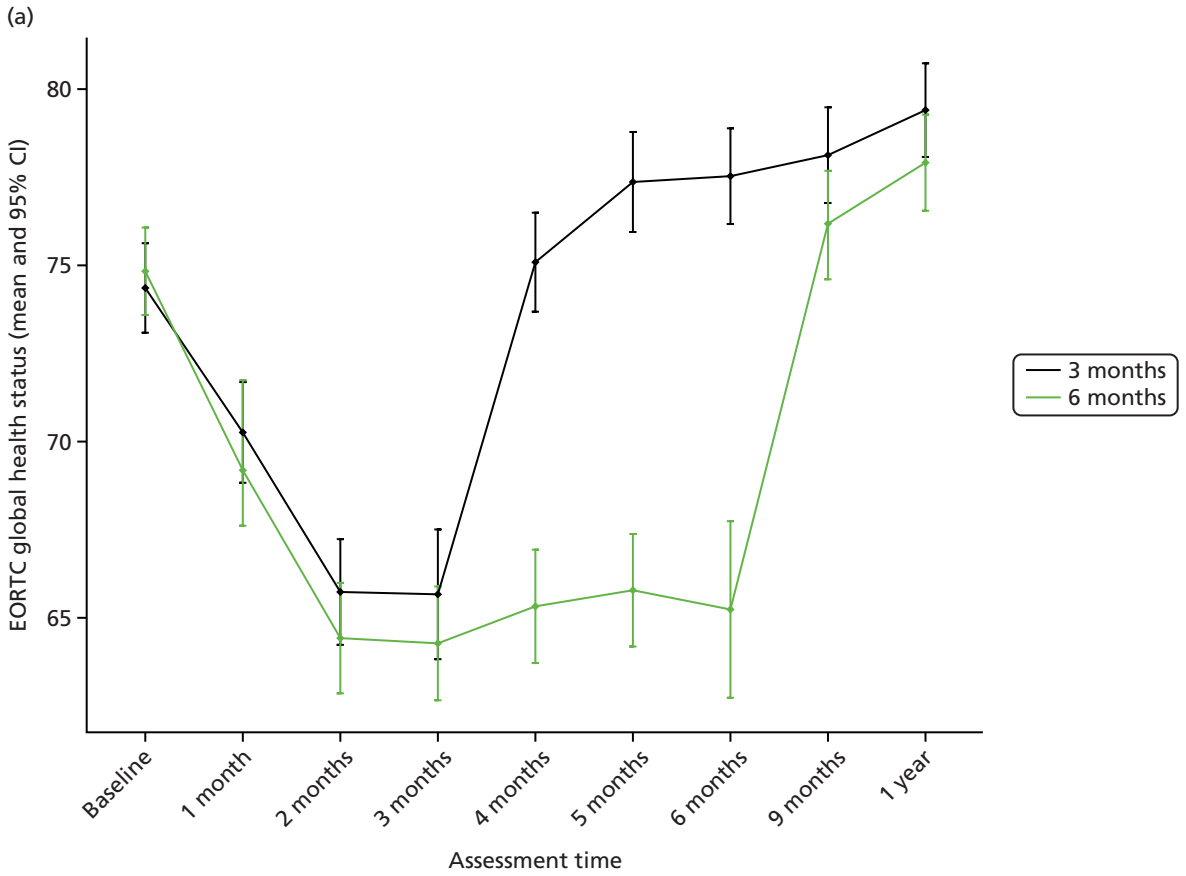

FIGURE 11 The EORTC global health status, by treatment group. a, Low return rate as patients were assessed at the start of the last cycle rather than at 6 months. Reproduced from Iveson *et al.*[16] © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/). (*continued*)

(b)

Number of patients completing questionnaire										
		Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Year 1
3 months of treatment	Completed (*n*)	796	719	660	456	543	522	509	642	593
	Expected (*n*)	916	908	901	898	894	891	882	877	866
	Expected (%)	87	79	73	51	61	59	58	73	69
6 months of treatment	Completed (*n*)	794	677	664	597	554	504	204	554	582
	Expected (*n*)	913	902	895	889	886	885	878	873	863
	Expected (%)	87	75	74	67	63	57	23[a]	64	67

FIGURE 11 The EORTC global health status, by treatment group. a, Low return rate as patients were assessed at the start of the last cycle rather than at 6 months. Reproduced from Iveson *et al.*[16] © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

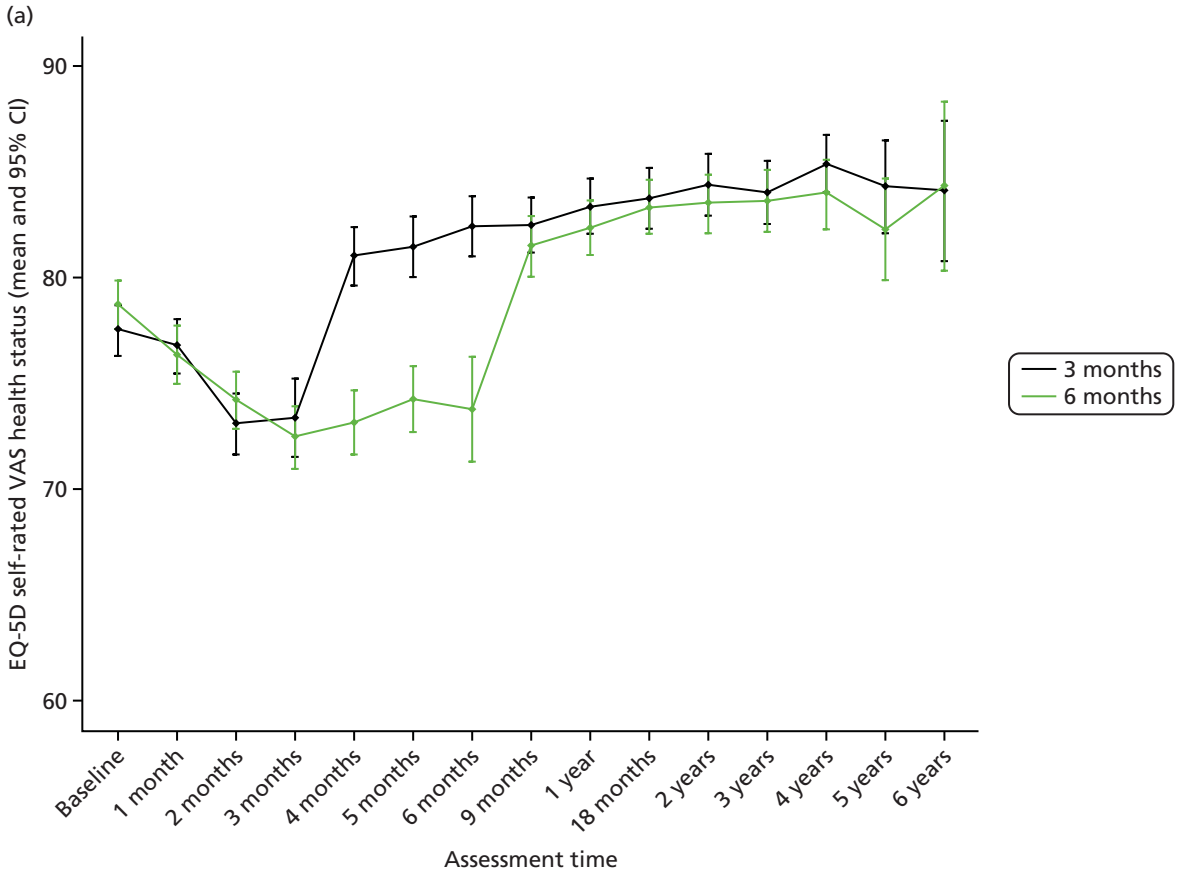

FIGURE 12 The EQ-5D self-rated visual analogue scale, by treatment group. Data beyond year 6 were omitted because of small numbers. a, Low return rate as patients were assessed at the start of the last cycle rather than at 6 months. VAS, visual analogue scale. Reproduced from Iveson *et al.*[16] © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/). (*continued*)

(b)

Number of patients completing questionnaire															
		Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Year 1	Month 18	Year 2	Year 3	Year 4	Year 5	Year 6
3 months of treatment	Completed (*n*)	692	631	594	415	498	478	470	571	541	528	497	423	362	197	59
	Expected (*n*)	916	907	901	898	894	891	882	877	865	842	807	752	588	317	84
	Expected (%)	76	70	66	46	56	54	53	65	63	63	62	56	62	62	70
6 months of treatment	Completed (*n*)	695	599	591	543	509	457	186	497	541	512	492	408	341	191	58
	Expected (*n*)	912	902	895	889	886	884	878	873	862	848	815	761	617	319	86
	Expected (%)	76	66	66	61	57	52	21[a]	57	63	60	60	54	55	60	67

FIGURE 12 The EQ-5D self-rated visual analogue scale, by treatment group. Data beyond year 6 were omitted because of small numbers. a, Low return rate as patients were assessed at the start of the last cycle rather than at 6 months. VAS, visual analogue scale. Reproduced from Iveson *et al.*[16] © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

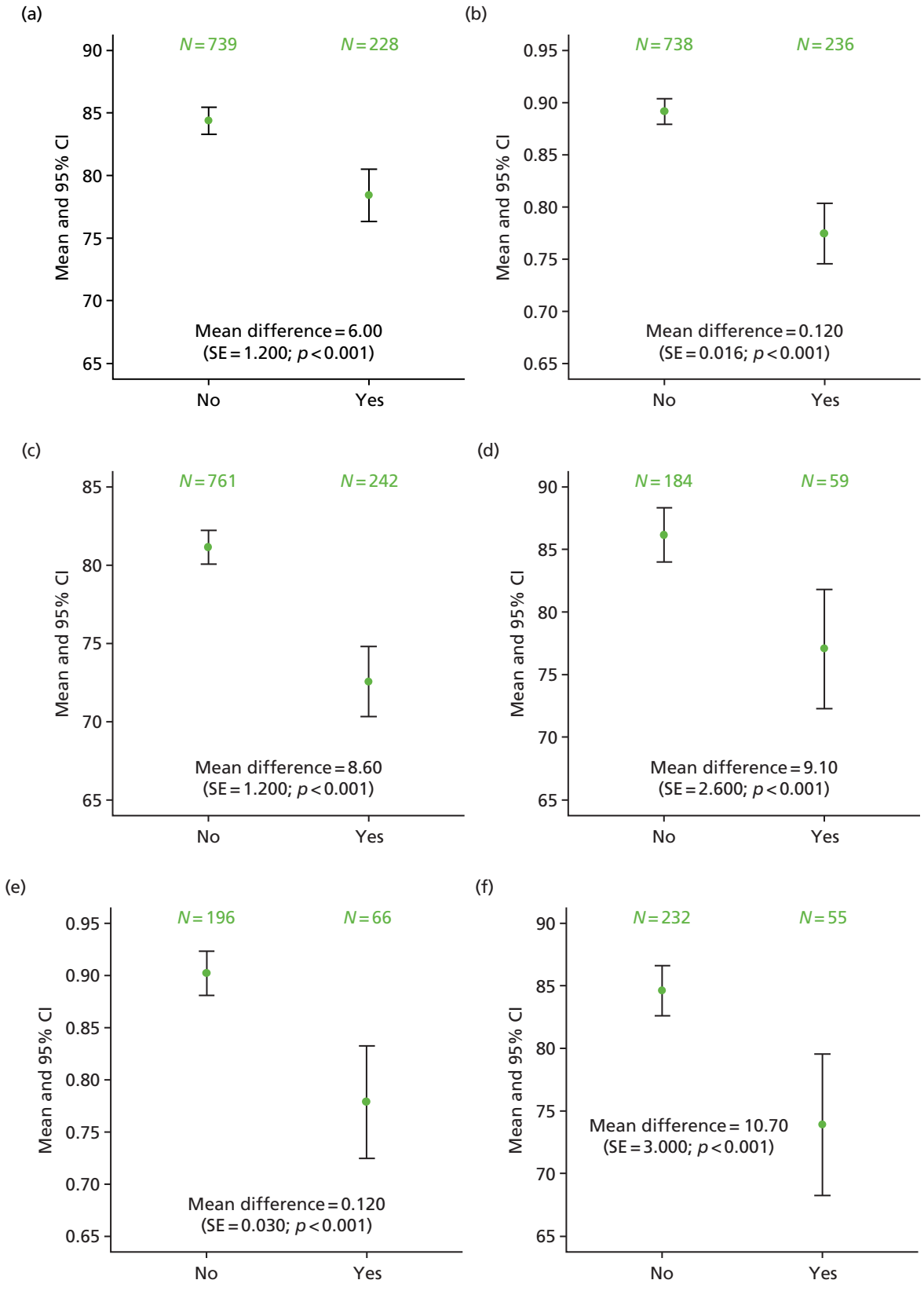

FIGURE 13 Differences in HRQoL assessments based on the degree of numbness/tingling/discomfort in hands or feet. (a) EQ-5D visual analogue scale 1 year; (b) EQ-5D-3L health index 1 year; (c) EORTC global quality of life 1 year; (d) EQ-5D visual analogue scale 3 years; (e) EQ-5D-3L health index 3 years; (f) EQ-5D visual analogue scale 5 years; and (g) EQ-5D-3L health index 5 years. No/yes on all the x-axes refers to whether or not the patient experienced 'quite a bit/very much numbness or tingling or discomfort in hands or feet' on the FACT/GOG-Ntx4 toxicity score. Adapted from Iveson *et al.*[16] (*continued*)

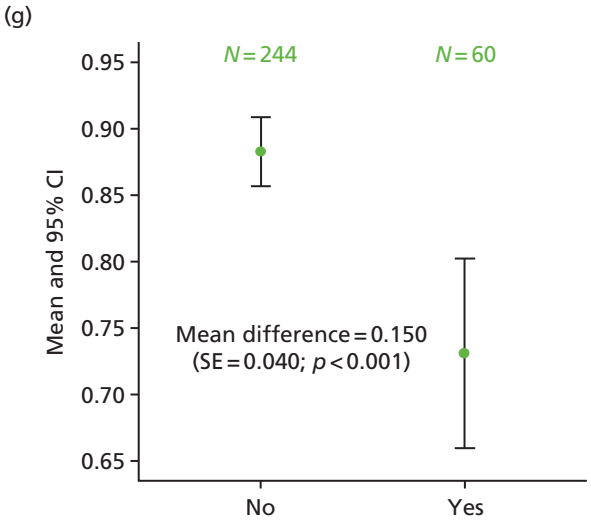

FIGURE 13 Differences in HRQoL assessments based on the degree of numbness/tingling/discomfort in hands or feet. (a) EQ-5D visual analogue scale 1 year; (b) EQ-5D-3L health index 1 year; (c) EORTC global quality of life 1 year; (d) EQ-5D visual analogue scale 3 years; (e) EQ-5D-3L health index 3 years; (f) EQ-5D visual analogue scale 5 years; and (g) EQ-5D-3L health index 5 years. No/yes on all the x-axes refers to whether or not the patient experienced 'quite a bit/very much numbness or tingling or discomfort in hands or feet' on the FACT/GOG-Ntx4 toxicity score. Adapted from Iveson *et al.*[16]

Chapter 4 Economic analyses

Methodology

The economic analysis was undertaken from the perspective of the UK NHS and Personal Social Services for the 2016 base year, adhering to good practice guidelines.[30,31] A within-trial analysis utilised the individual patient-level data on resource use, HRQoL (EQ-5D-3L) and survival.

Outcome data

The effectiveness measure for the economic analysis was the discounted QALY gain per patient; QALYs were calculated using quality-adjusted survival analysis.[32] Overall survival data from the SCOT study were partitioned into three health states: time on treatment (ToT), disease-free state post treatment and recurrence (*Figure 14*). The model begins with patients who have undergone surgery and are now assumed to be disease-free, who begin treatment with chemotherapy (ToT state). After completing treatment, patients move into the disease-free state and remain here until they experience a recurrence or die. Patients who experience a recurrence remain in the recurrence state until they die.

Kaplan–Meier survival estimates were used for computation of quality-adjusted survival time in each health state over the 8-year within-trial period. A separate model estimated HRQoL for each health state.

