Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial

*John A Bridgewater, Siân A Pugh, Tom Maishman, Zina Eminton, Jane Mellor, Amy Whitehead, Louise Stanton, Michael Radford, Andrea Corkhill, Gareth O Griffiths, Stephen Falk, Juan W Valle, Derek O'Reilly, Ajith K Siriwardena, Joanne Hornbuckle, Myrddin Rees, Timothy J Iveson, Tamas Hickish, O James Garden, David Cunningham, Timothy S Maughan, John N Primrose; on behalf of the New EPOC investigators**

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*New EPOC investigators are listed in the appendix (p 2)

UCL Cancer Institute, University College London, London, UK (Prof J A Bridgewater PhD); **Addenbrooke's Hospital, Cambridge, UK** (S A Pugh MRCP); **Southampton Clinical Trials Unit** (T Maishman PhD, Z Eminton BSc, J Mellor MSc, A Whitehead PhD, L Stanton MSc, M Radford, A Corkhill BSc, Prof G O Griffiths PhD) **and Department of Surgery** (Prof J N Primrose FMedSci), **University of Southampton, Southampton, UK; Bristol Cancer Institute, Bristol, UK** (S Falk MD); **Division of Cancer Sciences/The Christie NHS Foundation Trust, University of Manchester, Manchester, UK** (Prof J W Valle MD); **Manchester Royal Infirmary, Manchester, UK** (D O'Reilly FRCS, Prof A K Siriwardena MD); **Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, UK** (J Hornbuckle MD); **Basingstoke and North Hampshire Hospital, Basingstoke, UK** (M Rees MS); **University Hospital Southampton NHS Foundation Trust, Southampton, UK** (Prof T J Iveson MD); **Dorset Cancer Centre/Bournemouth University, Bournemouth, UK** (Prof T Hickish MD); **Clinical Surgery, University of Edinburgh, UK** (Prof O J Garden MD); **Royal Marsden Hospital, London, UK** (Prof D Cunningham FMedSci);

Summary

Background The interim analysis of the multicentre New EPOC trial in patients with resectable colorectal liver metastasis showed a significant reduction in progression-free survival in patients allocated to cetuximab plus chemotherapy compared with those given chemotherapy alone. The focus of the present analysis was to assess the effect on overall survival.

Methods New EPOC was a multicentre, open-label, randomised, controlled, phase 3 trial. Adult patients (aged ≥18 years) with *KRAS* wild-type (codons 12, 13, and 61) resectable or suboptimally resectable colorectal liver metastases and a WHO performance status of 0–2 were randomly assigned (1:1) to receive chemotherapy with or without cetuximab before and after liver resection. Randomisation was done centrally with minimisation factors of surgical centre, poor prognosis cancer, and previous adjuvant treatment with oxaliplatin. Chemotherapy consisted of oxaliplatin 85 mg/m² administered intravenously over 2 h, *l*-folinic acid (175 mg flat dose administered intravenously over 2 h) or *d,l*-folinic acid (350 mg flat dose administered intravenously over 2 h), and fluorouracil bolus 400 mg/m² administered intravenously over 5 min, followed by a 46 h infusion of fluorouracil 2400 mg/m² repeated every 2 weeks (regimen one), or oxaliplatin 130 mg/m² administered intravenously over 2 h and oral capecitabine 1000 mg/m² twice daily on days 1–14 repeated every 3 weeks (regimen two). Patients who had received adjuvant oxaliplatin could receive irinotecan 180 mg/m² intravenously over 30 min with fluorouracil instead of oxaliplatin (regimen three). Cetuximab was given intravenously, 500 mg/m² every 2 weeks with regimen one and three or a loading dose of 400 mg/m² followed by a weekly infusion of 250 mg/m² with regimen two. The primary endpoint of progression-free survival was published previously. Secondary endpoints were overall survival, preoperative response, pathological resection status, and safety. Trial recruitment was halted prematurely on the advice of the Trial Steering Committee on Nov 1, 2012. All analyses (except safety) were done on the intention-to-treat population. Safety analyses included all randomly assigned patients. This trial is registered with ISRCTN, number 22944367.

Findings Between Feb 26, 2007, and Oct 12, 2012, 257 eligible patients were randomly assigned to chemotherapy with cetuximab (n=129) or without cetuximab (n=128). This analysis was carried out 5 years after the last patient was recruited, as defined in the protocol, at a median follow-up of 66·7 months (IQR 58·0–77·5). Median progression-free survival was 22·2 months (95% CI 18·3–26·8) in the chemotherapy alone group and 15·5 months (13·8–19·0) in the chemotherapy plus cetuximab group (hazard ratio [HR] 1·17, 95% CI 0·87–1·56; p=0·304). Median overall survival was 81·0 months (59·6 to not reached) in the chemotherapy alone group and 55·4 months (43·5–71·5) in the chemotherapy plus cetuximab group (HR 1·45, 1·02–2·05; p=0·036). There was no significant difference in the secondary outcomes of preoperative response or pathological resection status between groups. Five deaths might have been treatment-related (one in the chemotherapy alone group and four in the chemotherapy plus cetuximab group). The most common grade 3–4 adverse events reported were: neutrophil count decreased (26 [19%] of 134 in the chemotherapy alone group *vs* 21 [15%] of 137 in the chemotherapy plus cetuximab group), diarrhoea (13 [10%] *vs* 14 [10%]), skin rash (one [1%] *vs* 22 [16%]), thromboembolic events (ten [7%] *vs* 11 [8%]), lethargy (ten [7%] *vs* nine [7%]), oral mucositis (three [2%] *vs* 14 [10%]), vomiting (seven [5%] *vs* seven [5%]), peripheral neuropathy (eight [6%] *vs* five [4%]), and pain (six [4%] *vs* six [4%]).