The EQ-5D-3L data were collected for a subsample of 1832 patients (about 30% of the study sample) at baseline and all follow-up times and combined with the UK EQ-5D-3L health-utility scores[20] to calculate utilities. *Table 4* details the characteristics of patients by EQ-5D subsample in comparison with the whole study sample. An interim analysis[33] of the SCOT study EQ-5D and AE data showed that adequate data were collected from the first 1832 patients in the SCOT study; therefore, discontinuation of the EQ-5D was recommended for new study recruits beyond that point. To control for plausible differences between the EQ-5D and total study populations, the HRQoL model included co-variables such as planned treatment, high-risk disease, gender, age and ethnicity. The model predicts health utilities for the average characteristics of the patients in each health state.

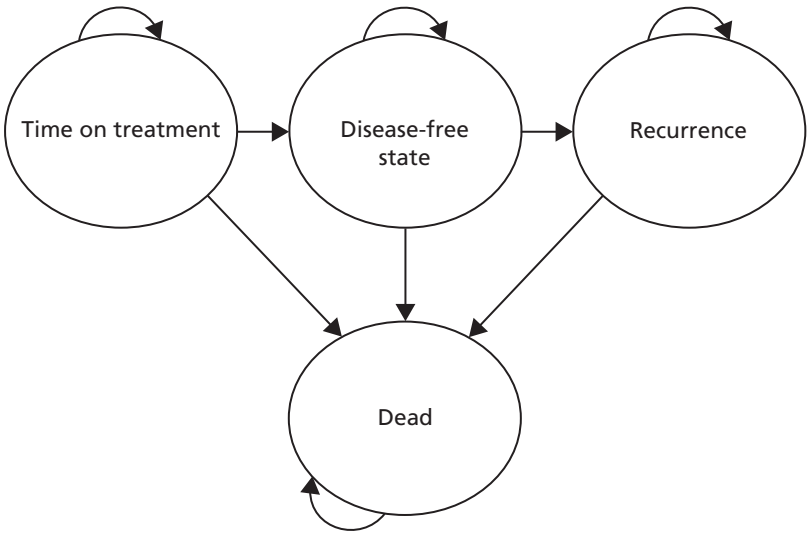

FIGURE 14 Partitioned survival model.

TABLE 4 Patient characteristics by EQ-5D subsample

Characteristic	Total ($N = 6065$)	Non-EQ-5D ($N = 4308$)	EQ-5D ($N = 1757$)	*p*-value
Planned treatment (%)				
Oxaliplatin and capecitabine	67.5	67.5	67.5	
Oxaliplatin and 5FU	32.5	32.5	32.5	0.99
Gender (%) and age (mean)				
Female	39.46	39.65	38.99	
Male	60.54	60.35	61.01	0.633
Age	63.43	63.35	63.62	0.3094
Disease risk (%)				
High	53.19	54.32	50.43	
Low	46.81	45.68	49.57	0.006
Ethnicity (%)				
White/Caucasian	94.02	82.61	77.95	
African/Caribbean	1.37	1.09	0.97	
South Asian	1.42	1.02	0.86	
Chinese	0.4	0.25	0.19	
Other	2.79	15.04	20.03	< 0.001

Note
Differences between groups were tested with a chi-squared test (planned treatment, gender, disease risk and ethnicity) or *t*-test (age).

A linear regression with SEs clustered at the individual level estimated the HRQoL, including the following independent variables: health state, treatment group and individual characteristics. Time in the health states – ToT, disease-free state and recurrence – was computed by integration of the Kaplan–Meier curves and then adjusted by HRQoL using the method of integrated quality-survival product to compute QALYs. This approach to quality-adjusted survival analysis avoids problems with informative censoring in survival analysis based on individual QALYs as an end point.[34]

Cost data

The main cost categories were chemotherapy treatment and hospitalisation. Costs associated with patient treatment were calculated by measuring and valuing resources used by trial participants during the treatment and follow-up periods. Patient-level resource-use data were collected for adjuvant chemotherapy dose/duration and hospitalisation during treatment and follow-up for the whole study sample. Costs were valued in 2016 Great British pounds. The oxaliplatin, capecitabine and 5FU doses administered were recorded, and the numbers of each were combined with their unit costs; the cost per mg of each drug was obtained from the *British National Formulary* 73, where the lowest price per unit available was used.[35] Hospitalisation costs incurred by patients receiving adjuvant chemotherapy and being treated for adverse reactions were recorded. Hospitalisation resource use data included overnight stays in an intensive care unit, a high-dependency unit and general medicine wards,[36] and inpatient chemotherapy administration as well as day cases and outpatient cases. Primary care costs (general practitioner visits) were less relevant to this context and were therefore excluded. Direct and non-direct costs for each hospitalisation were obtained from the Information Services Division of NHS Scotland.[37] Direct costs were attributed to medical, nursing, health professional, pharmacy, theatre, laboratory and other costs. For inpatient and day cases occurring within the treatment period, the pharmacy cost was subtracted to avoid double-counting

chemotherapy medication. The cost of treating AEs was assumed to be included in hospitalisation costs for patients attending hospital for night or day cases or during outpatient visits.

Given that the follow-up period differed among patients, the total cost per patient was estimated as the Kaplan–Meier survival analysis;[38] this allowed the average total cost to be estimated as the sum of the average cost for each period multiplied by the probability of surviving at the beginning of the period.

Cost-effectiveness

The cost and QALY outcomes for each treatment group were estimated and combined with the upper UK decision threshold for cost-effectiveness of £30,000 per QALY[30] to report outcomes in terms of NMB according to good reporting practice guidance.[39] The incremental NMB is the difference between the NMB of the two groups.

Analyses were performed using Stata 14.0 (StataCorp LP, College Station, TX, USA) to compare mean cost and mean QALY differences between the treatment groups (3-month vs. 6-month treatment) and the NMB was reported in line with recent reporting guidelines[39] and the UK reference case.[30] Discounting of costs and QALY outcomes beyond 1 year was applied at a rate of 3.5%.[30]

Bootstrapping (1000 iterations)[40] was used to account for uncertainty around the difference in costs and QALYs and to assess how this uncertainty affects the cost-effectiveness outcome. Uncertainty was reported through CIs and the computation of cost-effectiveness acceptability probabilities was estimated as a function of the threshold for the monetary value of a QALY.[41] Subgroup analyses were undertaken, in line with the main trial analyses, to consider cost-effectiveness of the two treatment duration strategies according to planned treatment regimen (oxaliplatin and 5FU or oxaliplatin and capecitabine), disease risk (high or low), gender and age.

Results

Cost-effectiveness analyses were conducted on information provided by the 6065 patients who consented to their data being used (see *Figure 1*).

Effectiveness

Kaplan–Meier estimates up to 8 years after randomisation were used to determine how overall survival time would be split into the three health states – ToT, disease-free and recurrence – for the two treatment groups, as shown in *Table 5*. As would be expected, ToT was significantly higher for patients in the 6-month treatment group, whereas disease-free was just outside the 5% statistical-significance level but

TABLE 5 Overall survival time (restricted mean survival) up to 8 years by health status and treatment group

Survival analysis (restricted mean survival)	3-month treatment, mean ($n = 3035$ patients)	6-month treatment, mean ($n = 3030$ patients)	Incremental difference	
			Mean	*p*-value
Time-on-treatment[a]	0.21	0.39	–0.18	0.000
Disease-free	5.93	5.74	0.19	0.053
Recurrence	0.73	0.77	–0.041	0.605
Total (overall survival)	6.87	6.90	–0.032	10.695

a Estimation of time-on-treatment was based on 3018 and 3013 patients for the 3-month and 6-month treatment groups respectively, owing to missing values.

Notes

Kaplan–Meier estimates were used for computation of expected time in each health state. Survival time (restricted mean survival) was estimated to 8 years post randomisation.

favoured the 3-month treatment group. No difference was seen between the groups for time in recurrence or overall survival. *Figure 15* shows the time of overall survival partitioned into ToT, disease-free state and recurrence state for the two treatment groups, as generated using Kaplan–Meier estimates.

Kaplan–Meier estimates of how overall survival time would be split into the three health states – ToT, disease-free and recurrence – for the two treatment groups, by subgroup, are shown in *Table 6*.

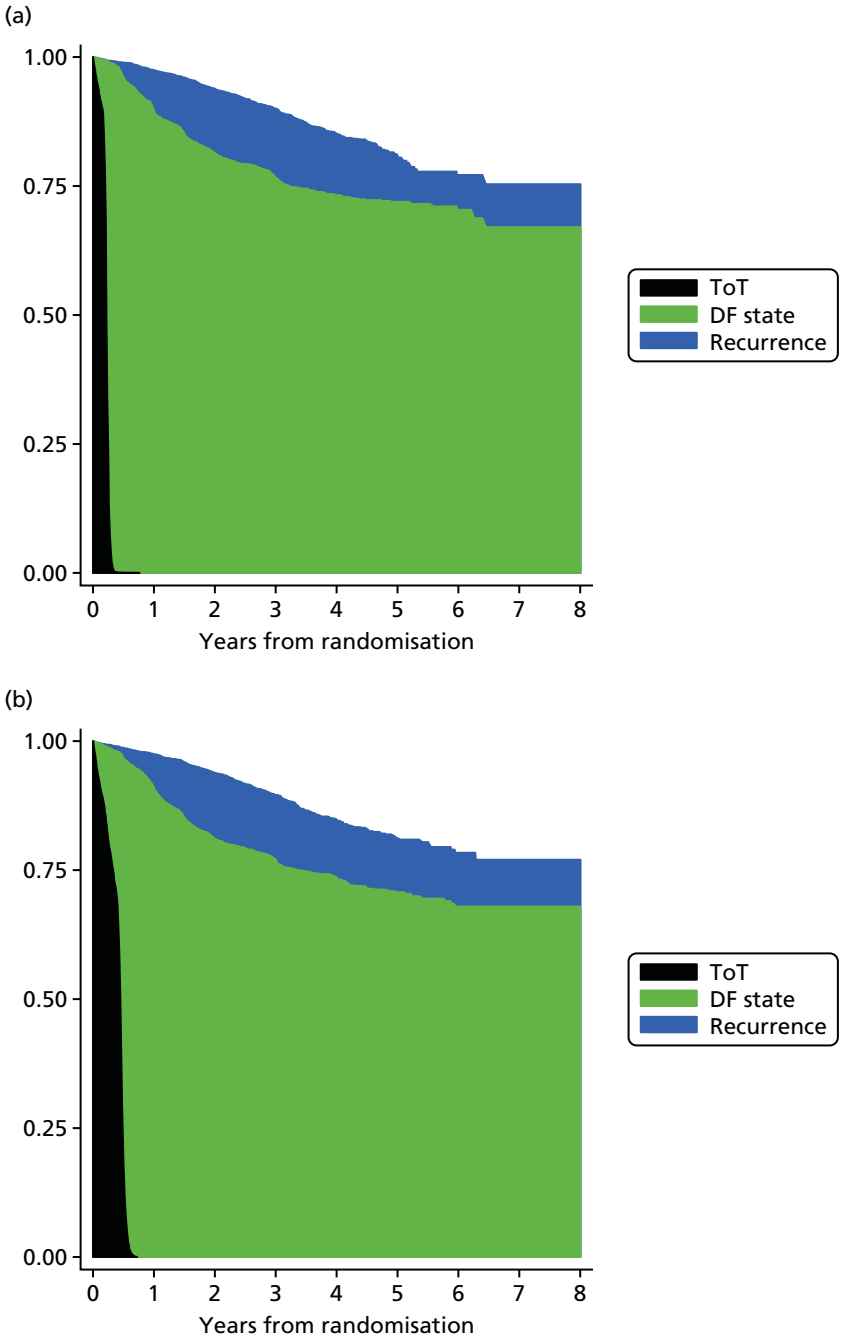

FIGURE 15 Overall survival partitioned into ToT, disease-free state after treatment, and recurrence, Kaplan–Meier estimates over 8 years, by treatment group at (a) 3 months and (b) 6 months. DF, disease free.

TABLE 6 Overall survival time by health state: subgroup analysis

Health state	3-month treatment, mean	6-month treatment, mean	Incremental difference, mean (*p*-value)	3-month treatment, mean	6-month treatment, mean	Incremental difference, mean (*p*-value)
By planned treatment	*Oxaliplatin and 5FU* (N = *1971)*			*Oxaliplatin and capecitabine* (N = *4094)*		
Patients (*n*)	984	987		2051	2043	
Recurrence	0.78	0.67	0.11 (0.336)	0.71	0.82	–0.10 (0.336)
Disease-free	5.81	5.96	–0.14 (0.360)	5.98	5.63	0.35 (0.004)
ToT	0.22	0.42	0.20 (< 0.001)	0.20	0.37	–0.17 (< 0.001)
Total (overall survival)	6.82	7.05	–0.22 (0.128)	6.90	6.83	0.071 (0.508)
By risk	*High risk* (N = *2839)*			*Low risk* (N = *3226)*		
Patients (*n*)	1424	1415		1611	1615	
Recurrence	0.95	0.86	0.08 (0.434)	0.55	0.71	–0.16 (0.158)
Disease-free	5.14	5.10	0.04 (0.739)	6.62	6.30	0.32 (0.016)
ToT	0.21	0.40	–0.18 (< 0.001)	0.21	0.39	–0.18 (< 0.001)
Total (overall survival)	6.31	6.36	–0.048 (0.736)	7.39	7.42	–0.023 (0.806)
By gender	*Female* (N = *2393)*			*Male* (N = *3672)*		
Patients (*n*)	1199	1194		1836	1836	
Recurrence	0.60	0.67	–0.07 (0.576)	0.82	0.84	–0.02 (0.817)
Disease-free	6.10	5.73	0.37 (0.006)	5.80	5.74	0.053 (0.690)
ToT	0.21	0.38	–0.16 (< 0.001)	0.21	0.40	–0.19 (< 0.001)
Total (overall survival)	6.92	6.78	0.14 (0.279)	6.82	6.98	–0.16 (0.195)
By age	*≥ 65 years* (N = *3065)*			*< 65 years* (N = *3000)*		
Patients (*n*)	1525	1540		1510	1490	
Recurrence	0.80	0.65	0.15 (0.287)	0.69	0.89	–0.20 (0.042)
Disease-free	5.72	5.69	0.03 (0.838)	6.10	5.78	0.31 (0.013)
ToT	0.21	0.38	–0.16 (< 0.001)	0.21	0.41	–0.20 (< 0.001)
Total (overall survival)	6.73	6.72	0.02 (0.900)	7.01	7.09	–0.077 (0.518)

Notes
Kaplan–Meier estimates were used for computation of expected time in each health state. Survival time was estimated up to 8 years post randomisation.

Table 7 shows the results of the utility model for non-missing observations. The effect of recurrence and ToT was captured by assigning a value of 1 to the EQ-5D responses occurring in those health states. ToT and recurrence have a significant negative effect on utility, as would be expected; however, the 3-month treatment group was estimated to have higher HRQoL ($p < 0.05$) even after controlling for recurrence and ToT. These results are consistent with the higher incidence of AEs in the 6-month than in the 3-month

TABLE 7 Health utilities regression

Variable	Coefficient	Standard error
Number of patients[a] (*n*)	1757	
Number of observations (*n*)	16,091	
Health states (reference: disease-free)		
ToT	–0.0394[d]	0.00408
Recurrence	–0.0578[d]	0.0139
Treatment group: 6 months	–0.0154[b]	0.00730
Other characteristics		
Oxaliplatin and capecitabine	0.00402	0.00783
High risk	–0.00911	0.00724
Male	0.0159[b]	0.00733
Age	0.00162[d]	0.000429
Ethnicity (reference: white/Caucasian)		
African/Caribbean	–0.0810[b]	0.0385
South Asian	–0.145[c]	0.0536
Chinese	–0.0447	0.0772
Other	0.0178	0.0217
Constant	0.866[d]	0.00944

a The total number of EQ-5D questionnaires reported by the patients included in the estimation.
b $p < 0.05$.
c $p < 0.01$.
d $p < 0.001$.

Notes
The constant in the model refers to a 65-year-old white female patient with low-risk, stage III disease, in the disease-free health state, who was treated with oxaliplatin and 5FU in the 3-month treatment group. Standard error clustered at the patient level.

treatment group. Patient characteristics were included in the model to adjust health utilities to the average values for the whole SCOT study sample, with and without the EQ-5D data. A statistically significant positive effect on HRQoL was associated with the variables male and age, with a negative effect seen for African/Caribbean and South Asian patients compared with white/Caucasian patients. Planned treatment and disease risk did not have a significant effect.

The results of the model follow the pattern of the evolution of EQ-5D scores over time as shown in *Figure 16*. After baseline, HRQoL decreased for both groups to 3 months; at this point, health utilities for those in the 3-month treatment group increased as they completed treatment, whereas lower HRQoL persisted for patients receiving 6 months of adjuvant chemotherapy. Changes in HRQoL were primarily related to ToT, although *Figure 16* illustrates that some difference in HRQoL was evident between the two groups beyond 6 months (completion of adjuvant chemotherapy).

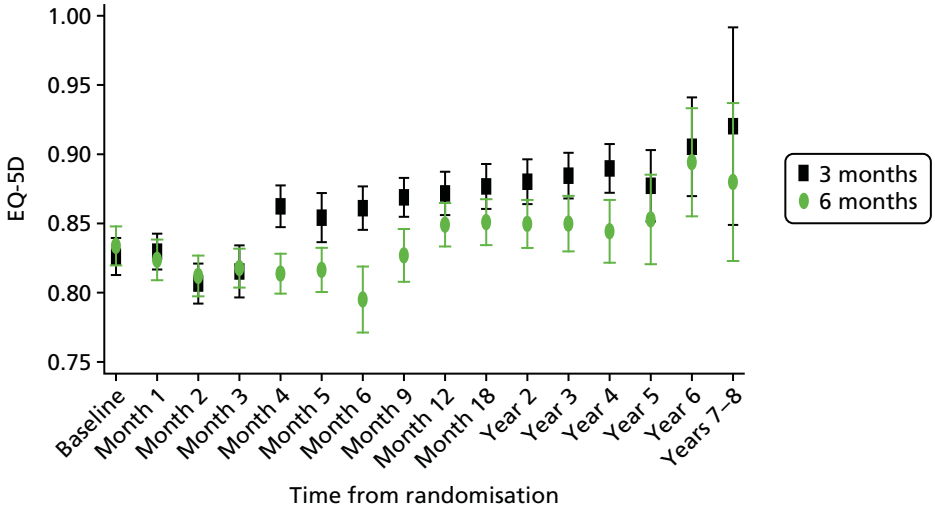

FIGURE 16 Evolution of EQ-5D utilities over time, by treatment group. Presented as means and 95% CIs.

Costs

The unit costs for treatment and hospitalisation are detailed in *Table 8*, and *Table 9* provides a detailed unit cost breakdown for each of the hospitalisation cost categories. *Tables 10* and *11* detail resource use for chemotherapy and hospitalisations, respectively, for each group of the intervention and by planned treatment regimen.

TABLE 8 Unit costs used for cost-effectiveness analyses

Adjuvant chemotherapy drug	Description	Cost (£)	Unit cost (£/mg)
Oxaliplatin	200 mg/40 ml concentrate of oxaliplatin for solution for infusion vials	595.65	2.98
Capecitabine	500-mg tablets of capecitabine, 120 tablets	146.00	2.43×10^{-3}
5FU (bolus)	500 mg/20 ml solution of 5FU for injection vials, 10 vials	64.00	1.28×10^{-2}
5FU (infusion)	2.5 g/100 ml solution of 5FU for infusion vials	32.00	1.28×10^{-2}
Hospitalisation type	**Description**	**Unit cost (£/night or case)**	
Intensive care unit	Night in intensive care unit	2190.35	
High-dependency unit	Night in intensive care unit	937.87	
General medicine	Night in general medicine unit	476.73	
Inpatient (clinical oncology)	Night in clinical oncology unit, as inpatient	896.88	
Day case (clinical oncology)	Day case at clinical oncology	813.22	
Outpatient (clinical oncology)	Outpatient attendance for clinical oncology	251.77	

Notes
The lowest priced medication for each drug at the appropriate dosage was used, as described in the *British National Formulary* 73.[35] Hospitalisation unit costs are based on information reported by Information Services Division Scotland 2017 (reports: R040 – nights, R042 – day cases, R044 – outpatient).[37]

TABLE 9 Hospitalisation unit costs

Hospitalisations	Cost per night or case (£)								Total cost (£)
	Medical	Nursing	Allied health professional	Pharmacy	Theatre	Laboratory	Other	Non-direct costs	
Intensive care unit[a]	284.24	1029.79	36.63	263.48	9.83	76.44	22.35	467.59	2190.35
High-dependency unit[a]	125.74	423.47	13.82	87.07		41.43	6.40	239.95	937.87
General medicine[a]	73.12	161.03	16.60	47.80	3.77	25.77	5.81	142.82	476.73
Inpatient (clinical oncology)[a]	103.47	198.66	74.87	157.15		30.71	38.25	293.77	896.88
Day case (clinical oncology)[b]	147.27	77.37	51.67	281.32		17.41	24.84	213.34	813.22
Outpatient (clinical oncology)[c]	–	–	–	–	–	–	192.40	59.37	251.77

a Report R040.
b Report R042.
c Report R044.
Notes
All outpatient indirect costs are included in the 'other' category.
Hospitalisation unit costs are based on information reported by Information Services Division Scotland 2017.[37]

TABLE 10 Adjuvant chemotherapy received by intervention and planned regimen (mg/patient)

Drug	All patients ($N = 6065$)			Oxaliplatin and 5FU ($N = 1971$)			Oxaliplatin and capecitabine ($N = 4094$)		
	3-month treatment, mean	6-month treatment, mean	Incremental difference: 3-month vs. 6-month; *p*-value	3-month treatment	6-month treatment	Incremental difference: 3-month vs. 6-month; *p*-value	3-month treatment	6-month treatment	Incremental difference: 3-month vs. 6-month; *p*-value
Patients (*n*)	3035	3030		984	987		2051	2043	
Oxaliplatin	842.1	1273.0	–430.8; < 0.001	875.8	1352.5	–476.7; < 0.001	826.0	1234.5	–408.5; < 0.001
Capecitabine	114,142.1	192,930.5	–78,788.4; < 0.001	3622.8	7110.4	–3487.7; 0.031	167,165.6	282,702.6	–115,537.0; < 0.001
5FU bolus	1293.9	2184.6	–890.7; < 0.001	3871.6	6391.7	–2520.1; < 0.001	57.3	152.1	–94.8; < 0.001
5FU continuous infusion	8012.8	14,196.1	–6183.3; < 0.001	23,991.7	41,645.9	–17,654.3; < 0.001	346.6	934.7	–588.1; < 0.001

TABLE 11 Hospital resources by intervention and planned regimen (night stay, day stay or appointment per patient)

Resource	All patients (*N* = 6065)			Oxaliplatin and 5FU (*N* = 1971)			Oxaliplatin and capecitabine (*N* = 4094)		
	3-month treatment, mean	6-month treatment, mean	Incremental difference: 3-month vs. 6-month; *p*-value	3-month treatment, mean	6-month treatment, mean	Incremental difference 3-month vs. 6-month; *p*-value	3-month treatment, mean	6-month treatment, mean	Incremental difference: 3-month vs. 6-month; *p*-value
Patients (*n*)	3035	3030		984	987		2051	2043	
0 to 3 months									
Intensive care unit[a]	0.013	0.022	–0.010; 0.222	0.006	0.020	–0.014; 0.198	0.016	0.023	–0.007; 0.475
High-dependency unit[a]	0.017	0.029	–0.012; 0.391	0.008	0.014	–0.006; 0.520	0.022	0.037	–0.015; 0.462
General/acute medicine[a]	0.846	0.753	0.093; 0.230	0.758	0.661	0.098; 0.421	0.888	0.798	0.090; 0.361
Inpatient visit[a]	0.143	0.148	–0.005; 0.859	0.186	0.209	–0.023; 0.669	0.122	0.118	0.004; 0.873
Outpatient visit[b]	4.588	4.633	–0.045; 0.667	6.777	6.522	0.256; 0.274	3.538	3.721	–0.183; 0.045
Day case[c]	2.643	2.653	–0.009; 0.919	4.254	4.193	0.062; 0.784	1.871	1.909	–0.038; 0.583
3 to 6 months									
Intensive care unit[a]	0.042	0.012	0.030; 0.119	0.013	0.018	–0.005; 0.743	0.055	0.009	0.046; 0.088
High-dependency unit[a]	0.011	0.009	0.002; 0.785	0.006	0.017	–0.011; 0.459	0.013	0.005	0.008; 0.293
General/acute medicine[a]	0.524	0.203	0.321; 0.000	0.611	0.226	0.385; 0.005	0.482	0.191	0.291; 0.001
Inpatient visit[a]	0.036	0.081	–0.045; 0.005	0.029	0.128	–0.098; 0.002	0.039	0.058	–0.020; 0.282
Outpatient visit[b]	2.123	3.585	–1.462; 0.000	2.408	5.200	–2.792; 0.000	1.987	2.805	–0.818; 0.000
Day case[c]	0.272	1.980	–1.708; 0.000	0.398	3.275	–2.876; 0.000	0.211	1.354	–1.143; 0.000

continued

TABLE 11 Hospital resources by intervention and planned regimen (night stay, day stay or appointment per patient) (*continued*)

Resource	All patients (*N* = 6065)			Oxaliplatin and 5FU (*N* = 1971)			Oxaliplatin and capecitabine (*N* = 4094)		
	3-month treatment, mean	6-month treatment, mean	Incremental difference: 3-month vs. 6-month; *p*-value	3-month treatment, mean	6-month treatment, mean	Incremental difference 3-month vs. 6-month; *p*-value	3-month treatment, mean	6-month treatment, mean	Incremental difference: 3-month vs. 6-month; *p*-value
6 to 12 months									
Intensive care unit[a]	0.027	0.059	–0.032; 0.082	0.021	0.087	–0.066; 0.042	0.030	0.046	–0.015; 0.489
High-dependency unit[a]	0.015	0.028	–0.014; 0.200	0.024	0.030	–0.006; 0.794	0.010	0.027	–0.017; 0.122
General/acute medicine[a]	0.842	1.353	–0.511; 0.001	1.036	1.737	–0.701; 0.024	0.749	1.168	–0.419; 0.011
Inpatient visit[a]	0.028	0.048	–0.020; 0.147	0.048	0.048	0.000; 0.996	0.019	0.047	–0.029; 0.042
Outpatient visit[b]	4.071	4.566	–0.495; 0.000	4.165	4.759	–0.594; 0.001	4.027	4.473	–0.447; 0.000
Day case[c]	0.399	0.629	–0.230; 0.000	0.477	0.888	–0.411; 0.000	0.362	0.504	–0.142; 0.004
> 12 months									
Intensive care unit[a]	0.050	0.053	–0.003; 0.874	0.057	0.065	–0.008; 0.801	0.047	0.047	–0.000; 0.993
High-dependency unit[a]	0.063	0.081	–0.018; 0.520	0.053	0.062	–0.009; 0.775	0.068	0.091	–0.023; 0.561
General/acute medicine[a]	2.317	2.474	–0.158; 0.467	2.466	2.065	0.402; 0.266	2.245	2.672	–0.427; 0.113
Inpatient visit[a]	0.133	0.110	0.023; 0.537	0.147	0.094	0.053; 0.374	0.126	0.117	0.008; 0.859
Outpatient visit[b]	8.623	8.755	–0.132; 0.615	8.747	8.380	0.367; 0.442	8.563	8.936	–0.373; 0.236
Day case[c]	1.319	1.441	–0.121; 0.330	1.311	1.498	–0.188; 0.397	1.323	1.413	–0.089; 0.553

a Number of nights' stay.
b Number of days.
c Number of appointments.

The mean costs incurred by patients, broken down by hospitalisation period, are presented in *Table 12*. As expected, adjuvant chemotherapy costs were higher for 6-month treatment duration ($p < 0.001$). Hospitalisation costs differed between treatment groups for the 4- to 6-month period ($p < 0.001$); however, the data also showed that 6-month-duration adjuvant chemotherapy was associated with higher hospitalisation costs over the 7- to 12-month period ($p = 0.030$), possibly reflecting the persistence of treatment-related complications owing to the longer treatment period. Adjuvant chemotherapy and hospitalisation costs for 6-month treatment duration would be expected to be double those for the 3-month regimen; in reality they were 1.67 and 1.45 times higher, respectively, for the 6-month treatment group. This is because only a proportion of patients randomised to the 6-month treatment group were able to complete the full course, owing to tolerability of the adjuvant treatment regimens. Some patients randomised to the 6-month treatment group completed only 4 or 5 months of chemotherapy, and hence treatment and hospitalisation costs are greater, but not doubled, in the 6-month treatment group. Thereby reducing expenditure on chemotherapy agents and time spent in hospital. Whereas 83.3% of patients randomised to 3-month treatment received full-duration therapy, only 58.8% of those randomised to the 6-month regimen received this; this is consistent with the more frequent reporting of AEs of diarrhoea and peripheral neuropathy leading to discontinuation. No difference in cost was seen between treatment groups beyond 12 months. Overall, cost was significantly higher for the 6-month treatment group ($p < 0.001$), being driven primarily by hospitalisation costs (–£2835) rather than the by cost of the adjuvant chemotherapy agents (–£1829) themselves.

Cost-effectiveness

The base-case cost-effectiveness analysis showed that the 3-month adjuvant chemotherapy strategy was significantly cheaper than the 6-month strategy, costing £4881 less over the 8-year analysis period (*Table 13*). The 3-month dosing strategy also resulted in the greatest QALY gain, although this did not reach statistical significance ($p = 0.33$), with uncertainty over the QALY indicated by wide 95% CIs. QALY gains for the 3-month treatment group are driven by the significantly better HRQoL. The 3-month treatment strategy was dominant, showing cost saving and improvement in QALYs, with an incremental NMB of £7246 per patient.

TABLE 12 Patient costs by treatment group

			Incremental difference 3-month vs. 6-month	
Time from the start of treatment	3-month treatment ($N = 3035$), mean (£/patient)	6-month treatment ($N = 3030$), mean (£/patient)	Mean (£/patient)	*p*-value
Adjuvant chemotherapy	2750	4579	–1829	< 0.001
Hospitalisation (0 to 3 months)	3576	3595	–19	0.816
Hospitalisation (4 to 6 months)	1790	4185	–2395	< 0.001
Hospitalisation (7 to 12 months)	2748	3054	–306	0.030
Hospitalisation (> 12 months)	8473	8588	–115	0.876
Total hospitalisation	16,587	19,422	–2835	< 0.001
Total	19,337	24,001	–4663	< 0.001

Note
Values refer to non-discounted average cost for each period conditional on survival.

TABLE 13 Cost estimates and quality-adjusted life-years by treatment group

Intervention strategy	Cost (£/patient), mean (95% CI)	Life expectancy, mean (95% CI)	QALYs, mean (95% CI)	NMB (Cost/QALY) (£), mean (95% CI)	Probable cost-effectiveness, λ = £30,000
3-month treatment	18,401 (17,538 to 19,328)	6.87 (6.73 to 6.99)	5.30 (5.17 to 5.40)	140,492 (135,327 to 145,658)	0.995
6-month treatment	23,282 (22,227 to 24,367)	6.90 (6.78 to 7.02)	5.22 (5.10 to 5.34)	133,246 (129,569 to 136,922)	0.005
Incremental difference, 3-month vs. 6-month	–4881 (–6269 to –3492)	–0.03 (–0.22 to 0.13)	0.08 (–0.086 to 0.230)	7246 (3469 to 11,023)	3-month dominant

Notes
Health utilities conditional on survival considered. Kaplan–Meier survival analysis estimator and partitioned survival analysis were used for costs and QALYs, respectively. CIs were computed using bootstrap sampling. Probability of cost-effectiveness was calculated using 1000 bootstrap replications.

Figure 17 shows the cost-effectiveness acceptability curve. Three-month-duration adjuvant chemotherapy for colorectal cancer shows 99% probability of being cost-effective at both the upper and the lower UK decision thresholds of £30,000 and £20,000 per QALY, respectively.[30] The 3-month regimen also represents the optimal choice across a range of willingness-to-pay (WTP) values.

Cost-effectiveness was assessed for various patient subgroups (treatment regimen, level of disease risk, gender and age), as shown in *Table 14*. Cost-effectiveness results were comparable for the base-case and most subgroups, with the exceptions being oxaliplatin and 5FU treatment and male gender; 3-month treatment was generally dominant and showed a 99% probability of being the cost-effective option. With oxaliplatin and 5FU treatment, the 3-month treatment group showed cost savings but had fewer QALY gains, which was driven by a slightly higher life expectancy in the 6-month treatment group. A relative QALY advantage for 3-month treatment was seen for oxaliplatin and capecitabine chemotherapy, high-risk disease, female patients and older patients. An interaction test of differences in incremental QALYs between subgroups concluded that only in the case of the chemotherapy regimen was there a statistically significant difference in QALYs between the 3-month and 6-month treatment groups, amounting to 0.19 QALY gains for oxaliplatin

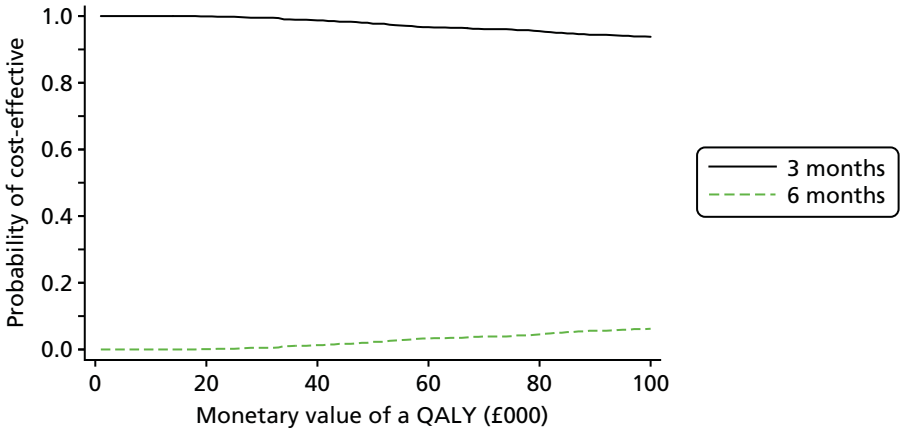

FIGURE 17 Cost-effectiveness acceptability curve: base-case analysis.

TABLE 14 Cost estimates and QALYs for patient subgroups

Intervention strategy	Cost per patient (£), mean (95% CI)	Life expectancy, mean (95% CI)	QALYs, mean (95% CI)	NMB (£30,000/QALY), mean (95% CI)	Probability cost-effectiveness λ = £30,000
Oxaliplatin and capecitabine					
3-month treatment	17,650 (16,668 to 18,919)	6.90 (6.75 to 7.04)	5.34 (5.17 to 5.48)	142,500 (136,469 to 148,531)	0.999
6-month treatment	21,503 (20,389 to 22,723)	6.83 (6.67 to 7.99)	5.16 (5.00 to 5.32)	133,253 (128,206 to 138,300)	0.001
Incremental difference	–3,853 (–5487 to –2030)	0.07 (–0.13 to 0.30)	0.19 (–0.001 to 0.38)	9247 (4178 to 14,315)	3-month dominant
Oxaliplatin and 5FU					
3-month treatment	19,641 (18,477 to 20,774)	6.83 (6.57 to 7.03)	5.21 (4.99 to 5.39)	136,679 (128,249 to 145,108)	0.772
6-month treatment	26,483 (24,659 to 28,292)	7.05 (6.87 to 7.23)	5.33 (5.15 to 5.51)	133,449 (127,107 to 139,791)	0.228
Incremental difference	–6841 (–9040 to –4756)	–0.22 (–0.52 to 0.03)	–0.12 (–0.38 to 0.13)	3229 (–2494 to 8953)	
High risk					
3-month treatment	19,057 (17,888 to 20,339)	6.31 (6.11 to 6.52)	4.84 (4.46 to 5.03)	126,450 (118,973 to 133,927)	0.997
6-month treatment	24,815 (23,481 to 26,362)	6.36 (6.15 to 6.54)	4.71 (4.53 to 4.87)	116,477 (110,700 to 122,254)	0.003
Incremental difference	–5758 (–7686 to –3924)	–0.05 (–0.32 to 0.24)	0.13 (–0.08 to 0.37)	9972 (4664 to 15,281)	3-month dominant
Low risk					
3-month treatment	17,671 (16,596 to 18,925)	7.39 (7.25 to 7.52)	5.72 (5.58 to 5.85)	153,997 (147,785 to 160,208)	0.922
6-month treatment	21,422 (20,305 to 22,573)	7.41 (7.28 to 7.53)	5.71 (5.55 to 5.85)	149,816 (145,425 to 154,206)	0.078
Incremental difference	–3751 (–5402 to –2153)	–0.02 (–0.20 to 0.17)	0.01 (–0.17 to 0.21)	4180 (–429 to 8791)	3-month dominant
Female					
3-month treatment	17,741 (16,408 to 18,934)	6.92 (6.74 to 7.08)	5.30 (5.13 to 5.47)	141,617 (133,821 to 149,413)	0.997
6-month treatment	22,228 (20,716 to 23,936)	6.78 (6.59 to 6.94)	5.10 (4.92 to 5.27)	130,893 (125,233 to 136,553)	0.003
Incremental difference	–4487 (–6518 to –2637)	0.14 (–0.11 to 0.39)	0.20 (–0.03 to 0.44)	10,723 (4880 to 16,567)	3-month dominant

continued

TABLE 14 Cost estimates and QALYs for patient subgroups (*continued*)

Intervention strategy	Cost per patient (£), mean (95% CI)	Life expectancy, mean (95% CI)	QALYs, mean (95% CI)	NMB (£30,000/QALY), mean (95% CI)	Probability cost-effectiveness λ = £30,000
Male					
3-month treatment	18,857 (17,737 to 20,098)	6.83 (6.63 to 7.03)	5.28 (5.11 to 5.43)	139,377 (132,810.1 to 145,944)	0.912
6-month treatment	23,695 (22,531 to 24,930)	6.98 (6.82 to 7.13)	5.29 (5.15 to 5.83)	135,055 (130,064 to 140,046)	0.088
Incremental difference	–4837 (–6613 to –3011)	–0.15 (–0.40 to 0.09)	–0.02 (–0.22 to 0.18)	4321 (–351 to 8994)	
≥ 65 years					
3-month treatment	19,364 (18,101 to 20,831)	6.73 (6.57 to 6.89)	5.24 (5.10 to 5.39)	137,918 (131,146 to 144,689)	0.985
6-month treatment	23,839 (21,981 to 24,917)	6.72 (6.52 to 6.87)	5.13 (4.98 to 5.27)	130,294 (125,355 to 135,234)	0.015
Incremental difference	–4474 (–5994 to –2090)	0.01 (–0.22 to 0.27)	0.11 (–0.09 to 0.32)	7623 (2789 to 12,457)	3-month dominant
< 65 years					
3-month treatment	17,572 (16,431 to 18,672)	7.01 (6.83 to 7.17)	5.35 (5.18 to 5.50)	142,872 (135,713 to 150,032)	0.977
6-month treatment	23,066 (21,838 to 24,435)	7.09 (6.94 to 7.24)	5.29 (5.12 to 5.46)	135,670 (130,541 to 140,799)	0.023
Incremental difference	–5493 (–7297 to –3870)	–0.08 (–0.32 to 0.14)	0.05 (–0.17 to 0.28)	7202 (1609 to 12,795)	3-month dominant

Notes
Health utilities conditional on survival considered. Kaplan–Meier survival analysis estimator and partitioned survival analysis were used for costs and QALYs, respectively. CIs were computed using bootstrap sampling. Probability of cost-effectiveness was calculated using 1000 bootstrap replications.

and capecitabine and –0.12 QALY gains for oxaliplatin and 5FU ($p = 0.066$). This relative advantage of 6-month treatment duration with oxaliplatin and 5FU was driven by the longer life expectancy gain (0.22 years vs. –0.007 years, interaction test $p = 0.106$). In the oxaliplatin and 5FU subgroup, 3-month treatment maintained a greater NMB, with an incremental NMB compared with 6-month treatment of £3229 and a 77% probability of being cost-effective. Therefore, although 3-month treatment with oxaliplatin and 5FU is associated with a slightly lower life expectancy, it remains the optimal treatment strategy. An interaction test of differences in incremental QALYs between the disease risk, gender and age subgroups showed no significant differences in incremental QALYs.

Figure 18 presents the cost-effectiveness acceptability curves for each of the subgroup analyses. For each subgroup, the 3-month strategy had the highest probability of being cost-effective over a wide range of WTP values. Only when a threshold higher than £60,000/QALY was considered did the 6-month regimen become the cost-effective strategy (with highest probability) for the oxaliplatin and 5FU treatment group.

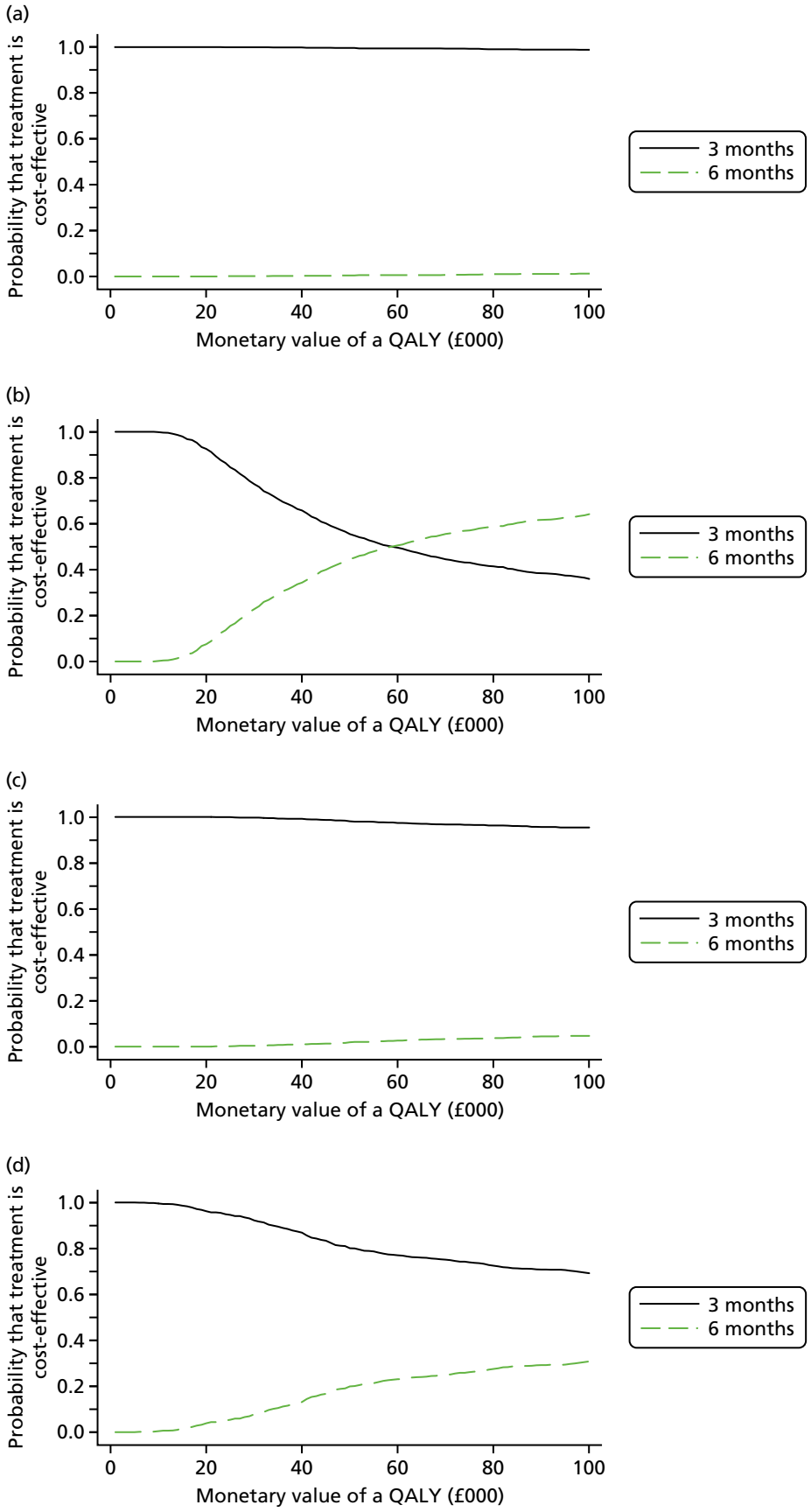

FIGURE 18 Cost-effectiveness acceptability curves: subgroup analysis. (a) Treatment: CAPOX; (b) treatment: FOLFOX; (c) risk: high; (d) risk: low; (e) gender: female; (f) gender: male; (h) age: ≥ 65 years; and (i) age: < 65 years. CAPOX, oxaliplatin and capecitabine; FOLFOX, oxaliplatin and 5FU. (*continued*)

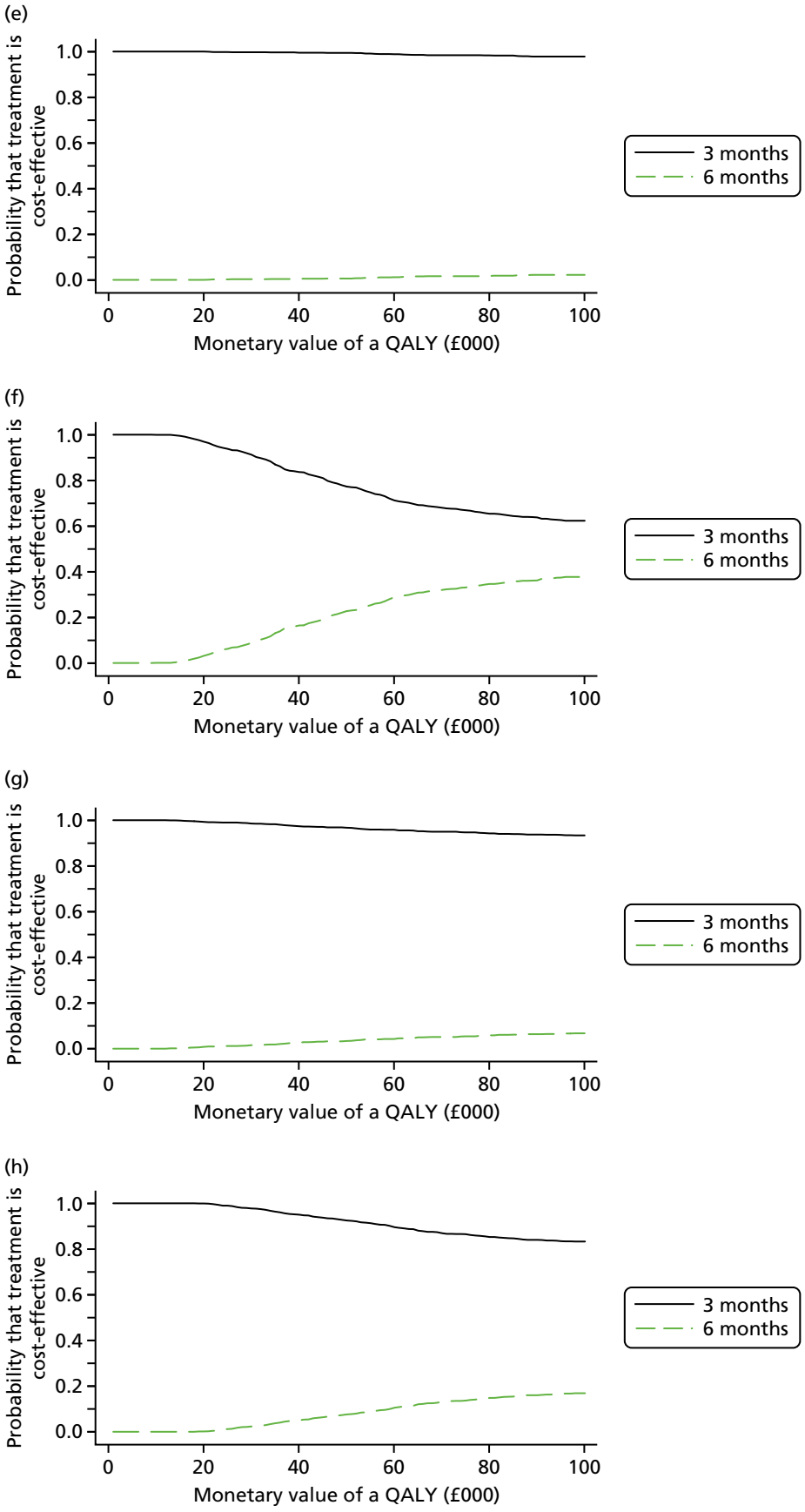

FIGURE 18 Cost-effectiveness acceptability curves: subgroup analysis. (a) Treatment: CAPOX; (b) treatment: FOLFOX; (c) risk: high; (d) risk: low; (e) gender: female; (f) gender: male; (h) age: ≥ 65 years; and (i) age: < 65 years. CAPOX, oxaliplatin and capecitabine; FOLFOX, oxaliplatin and 5FU.

Chapter 5 Discussion

Treatment with oxaliplatin and fluoropyrimidine is the usual adjuvant chemotherapy regimen for patients with high-risk stage II or stage III colorectal cancer,[5,9] with 6-month treatment duration being the accepted standard. However, oxaliplatin administration is associated with cumulative toxicity that is often characterised by chronic and often irreversible neuropathy.[6,7] Because the toxicity of oxaliplatin/fluoropyrimidine regimens is cumulative, reducing the duration of adjuvant treatment could potentially ameliorate such effects.[11] The SCOT clinical trial was conducted to determine whether or not reducting the duration of administration of oxaliplatin and fluoropyrimidine adjuvant chemotherapy from 6 months to 3 months is likely to compromise efficacy; the study also considered the effect of reducing treatment duration on toxicity, HRQoL and health economic parameters. It is our understanding that the SCOT study is the largest single randomised study of infusional adjuvant treatment for colorectal cancer to date.

Efficacy assessment

The SCOT study was designed to demonstrate that 3 months of adjuvant oxaliplatin-containing chemotherapy treatment was non-inferior to 6 months of treatment when used to treat patients with high-risk stage II or stage III colorectal cancer. The non-inferiority boundary was set to exclude a maximum 2.5% decrease in 3-year DFS comparing the 3-month and 6-month treatment groups; based on previous trials, this would result in an estimated 3-year DFS rate of 78%. The value of 2.5% was chosen because it was half of the difference in 3-year DFS seen in the MOSAIC study[6] when comparing the oxaliplatin-containing treatment and fluoropyrimidine only.[6] Clinicians who routinely treat colorectal cancer considered that this represents a small difference and would be 'an acceptable pay-off' for a significant reduction in the sequalae associated with persistent neuropathy and the potential for HRQoL improvements in patients for whom this treatment approach proved curative. This difference corresponds to a HR of 1.13, and it was planned that this would be detected with 90% power at the 2.5% one-sided statistical-significance level.

The study protocol planned for the recruitment of 9500 patients who were expected to experience a total of 2750 DFS events over the course of the trial. However, owing to problems with recruitment, a total of 6088 patients were randomised to study treatment and experienced 1482 events, thereby reducing the statistical power to demonstrate an effect to 66%. Despite this limitation, the trial successfully demonstrated that 3-month oxaliplatin-based adjuvant chemotherapy was non-inferior to 6 months of treatment ($p_{NI} = 0.012$) across the overall trial population (patients with high-risk stage II or stage III cancer of the colon or rectum); 3-year DFS rates were 77.1% of patients (SE = 0.8%) for 6-month treatment and 76.7% of patients (SE = 0.8%) for 3-month treatment, resulting in a HR of 1.006 (95% CI 0.909 to 1.114). The 3-year DFS rate seen for the 6-month treatment group in this study was similar to that seen with 6 months of oxaliplatin-containing adjuvant chemotherapy in the MOSAIC[6] and NSABP C-07[7] studies (78.2% and 76.1%, respectively), suggesting that the outcome observed in our 'control' group was comparable to previous findings.[6,7] The absolute reduction in 3-year DFS rate seen with 3-month treatment was 0.4% (SE = 1.1%).

Sensitivity analyses of DFS rate were conducted based on the actual duration of treatment that patients received. These analyses did not show non-inferiority for 3-month adjuvant chemotherapy but were inherently biased by the differential exclusion of patients not able to receive prolonged therapy because of the different target treatment durations for the treatment groups. In a setting such as this, where differential compliance is intrinsic to the treatments being compared, the ITT analysis is likely to represent a more appropriate reflection of the effect of the intervention.

It is important to note that the proportion of patients randomised with stage II disease (as opposed to stage III) was lower than seen in previous trials (18.3% vs. 40% in the MOSAIC trial and 30% in the

NASBP C-07 trial); the SCOT study recruitment, however, was restricted to patients with high-risk stage II disease, whereas the patients in the MOSAIC trial and the NASBP C-07 trial had all-risk stage II disease. The SCOT trial included a lower proportion of patients with stage II disease, which could lead to criticism that the trial populations had different baseline prognoses. However, because the forest plots did not identify dependence of the effect of duration of adjuvant chemotherapy on N-stage or T-stage disease, or between patients with high-risk stage II versus stage III disease, this indicates that effect of duration is not a real concern. It should be noted that, in many parts of the world, clinical practice for patients with high-risk, stage II disease or stage III disease (especially if over 70 years of age) involves single-agent fluoropyrimidine administered over 6 months, as the addition of oxaliplatin to the regimen for these patients has not been shown to improve survival.[42] The results of this trial do not provide information on duration of therapy for patients managed with single-agent fluoropyrimidine.

At the time the SCOT study started few data were available concerning the use of adjuvant chemotherapy for rectal cancer, as many adjuvant-treatment studies exclude these patients. Patients with rectal cancer were eligible to participate in the SCOT study if they had not received preoperative chemotherapy (short-course radiotherapy alone was allowed) and had undergone total mesorectal excision with an R0 resection. Forest plots did not appear to show any differences in the effect of duration of adjuvant chemotherapy when comparing patients with rectal and patients with colon cancer. Although definitive conclusions about the effect of treatment duration could not be drawn for patient subgroups from the SCOT trial, as a result of the small size of many subgroups and fewer numbers of DFS events, the results do raise important questions about how to manage patients with rectal cancer. Data from the SCOT study suggest that 3-month oxaliplatin-containing adjuvant chemotherapy could be considered for rectal cancer patients requiring adjuvant therapy.

This study did not attempt to address the potential impact of various other prognostic factors on the efficacy of standard or short duration oxaliplatin-based adjuvant chemotherapy, such as the sidedness of the cancer; RAS and BRAF status, which are known to have an impact on the prognosis of patients with metastatic disease; and microsatellite instability status.[43] These questions cannot be currently answered by the results of the SCOT study, but the findings of an ongoing translational-research substudy (TransSCOT) will provide more information.

Chemotherapy regimen

The results of both the SCOT study and data pooled for the IDEA collaboration[44] indicate that the effectiveness of 3 months of adjuvant chemotherapy may depend on the choice of chemotherapy regimen. When the effect of duration was assessed for the two chemotherapy regimens specified for the trial (oxaliplatin and capecitabine and oxaliplatin and 5FU), clear non-inferiority in terms of DFS was demonstrated for patients receiving oxaliplatin and capecitabine for 3 months compared with 6 months of treatment (HR 0.94, 95% CI 0.84 to 1.07; $p_{NI} = 0.002$); non-inferiority was not demonstrated when comparing patients receiving oxaliplatin and those receiving 5FU (HR 1.16, 95% CI 0.96 to 1.39; $p_{NI} = 0.591$). The reasons for this are not clear.

Achieving full-duration adjuvant chemotherapy treatment over 6 months is more difficult than over 3 months. In this study, 83.3% of patients randomised to 3-month adjuvant chemotherapy continued with the regimen for the planned duration; only 58.8% of those randomised to 6-month adjuvant chemotherapy continued for the planned duration. However, compliance data showed that 94–98% of patients in the 3-month treatment group and 82–85% in the 6-month treatment group were administered the full planned fluoropyrimidine dose depending on regimen choice; corresponding figures for oxaliplatin were 96–98% for the 3-month treatment group and 69–73% for the 6-month treatment group. As similar proportions of patients received the full planned doses of the individual chemotherapeutic agents for the two treatment groups, poor treatment compliance is unlikely to explain the difference in the duration effect between the two regimens. It should be noted that capecitabine is an oral drug that is self-administered at home and these assessments are based on the prescribed dose, and so detailed compliance data are not available. This could potentially have led to an underestimation of the dose intensity for patients receiving

oxaliplatin and capecitabine. However, this is considered unlikely as compliance with oral chemotherapy treatments is usually high.

The chemotherapy regimen that individual patients received was not randomised but rather was selected by the physician/patient. Thus, the particular chemotherapy combination may have been chosen due to particular patient characteristics; or there could be a real difference between the 3-month and 6-month regimens in the adjuvant setting.

- There may have been clinical reasons why a particular chemotherapy regimen was selected for an individual patient. For example, clinicians may have selected the oxaliplatin and capecitabine combination for patients who were perceived as frail in order to avoid the risk of neutropenic sepsis inherent with oxaliplatin and 5FU; similarly, the starting dose of capecitabine may have been reduced because of perceived frailty. However, some clinicians specifically avoid giving capecitabine to older patients because of the risks associated with this agent in those with impaired renal function. In this study, the reasons for selecting a particular adjuvant chemotherapy regimen for individual patients are not known.
- Alternatively, there may be real differences between treatment regimens associated with exposure to the component agents. For the oxaliplatin and capecitabine regimen, the oxaliplatin dose administered in each cycle is higher than that for oxaliplatin and 5FU; therefore, it can be presumed that higher peak exposure may be achieved. Two previous studies suggest that peak oxaliplatin concentration is key to clinical effect, which would be likely to favour the oxaliplatin and capecitabine regimen.[45,46] In addition, peak fluoropyrimidine exposure to is likely to be lower but the continuity of exposure is greater when fluoropyrimidine is given twice daily for 2 out of 3 weeks (compared with 5FU, which is given as bolus and then over 2 days every 2 weeks); if cells are cycling through S-phase sporadically, the greater continuity of fluoropyrimidine exposure with the capecitabine regimen could mean that there is a greater chance that tumour cells will be exposed at a critical phase in the cell cycle. It could be that micrometastatic disease is rendered more sensitive because of one or both of these differences.

Disease stage

Stage III colorectal cancer is a heterogeneous disease group; data from the IDEA collaboration and from multiple adjuvant trials have shown that patients with T1–3, N1 pathology have much better outcomes than those with either T4 or N2 features.[44] This has led to the evolution of the concept of high-risk (with either T4 or N2 disease) and low-risk (with T1–3, N1 disease) stage III patient populations. To optimally treat stage III colorectal cancer, it may be necessary to treat these groups in different ways. The SCOT study has similarly demonstrated that patients with T1–3, N1 disease have better 3-year DFS than those with either T4 or N2 pathology, but it did not show a difference in duration effect between these groups when this was assessed using a test for heterogeneity. Nonetheless, 3-month chemotherapy was clearly non-inferior for patients with T1–3, N1 colorectal cancer (HR 0.91, 95% CI 0.75 to 1.10). For patients with T4 and/or N2 pathology, outcomes were poorer when they received 3 months of treatment; the non-inferiority of this treatment duration in terms of DFS was not seen in this group of patients in the SCOT study (HR 1.07, 95% CI 0.94 to 1.22). The HR was > 1 for the 3-month compared with the 6-month duration, suggesting some loss of efficacy. However, the wide CIs mean that this result could reflect a wide spectrum of possible effects, from a small potential benefit with 3-month treatment to decreased efficacy beyond the non-inferiority boundary. It is important to note that the observed absolute reduction in 3-year DFS between the 3-month and the 6-month treatment groups was only 1.9%. Although non-inferiority was not formally met for high-risk stage III patients, in view of the small absolute difference in 3-year DFS the benefits of longer treatment duration need to be carefully balanced against the increased risk of cumulative chronic toxicity.

Some text in this paragraph is taken from Iveson *et al.*[16]

Among patients with T4 or N2 disease, the absolute increase in 3-year DFS rate comparing 6-month with 3-month treatment was 2.8% (95% CI –4.1% to 9.7%) for oxaliplatin and 5FU and 1.3% (95% CI –3.7% to 6.2%) for oxaliplatin and capecitabine (see *Figure 8*). In view of the difference in toxicity seen with longer duration treatment, patients are likely to accept a small reduction in DFS in exchange for reduced toxicity; this is especially true if they are able to receive oxaliplatin and capecitabine. There is less evidence to support use of short-duration adjuvant treatment if it is decided that the patient needs to receive oxaliplatin and 5FU or has T4 disease.

Safety and toxicity

To our knowledge, this is the largest randomised study of adjuvant chemotherapy for colorectal cancer and confirms the findings of previous studies by showing that oxaliplatin-based combination chemotherapy can be safely delivered, with a mortality rate of 0.5%.[6,47] The most common grade 3/4 side effects reported were peripheral neuropathy, diarrhoea, neutropenia, fatigue, pain, nausea and hand–foot syndrome, also consistent with previous studies. Although 12% of patients overall had grade 3/4 neutropenia, only 1.2% had febrile neutropenia; the febrile neutropenia rate in the MOSAIC study was 1.8%.[6]

The SCOT study results show that 6 months of adjuvant chemotherapy is associated with significantly greater toxicity than 3 months of treatment. This difference was most apparent for peripheral neuropathy, with 58% of patients in the 6-month treatment group reporting grade ≥ 2 neuropathy compared with 25% of patients in the 3-month treatment group. Peripheral neuropathy, as reported via a patient questionnaire, was significantly worse in the 6-month treatment group and persisted for ≥ 5 years. Other AEs that are important to patients, such as diarrhoea and hand–foot syndrome, were also significantly more common in patients undergoing 6 months of treatment. Our conclusions regarding long-term neuropathy consequences need to be interpreted in the light of a substantial number of missing data. However, the treatment effect and significance levels are substantial, with no evidence of bias between the treatment groups, and the analysis approach was adapted to make allowance for missing data.

The effects of toxicity early in treatment are important; in the SCOT study, 14% of patients in each group did not complete 3 months of treatment. A similar proportion (13%) of those stopping treatment in the first 3 months in an adjuvant study using oxaliplatin and capecitabine was reported in 2007.[47] Although the choice of chemotherapy was not randomised, in the SCOT study a greater proportion of patients receiving oxaliplatin and capecitabine (15%) appeared to stop treatment before 3 months than estimated for those receiving oxaliplatin and 5FU (11%).

Achieving full-duration adjuvant chemotherapy treatment over 6 months is more difficult than over 3 months. In this study, 83.3% of patients randomised to 3-month adjuvant chemotherapy continued with the regimen for the planned duration, whereas only 58.8% of those randomised to 6-month adjuvant chemotherapy continued for the planned duration. Problems with delivering 6 months of therapy were most pronounced for the oxaliplatin component, where the median percentage of full dose delivered was 96.6% for the 3-month treatment group as compared with 70.2% for the 6-month treatment group. Fluoropyrimidine treatment was not compromised to the same extent, with the median percentage of full doses delivered being 95.3% and 83.2% for the 3-month and 6-month treatment groups, respectively.

As expected, there was a difference in the toxicity profile according to fluoropyrimidine backbone, with more grade 3/4 neutropenia in those receiving oxaliplatin and 5FU (23% vs. 5%) and more grade 3/4 diarrhoea in those receiving oxaliplatin and capecitabine (15% vs. 9%). The frequency of these toxicities is consistent with those reported in other studies of adjuvant treatment.[6,47]

Peripheral neuropathy

The only chronic toxicity seen in the SCOT study was sensory peripheral neuropathy, which occurred with significantly lower frequency in the 3-month treatment group than in the 6-month treatment group (overall grade 3/4 toxicity was 4.1% in the 3-month treatment group compared with 16.5% in the 6-month treatment group). The study therefore met its aim of achieving a > 50% reduction in the incidence of grade 3/4 peripheral neuropathy by administering treatment over 3 months. The frequency of peripheral neuropathy reported here is higher than seen for 6-month adjuvant treatment in the MOSAIC, NSABP C-07 and XELOXA trials (12.4%, 8.2% and 11%, respectively).[6,7,47] Peripheral neuropathy in the SCOT study was assessed by the investigator using NCI CTCAE (version 3), which grades the condition on a scale of 0–4; neuropathy in the MOSAIC study was graded using NCI CTCAE (version 1), in the NSABP C-07 study using the NCI-Sanofi Neurosensory score (graded from 0–3) and in the XELOXA study using NCI CTCAE (version 3). As peripheral neuropathy has become recognised as the main dose-limiting toxicity with oxaliplatin, clinicians may be questioning patients more closely about such symptoms in more recent trials. The incidence and course of acute and chronic peripheral neuropathy as a result of oxaliplatin has been well documented using a comprehensive PRO measure (EORTC QLQ-CIPN 20).[11] This study showed that the incidence and severity of sensory peripheral neuropathy increases with the number of cycles of adjuvant chemotherapy received, in broad agreement with the findings of this study.

In the SCOT study, patients were administered either oxaliplatin and capecitabine or oxaliplatin and 5FU in a non-randomised manner. Although the cumulative oxaliplatin dose is similar for the two regimens (1040 mg/m^2 and 1020 mg/m^2, respectively), the individual doses of oxaliplatin are higher with oxaliplatin and capecitabine (130 mg/m^2 every third week compared with 85 mg/m^2 every second week with oxaliplatin and 5FU). However, the rates of grade ≥ 2 peripheral neuropathy were similar irrespective of the fluoropyrimidine backbone for both the 3-month (21.3% with oxaliplatin and 5FU and 25.7% with oxaliplatin and capecitabine) and the 6-month (57.7% and 58.1%) groups.

In this study, some of the patients who were randomised to receive either 3- or 6-month duration of adjuvant chemotherapy had persistent neuropathy over ≥ 5 years, with neuropathy frequency being significantly higher ($p < 0.001$) at 3, 4 and 5 years for those randomised to the 6-month duration treatment. The level of chronic peripheral neuropathy seen in the SCOT study is in line with that previously reported 18 months after treatment using EORTC QLQ-CIPN 20,[48] with 50% of patients reporting < 10% reduction in sensory neuropathy scores and 19% reporting > 30% reduction in sensory neuropathy scores compared with baseline.[11]

The MOSAIC[6] and the NSABP C-07[7] studies showed rates of grade 3 neuropathy reported at 1 year of 1.1% and 0.6%, respectively. It is now recognised that persistent peripheral neuropathy is a major side effect for patients who have received oxaliplatin, especially in the adjuvant setting. For the majority of these patients neuropathy is a significant problem; because of this, it may be better detected using a more in-depth PRO measure such as the FACT/GOG-Ntx4 questionnaire rather than grading it using the NCI CTCAE.

Health-related quality of life

Health-related quality of life (measured using QLQ-C30 Global Health Status and EQ-5D-3L) declined while patients were receiving adjuvant chemotherapy. HRQoL was, therefore, reduced for longer in patients randomised to receive 6-month treatment compared with 3-month treatment. HRQoL improved after stopping treatment and within 1 year there were no clinically important differences between the two treatment groups. EQ-5D health status, assessed using both the self-rated visual analogue scale and the EQ-5D-3L utility index, did not differ between 9 months and the 7-year follow-up based on the minimal clinically important differences for health utilities in cancer.[23]

Health-related quality of life and peripheral neuropathy

It is accepted that clinician assessment of neuropathy using methods such as the CTCAE criteria are less sensitive than PRO tools such as the FACT/GOG-Ntx4 or the EORTC QLQC CIPN 20.[49] In this study, we supplemented the CTCAE analyses with specific assessment of peripheral neuropathy using the FACT/GOG-Ntx4.

Health-related quality of life appeared to recover within 1 year of starting treatment; however, chronic sensory peripheral neuropathy persisted for ≥ 5 years. Patients who recorded a greater degree of neuropathy symptoms had significantly worse HRQoL at 12, 36 and 60 months than those with lesser symptoms. These differences in HRQoL reached at least minimal clinically important levels. Similar findings were reported for a Dutch study, in which there was a correlation between neuropathy symptoms and HRQoL for the 10% of patients with the worst neuropathy symptoms (as measured by the EORTC QLQ-CIPN 20), with a reduction in the HRQoL scores (as measured by the QLQ-C3020) from 2 to 11 years after oxaliplatin treatment for colorectal cancer.[50] It appears that a lack of an overall difference in HRQoL scores does not reflect the meaningful differences experienced by patients with the worst long-term, chronic, neuropathy.

Health economic assessment

The results of the economic evaluation showed that a 3-month duration adjuvant regimen is cheaper and a dominant strategy for chemotherapy treatment for patients with high-risk, stage II or stage III colorectal cancer. The shorter treatment duration significantly reduced costs related to adjuvant chemotherapy administration and hospitalisation. The 3-month treatment group showed significantly better patient HRQoL during the treatment period, with no significant impact on overall survival, leading to an overall QALY gain that did not reach statistical significance. The probabilistic analysis and exploration of cost-effectiveness acceptability showed little uncertainty in the economic results over a wide range of WTP thresholds.

Four subgroup analyses came to similar conclusions, with the 3-month treatment group being the dominant or cost-effective strategy given a £30,000 cost per QALY threshold. The type of chemotherapy administered showed the greatest subgroup affect on cost-effectiveness. The interaction between planned treatment and QALY differences between the two treatment groups was statistically significant. With oxaliplatin and 5FU chemotherapy, the 6-month treatment group generated more QALYs than seen for the 3-month treatment group, which were primarily driven by longer estimates of disease-free and overall survival. HRQoL differences between groups favoured 3-month treatment but the survival gains for the 6-month oxaliplatin and 5FU regimen were relevant over the 8-year follow-up period, resulting in an overall QALY gain. Nonetheless, at a decision threshold of £30,000/QALY the NMB was larger for 3-month treatment (incremental gain of £3229 per patient) and, therefore, the 6-month duration treatment would not be considered cost-effective from a UK perspective.[30]

Modelling an 8-year patient follow-up period allowed exploration of cost-effectiveness outcomes over this longer time period. Key cost differences occurred within the first year after randomisation, where 6-month treatment was nearly twice the cost of 3-month chemotherapy when including associated hospitalisations. When considering years 1 to 8 there were minimal differences in hospitalisation costs between groups; however, over the entire 8-year analysis period the total costs per patient were significantly different and favoured 3-month treatment. Differences in costs between the treatment groups over an even longer term would not be expected, with extrapolation beyond 8 years being unlikely to change outcomes unless there were substantial differences in survival rate. The 8-year follow-up also allows thorough consideration of the QALY results, which are driven by event timing. The small differences in life expectancy are subject to uncertainty in both the base-case and subgroup analyses, yet the overall HRQoL is consistently higher for the 3-month treatment group across all analyses. The maximum benefit in terms of HRQoL is seen 3 to 6 months after randomisation, at which time patients receiving 3-month duration chemotherapy have stopped treatment. The negative impact on HRQoL for the 6-month treatment group is accounted for by chemotherapy-related AEs.[33]

Study context

The SCOT trial is part of a wider initiative, the IDEA collaboration, which aims to consolidate the results from all trials being conducted worldwide (SCOT, TOSCA,[51] IDEA France,[52] CALGB/SWOG 80702, ACHIEVE,[53] and HORG[54]) that are attempting to address whether or not the duration of oxaliplatin-based adjuvant chemotherapy can be reduced to 3 months for patients with stage III colon cancer.[14] The results of the SCOT trial are consistent with those from the IDEA collaboration in indicating that the relative effect of shortening the duration of adjuvant chemotherapy may depend on the choice of chemotherapy regimen (oxaliplatin and 5FU vs. oxaliplatin and capecitabine; $p = 0.069$ heterogeneity in the SCOT study).[55] When the effect of duration was considered separately for each regimen, oxaliplatin and capecitabine showed non-inferiority for 3-month treatment in terms of DFS when compared with 6-month duration adjuvant chemotherapy; for reasons that are not clear, this was not the case for oxaliplatin and 5FU adjuvant chemotherapy. The choice of chemotherapy was not randomised but was chosen by the physician and patient, with the reasons for selection of a particular regimen being unknown.

Limitations of the study

Some text in this paragraph is taken from Iveson *et al.*[16]

The SCOT study was underpowered owing to issues with recruitment, which meant that fewer patients than planned participated in the trial. However, the 95% CIs for the HR for the primary analysis lay below the non-inferiority boundary and the results were consistent with those of individual studies conducted within the IDEA group, particularly when considering how the duration effect depended on treatment regimen and disease risk. This consistency with other studies indicates that the results of the SCOT study are unlikely to represent a false-positive, in terms of showing non-inferiority. The concept that underpowered studies are more likely to produce false-positives (ignoring the factor of publication bias, which does not apply to a large scale enterprise such as the SCOT study) is disputed.[56]

Despite the size of the SCOT study, there are limitations to the reliability of the conclusions that can be drawn for some patient subgroups. In particular, the SCOT study and the IDEA results indicate that the duration effect differs according to the non-randomised choice of oxaliplatin and 5FU and oxaliplatin and capecitabine chemotherapy; although non-inferiority could be shown for oxaliplatin and capecitabine, the results for oxaliplatin and 5FU are less conclusive. Examination of results within the two stage III risk groups (T1–3, N1 and T4 or N2) are similarly compromised.

Some limitations were also associated with the cost-effectiveness analyses presented, which generally relate to the need for data censoring given the minimum 3-year follow-up and relatively high survival rates (in the region of 75% after 8 years). The cost and quality-adjusted survival methodology used (Kaplan–Meier sample average and partitioned survival analysis, respectively) were chosen to reduce censoring-related bias. Lifetime extrapolation was not undertaken for the base-case within trial analysis given the non-inferiority of overall survival and DFS, and dominance of the 3-month treatment group. However, a lifetime analysis may improve the evidence for subgroup analyses where non-inferiority criterion were not met and the dominance conclusion was subject to uncertainty. Future work will explore lifetime analyses for the subgroups.

It should be noted that, although the SCOT study results are applicable to all patients who might be considered for 6 months of adjuvant combination chemotherapy with oxaliplatin and fluoropyrimidine, there are patients who are currently treated with 6 months of adjuvant fluoropyrimidine only (some patients with high-risk stage II disease or older patients with stage III disease). The SCOT study results are not applicable to patients receiving single agent fluoropyrimidine.

Chapter 6 Conclusions

The SCOT study achieved its primary end point for the overall trial population, showing that 3 months of oxaliplatin-containing adjuvant chemotherapy is non-inferior to 6 months of the same regimen. Three-month oxaliplatin-based chemotherapy should, therefore, be considered as an adjuvant regimen, particularly to oxaliplatin and capecitabine combination therapy. As the study recruited 6088 patients with conventionally defined high-risk stage II and stage III colorectal cancer from a large number of centres and countries and made use of standard chemotherapy regimens, the study findings are applicable to a typical patient with colorectal cancer who needs adjuvant chemotherapy treatment.

Although 3-month treatment with oxaliplatin and capecitabine was statistically non-inferior to 6-month treatment, the study did not demonstrate with statistical certainty non-inferiority for the 3-month oxaliplatin and 5FU regimen. Similarly, for patients with T1–3, N1 disease, the SCOT study demonstrated non-inferiority for 3-month adjuvant treatment; however, for patients with T4 or N2 pathology, a small absolute decrease in 3-year DFS was seen with 3-month duration treatment for both the oxaliplatin and capecitabine and the oxaliplatin and 5FU regimens. In both cases, these absolute differences are small with wide CIs. Therefore, in young, fit patients with very poor prognosis, a more aggressive approach, with longer treatment duration, might be appropriate.

The SCOT results are supported by the IDEA collaboration, which also showed that the effect of duration of adjuvant treatment was influenced by the choice of chemotherapy regimen and was similarly dependent on whether the patient had low- or high-risk stage III disease.

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Six-month treatment is associated with a considerable increase in toxicity compared with 3-month treatment. The toxicity profiles of the oxaliplatin and capecitabine and oxaliplatin and 5FU regimens differ, with diarrhoea and hand–foot syndrome more common with capecitabine and neutropenia more common with 5FU. This study confirmed that patients receiving 6-month duration treatment experience significantly greater acute and chronic neurotoxicity, with chronic neurotoxicity persisting to $\geq$ 5 years. Patients with the worst chronic neuropathy had significantly poorer HRQoL. Neuropathy is, therefore, a significant chronic side effect of oxaliplatin therapy for patients receiving 6 months of adjuvant chemotherapy. In view of the increased toxicity seen with longer therapy and the consequential effects on long-term HRQoL, there should always be a discussion with the individual patient about the most appropriate duration of treatment, balancing the potential for longer treatment to achieve small efficacy benefits with the likelihood of increased toxicity and poorer HRQoL. The final decision on treatment duration and regimen for each individual will depend on a careful discussion between the clinician and patient, taking into account the risk of recurrence, the likely absolute difference in DFS and risk of long-term toxicity, and the strength of evidence for that particular disease context available from both the SCOT study and the wider IDEA analysis.

This study found that, compared with traditional 6-month adjuvant chemotherapy, the 3-month treatment strategy costs significantly less and has no significant detrimental impact on patient outcome (HRQoL and survival). The 3-month regimen was found to dominate 6-month adjuvant chemotherapy for patients with high-risk stage II or stage III colorectal cancer. Cost-effectiveness is affected by the type of chemotherapy regimen used; however, the 3-month strategy was the optimal choice for both the oxaliplatin and capecitabine and the oxaliplatin and 5FU regimens based on relevant WTP thresholds. This economic evaluation adds to the evidence showing that 3-month treatment is not only cost-effective but also dominant over the current standard of 6-month treatment; little uncertainty is associated with this conclusion, which supports the economic case that 3-month treatment is sufficient for most patients.

Implications for practice and implications for research

The findings of this research indicate that 3 months of adjuvant chemotherapy may be sufficient for some patients. For patients with low-risk stage III disease (T1–3, N1) receiving adjuvant oxaliplatin and capecitabine chemotherapy, 3 months of treatment is sufficient. Many low-risk stage III patients receiving adjuvant oxaliplatin and 5FU chemotherapy and high-risk stage III patients receiving adjuvant oxaliplatin and capecitabine chemotherapy may be considered for 3 months of treatment. The optimum duration of adjuvant treatment for high-risk stage III patients is less certain.

Research is needed on the influence of T4 or N2 on the required duration of adjuvant treatment for high-risk stage III patients.

Further research should be conducted to identify any specific patient groups (e.g. patients with specific high-risk pathological features) for whom 6 months of adjuvant chemotherapy might be appropriate and if this is dependent on the regimen selected. The translational tissue samples from the SCOT study (3383 tumour samples and 3100 blood samples) and from other similar studies should be used to build molecular predictors of which patients may benefit from longer treatment. Some of this work is currently under way for the SCOT study.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review and appropriate agreements being in place.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Baseline characteristics of analysis subgroups

TABLE 15 Characteristics of patients assessed with NCI CTC AE

Characteristic	Randomised treatment group	
	3 months of treatment	6 months of treatment
Gender,* n *(%)		
Female	166 (38.2)	165 (38.0)
Male	268 (61.8)	269 (62.0)
Total	434 (100)	434 (100)
Age at registration		
Median (years)	63	65
IQR (years)	59–69	58–70
Range (years)	27–83	20–78
Total (*n*)	434	434
Performance status at randomisation,* n *(%)		
0	276 (63.6)	263 (60.6)
1	158 (36.4)	171 (39.4)
Total	434 (100.0)	434 (100.0)
Disease site,* n *(%)		
Colon	354 (81.6)	355 (81.8)
Rectum	80 (18.4)	79 (18.2)
Total	434 (100.0)	434 (100.0)
T stage,* n *(%)		
0	0 (0.0)	1 (0.2)
1	11 (2.5)	10 (2.3)
2	43 (9.9)	39 (9.0)
3	246 (56.7)	250 (57.6)
4	134 (30.9)	134 (30.9)
Total	434 (100.0)	434 (100.0)
N stage,* n *(%)		
0	58 (13.4)	56 (12.9)
1	250 (57.6)	255 (58.8)
2	126 (29.0)	123 (28.3)
Total	434 (100.0)	434 (100.0)

continued

TABLE 15 Characteristics of patients assessed with NCI CTC AE (*continued*)

Characteristic	Randomised treatment group	
	3 months of treatment	6 months of treatment
Planned treatment*, n *(%)		
FOLFOX	155 (35.7)	158 (36.4)
CAPOX	279 (64.3)	276 (63.6)
Total	434 (100.0)	434 (100.0)
If CAPOX planned, starting dose of capecitabine*, n *(%)		
750 mg/m^2	5 (27.8)	5 (22.7)
800 mg/m^2	0 (0.0)	0 (0.0)
1000 mg/m^2	13 (72.2)	17 (77.3)
Total	18 (100.0)	22 (100.0)
High-risk stage II*, n *(%)		
No	377 (86.9)	378 (87.1)
Yes	57 (13.1)	56 (12.9)
Total	434 (100.0)	434 (100.0)

CAPOX, oxaliplatin and capecitabine; FOLFOX, oxaliplatin and 5FU.

TABLE 16 Characteristics of patients assessed with EQ-5D

Characteristic	Randomised treatment group	
	3 months of treatment	6 months of treatment
Gender*, n *(%)		
Female	361 (39.4)	363 (39.8)
Male	555 (60.6)	549 (60.2)
Total	916 (100.0)	912 (100.0)
Age at registration		
Median (years)	64	65
IQR (years)	59–70	59–70
Range (years)	24–83	20–83
Total (*n*)	916	912
Performance status at randomisation*, n *(%)		
0	595 (65.0)	581 (63.7)
1	321 (35.0)	331 (36.3)
Total	916 (100.0)	912 (100.0)

TABLE 16 Characteristics of patients assessed with EQ-5D (*continued*)

Characteristic	Randomised treatment group	
	3 months of treatment	6 months of treatment
Disease site*, n *(%)		
Colon	755 (82.4)	750 (82.2)
Rectum	161 (17.6)	162 (17.8)
Total	916 (100.0)	912 (100.0)
T stage*, n *(%)		
0	0 (0.0)	1 (0.1)
1	22 (2.4)	25 (2.7)
2	84 (9.2)	80 (8.8)
3	527 (57.5)	516 (56.6)
4	282 (30.8)	290 (31.8)
X	1 (0.1)	0 (0.0)
Total	916 (100.0)	912 (100.0)
N stage*, n *(%)		
0	140 (15.3)	141 (15.5)
1	519 (56.7)	517 (56.7)
2	257 (28.1)	254 (27.9)
Total	916 (100.0)	912 (100.0)
Planned treatment*, n *(%)		
FOLFOX	292 (31.9)	297 (32.6)
CAPOX	624 (68.1)	615 (67.4)
Total	916 (100.0)	912 (100.0)
If CAPOX planned, starting dose of capecitabine*, n *(%)		
750 mg/m^2	84 (22.3)	83 (22.4)
800 mg/m^2	18 (4.8)	18 (4.9)
1000 mg/m^2	274 (72.9)	270 (72.8)
Total	376 (100.0)	371 (100.0)
High-risk stage II*, n *(%)		
No	778 (84.9)	774 (84.9)
Yes	138 (15.1)	138 (15.1)
Total	916 (100.0)	912 (100.0)

CAPOX, oxaliplatin and capecitabine; FOLFOX, oxaliplatin and 5FU.

TABLE 17 Characteristics of patients assessed with EORTC QLQ-C30/CR29

Characteristic	Randomised treatment group	
	3 months of treatment	6 months of treatment
Gender*, n *(%)		
Female	361 (39.4)	363 (39.8)
Male	555 (60.6)	550 (60.2)
Total	916 (100.0)	913 (100.0)
Age at registration		
Median (years)	64	65
IQR (years)	59–70	59–70
Range (years)	24–83	30–83
Total (*n*)	916	913
Performance status at randomisation*, n *(%)		
0	595 (65.0)	582 (63.7)
1	321 (35.0)	331 (36.3)
Total	916 (100.0)	913 (100.0)
Disease site*, n *(%)		
Colon	755 (82.4)	751 (82.3)
Rectum	161 (17.6)	162 (17.7)
Total	916 (100.0)	913 (100.0)
T stage*, n *(%)		
0	0 (0.0)	1 (0.1)
1	22 (2.4)	25 (2.7)
2	84 (9.2)	80 (8.8)
3	527 (57.5)	517 (56.6)
4	282 (30.8)	290 (31.8)
X	1 (0.1)	0 (0.0)
Total	916 (100.0)	913 (100.0)
N stage*, n *(%)		
0	140 (15.3)	141 (15.4)
1	519 (56.7)	518 (56.7)
2	257 (28.1)	254 (27.8)
Total	916 (100.0)	913 (100.0)
Planned treatment*, n *(%)		
FOLFOX	292 (31.9)	297 (32.5)
CAPOX	624 (68.1)	616 (67.5)
Total	916 (100.0)	913 (100.0)

TABLE 17 Characteristics of patients assessed with EORTC QLQ-C30/CR29 (*continued*)

Characteristic	Randomised treatment group	
	3 months of treatment	6 months of treatment
If CAPOX planned, starting dose of capecitabine,* n *(%)		
750 mg/m^2	84 (22.3)	84 (22.6)
800 mg/m^2	18 (4.8)	18 (4.8)
1000 mg/m^2	274 (72.9)	270 (72.6)
Total	376 (100.0)	372 (100.0)
High-risk stage II,* n *(%)		
No	778 (84.9)	775 (84.9)
Yes	138 (15.1)	138 (15.1)
Total	916 (100.0)	913 (100.0)

CAPOX, oxaliplatin and capecitabine; FOLFOX, oxaliplatin and 5FU.

TABLE 18 Characteristics of patients assessed with GOG-Ntx4

Characteristic	Randomised treatment group	
	3 months of treatment	6 months of treatment
Gender,* n *(%)		
Female	562 (38.9)	548 (38.4)
Male	883 (61.1)	878 (61.6)
Total	1445 (100.0)	1426 (100.0)
Age		
Median (years)	64	65
IQR (years)	58–70	59–70
Range (years)	24–83	20–85
Total (*n*)	1445	1426
Performance status at randomisation,* n *(%)		
0	993 (68.7)	965 (67.7)
1	452 (31.3)	461 (32.3)
Total	1445 (100.0)	1426 (100.0)
Disease site,* n *(%)		
Colon	1169 (80.9)	1155 (81.0)
Rectum	276 (19.1)	271 (19.0)
Total	1445 (100.0)	1426 (100.0)

continued

TABLE 18 Characteristics of patients assessed with GOG-Ntx4 (*continued*)

Characteristic	Randomised treatment group	
	3 months of treatment	6 months of treatment
T stage*, n *(%)		
0	0 (0.0)	1 (0.1)
1	35 (2.4)	42 (2.9)
2	133 (9.2)	126 (8.8)
3	831 (57.5)	806 (56.5)
4	445 (30.8)	451 (31.6)
X	1 (0.1)	0 (0.0)
Total	1445 (100.0)	1426 (100.0)
N stage*, n *(%)		
0	232 (16.1)	230 (16.1)
1	830 (57.4)	816 (57.2)
2	383 (26.5)	380 (26.6)
Total	1445 (100.0)	1426 (100.0)
Planned treatment*, n *(%)		
FOLFOX	467 (32.3)	458 (32.1)
CAPOX	978 (67.7)	968 (67.9)
Total	1445 (100.0)	1426 (100.0)
If CAPOX planned, starting dose of capecitabine*, n *(%)		
750 mg/m^2	159 (21.8)	149 (20.6)
800 mg/m^2	28 (3.8)	30 (4.1)
1000 mg/m^2	543 (74.4)	545 (75.3)
Total	730 (100.0)	724 (100.0)
High-risk stage II		
No	1215 (84.1)	1199 (84.1)
Yes	230 (15.9)	227 (15.9)
Total	1445 (100.0)	1426 (100.0)

CAPOX, oxaliplatin and capecitabine; FOLFOX, oxaliplatin and 5FU.

Appendix 2 Reasons for missing quality of life questionnaires, examination of pattern of missingness and sensitivity analysis

It can be seen that the reasons are broadly similar between the treatment groups, the most common reason being 'other'. Examination of a random sample of the free text on the CRFs when the reason for 'other' was entered indicates that in the vast majority of cases this was an error of some sort (e.g. form was not returned, a site error occurred, patient forgot). The high proportion of 'not required' for GOG-Ntx4 is a result of administrative delay in implementing the amendment to extend the recording period for the questionnaire.

TABLE 19 Reasons for missing questionnaires as recorded on study CRF

	Treatment group	
Missing questionnaires: reason	3 months	6 months
EORTC questionnaire*, n *(%)		
Complete	6629 (81.4)	7420 (80.2)
Patient refused	175 (2.1)	168 (1.8)
Patient relapsed/evidence of new tumour	56 (0.7)	53 (0.6)
Patient unfit	33 (0.4)	46 (0.5)
Other	1233 (15.1)	1542 (16.7)
Not required	19 (0.2)	28 (0.3)
EQ-5D questionnaire*, n *(%)		
Complete	8924 (76.2)	9684 (75.3)
Patient refused	256 (2.2)	273 (2.1)
Patient relapsed/evidence of new tumour	213 (1.8)	181 (1.4)
Patient unfit	73 (0.6)	89 (0.7)
Other	2204 (18.8)	2573 (20.0)
Not required	46 (0.4)	55 (0.4)
GOG-Ntx4 questionnaire*, n *(%)		
Complete	9658 (64.4)	10,858 (65.6)
Patient refused	263 (1.8)	281 (1.7)
Patient relapsed/evidence of new tumour	190 (1.3)	187 (1.1)
Patient unfit	74 (0.5)	101 (0.6)
Other	2890 (19.3)	3255 (19.7)
Not required	1924 (12.8)	1871 (11.3)

Table 20 shows the proportion of missing PRO questionnaires by baseline patient characteristics. It can be seen that the proportion is very similar for all baseline characteristics, with the difference in general being very small and never exceeding 5%.

Table 21 summarises the comparison of the three most important PRO end points at key time points. The first column is taken from the imputation analysis as presented in the paper, the second column is based on observed data and the last column is based on an imputation restricted to patients who completed a baseline questionnaire. This last analysis was carried out to ensure that the analysis set could not be influenced by a patient's subsequent experience on the study (e.g. patients who should have completed at baseline but were missed and subsequently completed a follow-up form because they developed neurotoxicity are omitted from this analysis).

At all time points the mean differences are similar and consistent in terms of statistical significance.

TABLE 20 Missing questionnaires (yes/no) by baseline characteristics

	EORTC missing, *n* (%)		EQ-5D missing, *n* (%)		GOG-Ntx4 missing, *n* (%)	
Characteristic	No	Yes	No	Yes	No	Yes
Gender						
Female	5371 (79.8)	1362 (20.2)	7103 (74.9)	2376 (25.1)	7753 (64.4)	4286 (35.6)
Male	8678 (81.3)	1991 (18.7)	11,505 (76.2)	3587 (23.8)	12,763 (65.4)	6750 (34.6)
Age group (years)						
≤ 50	1326 (81.3)	304 (18.7)	1715 (75.1)	570 (24.9)	1940 (65.4)	1026 (34.6)
≤ 70	9529 (80.9)	2250 (19.1)	12,666 (76.2)	3958 (23.8)	13,961 (65.0)	7503 (35.0)
> 70	3194 (80.0)	799 (20.0)	4227 (74.7)	1435 (25.3)	4615 (64.8)	2507 (35.2)
Performance status						
0	9259 (80.6)	2222 (19.4)	12,190 (75.4)	3980 (24.6)	14,112 (65.4)	7451 (34.6)
1	4790 (80.9)	1131 (19.1)	6418 (76.4)	1983 (23.6)	6404 (64.1)	3585 (35.9)
T-stage						
X/0/1	406 (77.3)	119 (22.7)	536 (74.5)	183 (25.5)	583 (63.9)	330 (36.1)
2	1278 (81.2)	296 (18.8)	1710 (76.8)	518 (23.2)	1888 (65.6)	991 (34.4)
3	8082 (81.7)	1811 (18.3)	10,783 (76.8)	3250 (23.2)	11,866 (65.7)	6200 (34.3)
4	4283 (79.2)	1127 (20.8)	5579 (73.5)	2012 (26.5)	6179 (63.7)	3515 (36.3)
N-stage						
0	2121 (82.5)	451 (17.5)	3072 (77.2)	908 (22.8)	3566 (66.3)	1810 (33.7)
1	8004 (81.1)	1863 (18.9)	10,514 (76.2)	3287 (23.8)	11,724 (65.5)	6172 (34.5)
2	3924 (79.1)	1039 (20.9)	5022 (74.0)	1768 (26.0)	5226 (63.1)	3054 (36.9)
Treatment						
FOLFOX	5479 (82.1)	1197 (17.9)	6935 (76.8)	2090 (23.2)	7897 (67.7)	3765 (32.3)
CAPOX	8570 (79.9)	2156 (20.1)	11,673 (75.1)	3873 (24.9)	12,619 (63.4)	7271 (36.6)

CAPOX, oxaliplatin and capecitabine; FOLFOX, oxaliplatin and 5FU.

TABLE 21 Sensitivity analysis of PRO results

Difference	Imputed (as in manuscript), mean (SE)	Observed data only, mean (SE)	Imputed (restricted to patients who completed baseline questionnaire), mean (SE)
GOG-Ntx4 questionnaire			
Difference[a] at 6 months	–1.99 (0.17)[b]	–2.31 (0.35)[b]	–2.16 (0.28)[b]
Difference at 12 months	–2.48 (0.15)[b]	–2.54 (0.23)[b]	–2.30 (0.20)[b]
Difference at 5 years	–2.07 (0.33)[b]	–1.90 (0.42)[b]	–1.90 (0.34)[b]
EORTC-QLQ-C30 global quality of life			
Difference at 6 months	11.58 (1.00)[b]	12.00 (1.41)[b]	12.72 (1.82)[b]
Difference at 12 months	1.48 (0.85)[c]	1.57 (0.99)[c]	1.22 (0.86)[c]
EQ-5D Visual Analogue Scale			
Difference at 6 months	9.80 (1.04)[b]	7.05 (1.52)[b]	7.36 (0.90)[b]
Difference at 12 months	1.45 (0.88)[c]	1.68 (0.96)[c]	1.31 (1.00)[c]

a Difference at 3–6 months.
b $p < 0.001$.
c $p > 0.05$.

Appendix 3 Short Course Oncology Therapy site recruitment and principal investigators

Site name	Principal investigator(s)	Total recruitment (*n*)
Beatson West of Scotland Cancer Centre	Professor Jim Cassidy	141
	Dr Ashita Waterson	
Royal United Hospital Bath	Dr Gareth Rees	111
	Dr Louise Medley	
	Dr Emma De Winton	
Addenbrookes Hospital	Dr Charles Wilson	97
Royal Cornwall Hospital	Dr Richard Ellis	94
Royal Surrey County Hospital	Dr Gary Middleton	93
	Dr Sharadah Essapen	
Castle Hill Hospital	Dr Amandeep Dhadda	91
Mount Vernon Hospital	Dr Rob Hughes	89
Bristol Oncology Centre	Dr Stephen Falk	85
Queen's Hospital	Dr Sherif Raouf	83
Southampton General Hospital	Dr Timothy Iveson	81
Western General Hospital	Dr Lesley Dawson	80
Christie Hospital NHS Trust	Dr Mark Saunders	77
Salisbury District Hospital	Dr Timothy Iveson	77
	Dr Alaaeldin Shablak	
Velindre NHS Trust Hospital	Dr Alison Brewster	76
St Bartholomews Hospital	Dr David Propper	74
Queen Alexandra Hospital	Dr Ann O'Callaghan	73
Sjællands Universites Hospital, Næstved	Dr Neils Henrik Holländer	70
Princess Alexandra Hospital	Dr John Bridgewater	69
Royal Marsden Hospital (Sutton)	Professor David Cunningham	67
Leicester Royal Infirmary	Professor Will Steward	59
	Professor Anne Thomas	
Worcester Royal Hospital	Dr David Farrugia	59
	Dr Mark Churn	
Singleton Hospital	Professor John Wagstaff	57
Birmingham Heartlands Hospital	Dr Ian Geh	55
	Dr Shobhit Baijal	
Maidstone and Tunbridge Wells NHS Trust	Dr Mark Hill	55
Royal Shrewsbury Hospitals NHS Trust	Dr Saif Awwad	54
	Dr Abel Zachariah	

APPENDIX 3

Site name	Principal investigator(s)	Total recruitment (*n*)
Northampton General Hospital NHS Trust	Dr Kinnari Patel	53
	Dr Craig Macmillan	
	Dr Roshan Agarwal	
Russells Hall Hospital	Professor David Ferry	51
	Dr Simon Grumett	
Lincoln County Hospital	Dr Tom Sheehan	50
	Dr Zuzana Stokes	
Fife Health Board	Dr Catriona Mclean	48
King Edward VII Hospital	Dr Marcia Hall	48
	Dr Maher Hadaki	
Royal Hampshire County Hospital	Dr Virginia Hall	48
	Dr Sanjay Raj	
	Dr David Nolan	
Sunderland Royal Hospital	Dr Ashraf Azzabi	48
West Suffolk Hospital	Dr Anne Margaret Moody	48
Hammersmith Hospital	Dr Charles Lowdell	47
Churchill Hospital	Dr Andrew Weaver	46
Aarhus University Hospital	Dr René Krøjgaard Olesen	45
Yeovil District Hospital	Dr Stephen Falk	43
	Dr Julie Walther	
	Dr Erica Beaumont	
	Dr Matthew Sephton	
Kettering General Hospital	Dr Craig Macmillan	42
	Dr Guy Faust	
	Dr Roshan Agarwal	
Crosshouse Hospital	Dr Jeffery White	41
Musgrove Park Hospital	Dr Julie Walther	41
	Dr Clare Barlow	
Worthing Hospital	Dr Andrew Webb	41
Hinchingbrooke Hospital	Dr Cheryl Palmer	40
Great Western Hospital	Dr Claire Hobbs	39
	Dr Sarah Lowndes	
Hospital Universitari Vall D Hebron	Dr Elena Elez Meelez	39
Monklands District General Hospital	Dr Ashita Waterston	39
	Dr Clinton Ali	
	Dr Anne Mckillop	
Wycombe Hospital	Dr Andrew Weaver	39
Aalborg Hospital	Dr Jorgen Hansen	38
	Dr Mette Yilmaz	

Site name	Principal investigator(s)	Total recruitment (*n*)
Ipswich Hospital	Dr Rubin Soomal	38
	Dr Liz Sherwin	
Pilgrim Hospital	Dr Tom Sheehan	38
	Dr Zuzana Stokes	
Raigmore Hospital	Dr David Whillis	38
	Dr Neil Mcphail	
St James's University Hospital	Dr Daniel Swinson	38
Stepping Hill Hospital	Dr Jurjees Hasan	38
Weston Park Hospital NHS Trust	Dr Simon Pledge	38
Withybush General Hospital	Dr Vallipuram Vigneswaran	38
Belfast City Hospital	Dr Richard Wilson	37
Glan Clwyd Hospital	Dr Simon Gollins	37
Guy's and St Thomas' NHS Trust	Dr Nicholas Maisey	37
Poole Hospital NHS Trust	Dr Tamas Hickish	37
	Dr Amelie Harle	
Royal Bournemouth Hospital	Dr Tamas Hickish	37
Wrexham Maelor Hospital	Dr Simon Gollins	37
Hillerød Hospital	Dr Svend Erik Nielsen	36
Queen Elizabeth Hospital – King's Lynn	Dr Athar Ahmad	36
	Dr Gail Horan	
St George's Hospital	Dr Fiona Lofts	36
University College London Hospital	Dr John Bridgewater	36
York Hospital	Dr Kim Last	36
Nottingham University Hospital NHS Trust	Dr Eric Bessell	35
	Dr Vanessa Potter	
	Dr Georgina Walker	
Royal Berkshire Hospital	Dr James Gildersleve	35
Wexham Park Hospital	Dr Marcia Hall	35
	Dr Maher Hadaki	
South Tyneside District Hospital	Dr Shraf Azzabi	34
Broomfield Hospital	Professor Saad Tahir	33
	Dr Gopalakrishnan Srinivasan	
Eastbourne District General	Dr Fiona Mckinna	33
ICO L'Hospitalet	Dr Ramon Salazar	33
	Dr Gemma Soler	
Torbay Hospital	Dr Nangi Lo	33
Conquest Hospital	Dr Timothy Sevitt	32

APPENDIX 3

Site name	Principal investigator(s)	Total recruitment (*n*)
Luton and Dunstable Hospital	Dr Suzannah Mawdsley	32
	Dr Faye Lim	
	Professor Peter Hoskin	
Aberdeen Royal Infirmary	Dr Leslie Samuel	31
Basingstoke and North Hampshire Hospital	Dr Charlotte Rees	31
North Middlesex University Hospital	Dr John Bridgewater	31
Queen's Hospital Burton	Dr Prabir Chakraborti	31
	Dr Pugazhenthi Pattu	
	Dr Majusha Keni	
Blackpool Victoria Hospital	Dr Shabbir Susnerwala	30
	Dr Sin Chong Lau	
Cheltenham General Hospital	Dr David Farrugia	30
Regionshospitalet Herning	Dr Nina Keldsen	30
Diana Princess of Wales Hospital	Dr Rajarshi Roy	29
Dorset County Hospital	Dr Richard Osborne	29
	Dr Maxine Flubacher	
Cumberland Infirmary	Dr Jonathan J Nicoll	28
Gloucestershire Royal Hospital	Dr David Farrugia	28
Hereford County Hospital	Dr Nick Reed	28
Rigshospitalet	Dr Lone Nørgaard	28
Wansbeck Hospital	Dr Werner Dobrowsky	28
	Dr Sandeep Singhal	
Charing Cross Hospital	Dr Charles Lowdell	27
	Dr Susan Cleator	
Peterborough Hospital	Dr Karen Mcadam	27
	Dr Abigail Hollingdale	
Queen Elizabeth Hospital (Gateshead)	Dr Werner Dobrowsky	27
	Dr Fiona McDonald	
	Dr Mark Katory	
Queen Elizabeth Hospital (Birmingham)	Dr Neil Steven	27
Scarborough Hospital	Dr Mohan Hingorani	27
	Dr Pugazhenthi Pattu	
Southend Hospital	Dr David Tsang	27
James Cook University Hospital	Dr Nicholas Wadd	27
Altnagelvin Hospital	Dr Russell Houston	26
	Dr Claire Harrison	
	Dr Sonali Dasgupta	
Scunthorpe General Hospital	Dr Abdel Hamid	26
	Dr Lorcan O'Toole	

Site name	Principal investigator(s)	Total recruitment (*n*)
Good Hope Hospital	Dr John Glaholm	25
	Dr Shobhit Baijal	
Royal Sussex County Hospital	Dr Andrew Webb	25
Hospital Donostia	Dr Adelaida-Lacasta Munoa	24
New Cross Hospital	Dr Mark Churn	24
	Dr Simon Grummet	
University Hospital of North Staffordshire	Dr Fawzi Adab	24
Countess of Chester Hospital	Dr Adrian Moss	23
	Dr Shaker Abdallah	
	Dr Dale Vimalachandran	
University Hospital of Lewisham	Professor George Mikhael	23
	Dr Jessica Brady	
Royal Derby Hospital	Dr Rajendra Kulkarni	23
Medway Maritime Hospital	Dr Jeff Summers	22
	Dr Christos Mikropoulos	
Royal Preston Hospital	Dr Shabbir Susnerwala	22
	Dr Deborah Williamson	
University Hospital of North Durham	Dr Fareeda Coxon	22
Complejo Hospitalario Universitario de Santiago	Dr Rafael Lopez	21
Forth Valley Royal Hospital	Dr Ghazia Shaikh	21
	Dr Saranya Kakumanu	
	Dr Stephen Harrow	
	Dr Adnan Shaukat	
	Dr Aisha Tufail	
	Dr Dawn Storey	
Kent and Canterbury Hospital	Professor Roger James	21
	Dr Julia Hall	
	Dr Rakesh Raman	
Basildon Hospital	Dr David Tsang	20
Clatterbridge Centre for Oncology	Dr David Smith	20
	Dr Julie O'Hagan	
Freeman Hospital	Dr Fareeda Coxon	20
Stoke Mandeville Hospital	Dr Andrew Weaver	20
Darlington Memorial Hospital	Dr Fareeda Coxon	19
Harrogate District Hospital	Dr Kim Last	19
Hospital Del Mar	Dr Joaquim Bellmunt	19
Queen Elizabeth Hospital (London)	Dr Nicholas Maisey	19
	Dr Asad Qureshi	
Royal Marsden Hospital (London)	Professor David Cunningham	19

APPENDIX 3

Site name	Principal investigator(s)	Total recruitment (*n*)
Sjællands Universites Hospital, Roskilde	Dr Jim Stenfatt Larsen	19
St Helens and Knowsley NHS Trust	Dr Ernest Marshall	19
Karolinska University Hospital	Dr Gisela Naucler	18
	Dr Jan-Erik Frödin	
Lister Hospital	Dr Rob Hughes	18
St Mary's Hospital (Low)	Dr Christopher Baughan	18
	Dr Harish Reddy	
Glangwili General Hospital	Dr Margaret Wilkins	18
	Dr Thi Mau-Don Phan	
William Harvey Hospital	Professor Roger James	18
	Dr Julia Hall	
Bronglais General Hospital	Dr Alan Axford	17
	Dr Sajid Durrani	
	Dr Elin Jones	
Darent Valley Hospital	Dr Andrew Gaya	17
	Dr Hazif Al Gurafi	
	Dr Riyaz Nazeerul Haq Shah	
Hairmyres Hospital	Dr Grainne Dunn	17
Kidderminster Hospital	Dr Mark Churn	17
The Royal Oldham Hospital	Dr Saifee Mullamitha	17
Ayr Hospital	Dr Jeffery White	16
Craigavon Area Hospital	Dr Richard Park	16
Esbjerg Hospital	Dr Brita Bjerregaard	16
King's Mill Hospital	Dr Ivo Hennig	16
	Dr Eleanor James	
	Dr Eliot Chadwick	
	Dr Christina Lopezesccola	
Warrington and Halton Hospitals NHS Trust	Dr Adrian Moss	16
	Dr Amy Ford	
Herlev Hospital	Dr Kirsten Vistisen	15
Hospital Arnau De Villanova Lleida	Dr Antonia Salud	15
Macclesfield District General Hospital	Dr Catherine Mcbain	15
	Dr Ganesh Radhakrishna	
Bradford Royal Infirmary	Dr Chris Bradley	14
	Dr Andrew Conn	
North West London Hospitals NHS Trust	Dr Nicola Anyamene	14
Royal Free Hospital	Dr Astrid Mayer	14
Sønderborg Hospital	Dr Jurij Bogovic	14
University Hospital of North Tees	Dr David Wilson	14

Site name	Principal investigator(s)	Total recruitment (*n*)
Bendigo Hospital	Dr Robert Blum	13
Bishop Auckland General Hospital	Dr Nick Wadd	13
	Dr Fareeda Coxon	
Central Hospital Vasteras	Dr Henry Letocha	13
	Dr Andrzej Piwowar	
City Hospital Trust	Dr Daniel Rea	13
	Dr Pankaj Punia	
Manor Hospital	Dr Andrew Hartley	13
	Dr Victoria Kunene	
Royal Hobart Hospital	Dr Ray Lowenthal	13
	Dr David Boadle	
Royal Albert Edward Infirmary	Dr Gregory Wilson	13
	Dr Elena Takeuchi	
	Dr Francisca Elena Marti	
Weston General Hospital	Dr Marjorie Tomlinson	13
	Dr Reuben West	
Austin Hospital	Dr Niall Tebbutt	12
Bankstown – Lidcombe Hospital	Dr Ray Asghari	12
Nambour General Hospital	Dr Michelle Cronk	12
Queen Elizabeth The Queen Mother Hospital	Professor Roger James	12
	Dr Julia Hall	
Bedford Hospital NHS Trust	Professor Robert Thomas	11
Hospital Universitario De Canarias	Dr Marta Llanos	11
Hospital Clinico Universitario De Valencia	Dr Andres Cervantes	11
Royal Marsden Hospital (Kingston)	Dr David Cunningham	11
Uppsala University Hospital	Dr Bengt Glimelius	11
West Cumberland Hospital	Dr Jonathan J Nicoll	11
West Middlesex University Hospitals	Dr Pippa Riddle	11
Hospital Clinic I Provincial De Barcelona	Dr Cristina Nadal	10
	Dr Estela Pineda	
North Devon District Hospital	Dr Mark Napier	10
Sandwell General Hospital	Dr Daniel Rea	10
	Dr Pankaj Punia	
Southport and Formby District General Hospital	Dr Arthur Sun Myint	10
	Dr Nasim Ali	
St Mary's Hospital London	Dr Susan Cleator	10
The Tweed Hospital	Professor Ehtesham Abdi	10
Ysbyty Gwynedd Hospital	Dr Nick Stuart	10
	Dr Catherine Bale	

APPENDIX 3

Site name	Principal investigator(s)	Total recruitment (*n*)
Ballarat Hospital	Dr Geoff Chong	9
Canberra Hospital	Professor Desmond Yip	9
Centrallasarettet Vaxjo	Dr Eva Fernebro	9
	Dr Ulrika Palenius	
Complejo Hospitalario Universitario De Albacete	Dr Carmen Alonso Lopez	9
Hospital Universitario Marques De Valdecilla	Dr Fernando Rivera-Herrero	9
St John of God Hospital Bunbury	Dr Martin Buck	9
Airedale General Hospital	Dr Andrew Conn	8
Aintree University Hospitals	Dr David Smith	8
	Dr Julie Hagan	
Alfred Hospital	Dr Andrew Haydon	8
Auckland Hospital	Dr George Laking	8
Concord Repatriation General Hospital	Professor Philip Beale	8
Flinders Medical Centre	Dr Chris Karapetis	8
Hospital Universitario Madrid Norte Sanchinarro	Dr Antonio Cubillo	8
North Tyneside General Hospital	Dr Philip Atherton	8
Royal Devon and Exeter Hospital	Dr Melanie Osborne	8
	Dr Mark Napier	
County Hospital Ryhov	Dr Helga Hagman	7
Hospital La Fe	Dr Jorge Aparicio	7
Hospital Virgen De La Arrixaca	Dr Miguel Marin Vera	7
Inverclyde Royal Hospital	Dr Stephen Harrow	7
	Dr Dawn Storey	
Royal Lancaster Infirmary	Dr David Fyfe	7
	Dr David Eaton	
Royal Brisbane and Women's Hospital	Dr Matthew Burge	7
Whittington Hospital	Dr Daniel Hochhauser	7
	Dr Pauline Leonard	
University Hospital of Hartlepool	Dr David Wilson	7
University Hospital Linköping	Dr Maria Albertsson	7
Cabrini Hospital	Dr Andrew Haydon	6
Calderdale and Huddersfield NHS Foundation Trust	Dr Jo Dent	6
Dumfries and Galloway Royal Infirmary	Dr Lesley Dawson	6
Hospital Miguel Servet	Dr Antonio Anton	6
Hospital De Txagorritxu	Dr Severina Dominguez	6
Leighton Hospital	Dr Chan Ton	6
	Dr Michael Braun	

Site name	Principal investigator(s)	Total recruitment (*n*)
Milton Keynes General Hospital	Dr Jill Stewart	6
	Dr Gerard Andrade	
	Dr Somnath Mukherjee	
Prince of Wales Hospital	Professor David Goldstein	6
Queen Elizabeth Hospital (Australia)	Professor Tim Price	6
Royal North Shore Hospital	Dr Alex Guminski	6
	Associate Professor Nick Pavlakis	
St Vincent's Hospital	Dr Eva Segelov	6
Essex County Hospital	Dr Bruce Sizer	5
Falu Hospital	Dr Ake Berglund	5
Pinderfields General Hospital	Dr Gireesh Kumaran	5
	Dr Konstantinos Kamposioras	
Campbelltown Hospital	Dr Lorraine Chantrill	4
Christchurch Hospital	Dr Mark Jeffery	4
Furness General Hospital	Dr Alison Birtle	4
	Dr David Eaton	
Illawarra Cancer Centre (Wollongong Hospital)	Dr Morteza Aghmesheh	4
Kalmar County Hospital	Dr Charlotte Bratthall	4
Nevil Hall Hospital	Dr Nayyer Iqbal	4
	Dr Mohammed Harb	
	Dr Keith Yinn	
Nepean Cancer Care Centre	Dr Jenny Shannon	4
Norrlands University Hospital	Dr Birgitta Lindh	4
Princess Alexandra Hospital (Australia)	Dr Warren Joubert	4
Royal Darwin Hospital	Dr Narayan Karanth	4
St John of God Hospital Subiaco	Dr Siobhan Ng	4
	Dr Tom Van Hagen	
Tamworth Base Hospital	Dr Mathew George	4
Antrim Area Hospital	Dr Colin Purcell	3
St Richard's Hospital	Dr Suhail Baluch	3
	Dr Ann O'Callaghan	
	Dr Yasser Haba	
Wellington Hospital	Dr Anne O'Donnell	3
Ballarat Oncology and Haematology Services	Dr George Kannourakis	2
Coffs Harbour Health Campus	Dr Karen Briscoe	2
Gosford Hospital	Dr Susan Tiley	2
Hallands Hospital	Dr Lotta Lundgren	2
Royal Perth Hospital	Dr David Ransom	2
University Hospital of Skåne	Dr Margareta Heby	2

APPENDIX 3

Site name	Principal investigator(s)	Total recruitment (*n*)
Armidale Hospital	Associate Professor Nick Pavlakis	1
Dunedin Hospital	Dr Chris Jackson	1
Hospital De Cruces	Dr Guillermo Lopez Vivanco	1
ICO Del Hospital Josep Trueta	Dr Bernardo Queralt	1
Royal Liverpool University Hospital	Dr David Smith	1
Sundsvall Härnösand County Hospital	Dr Petra Flygare	1

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