Interpretation Although the addition of cetuximab to chemotherapy improves the overall survival in some studies in patients with advanced, inoperable metastatic disease, its use in the perioperative setting in patients with operable disease confers a significant disadvantage in terms of overall survival. Cetuximab should not be used in this setting.

Funding Cancer Research UK.

Introduction

Colorectal cancer is the fourth most common cancer in the UK. Substantial improvements in its management, with increasingly sophisticated combinations of systemic therapy and surgery, together with earlier diagnosis, have resulted in more than a doubling of the 5-year survival from 25% to 50% in the past 50 years. In the setting of metastatic disease, outcomes are improving and, after liver resection, approximately 30% of patients will be long-term survivors.[1] Unfortunately, the majority of patients will have disease recurrence.

The EPOC study (EORTC 40983) showed an improvement in progression-free survival of 7% with the addition of perioperative systemic chemotherapy to surgical resection for colorectal liver metastasis.[2] As a consequence, this treatment has become standard of care in most UK centres.[3] The New EPOC study was a logical progression from the EPOC study, assessing the benefit of adding cetuximab, an antibody to EGFR with confirmed efficacy in advanced disease,[4] to perioperative systemic chemotherapy. Unexpectedly, this addition resulted in a shorter progression-free survival in the patients treated with cetuximab, and the study was closed to recruitment by the trial steering committee on advice from the independent data monitoring committee on Nov 1, 2012. The previously published results of the interim analysis showed the progression-free survival in the chemotherapy alone group to be 20·5 months (16·8–26·7), compared with 14·1 months (95% CI 11·8–15·9) in the chemotherapy plus cetuximab group, with a hazard ratio (HR) of 1·48 (1·04–2·12; p=0·030),[5] at a median follow-up of 21 months.

Since the New EPOC trial began accrual (Feb 26, 2007), several studies have evaluated the use of antibodies to EGFR in advanced colorectal cancer. Some studies found improved outcomes,[6,7] whereas others showed no difference.[8,9] Importantly, none have shown a detriment similar to the previously published New EPOC study. The present analysis was done after long-term follow-up of patients using a more complete dataset, not available at the time of the interim analysis, to assess the effect of the combination treatment on overall survival.

Methods

Study design and participants

This multicentre, open-label, randomised, controlled, phase 3 study was coordinated by the Cancer Research UK Southampton Clinical Trials Unit. All patients were recruited from 39 UK National Health Service hospitals (appendix pp 3, 4), in secondary care settings.

Eligible patients were aged 18 years or older, with a WHO performance status of 2 or lower, and resectable or suboptimally resectable colorectal liver metastasis without detectable extrahepatic distant metastatic disease. There was no limit to the number of metastases. The protocol mandated that the primary cancer should be resected before trial entry or deemed resectable. Patients were excluded if they had any uncontrolled medical comorbidity likely to interfere with treatment or

Research in context

Evidence before this study

Before designing the New EPOC trial, PubMed, American Society of Clinical Oncology abstracts, and European Society of Medical Oncology abstracts were searched for articles published in English using the search terms "colorectal cancer", "colorectal liver metastases", "chemotherapy", "epidermal growth factor receptor", "cetuximab", and "panitumumab". The search was done in January, 2006, and no date restrictions were applied. No meta-analysis was carried out, as in 2006 only one adequately powered trial of perioperative chemotherapy had been done.

Survival outcomes of chemotherapy for advanced colorectal cancer have improved during the past two decades, in part because of improvements in systemic therapies, including targeted therapies such as cetuximab, an antibody to EGFR. Some, but not all, studies of chemotherapy plus cetuximab have shown the combination to improve the overall survival of patients with advanced inoperable *KRAS* wild-type colorectal cancer. By contrast, the interim analysis of the New EPOC randomised trial showed that this combination significantly shortened progression-free survival in patients with operable colorectal liver metastases. At that time, overall survival data were immature.

Added value of this study

This mature analysis shows that in the perioperative setting, cetuximab shortens overall survival by 2 years compared with chemotherapy alone. This detriment was most notable in patients who had features suggestive of a better prognosis and, crucially, post-progression survival was significantly worse. Toxicity from systemic therapy and complications of surgery could not explain these findings.

Implications of all the available evidence

This study suggests that the addition of cetuximab to chemotherapy in the perioperative setting in patients with operable colorectal liver metastases induces, in some individuals, multisite metastatic recurrence and a shorter overall survival than does chemotherapy alone. These data emphasise that the use of biological agents might have unpredictable results compared with conventional chemotherapy. Cetuximab should not be used in patients with operable colorectal liver metastases.

and MRC Oxford Institute for Radiation Oncology, Department of Oncology, University of Oxford, Oxford, UK (Prof T S Maughan FMedSci)

Correspondence to:
Prof John Primrose, Department of Surgery, Southampton General Hospital, University of Southampton, Southampton SO16 6YD, UK
j.n.primrose@soton.ac.uk

or

Prof John Bridgewater, UCL Cancer Institute, University College London, London WC1E 6AG, UK
j.bridgewater@ucl.ac.uk

See **Online** for appendix

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assessment of response; any psychiatric or neurological disorder affecting ability to consent or comply with medication; partial or complete bowel obstruction; pre-existing peripheral neuropathy of grade 1 or worse according to common toxicity criteria; a personal or family history of dihydropyrimidine dehydrogenase deficiency, Gilbert's syndrome, or other congenital abnormality of biliary transport; platelet counts less than 100×10^9 per L, an absolute neutrophil count less than $1\cdot5\times10^9$ cells per L, serum bilirubin greater than one and a quarter times the upper limit of normal, or alkaline phosphatase greater than five times the upper limit of normal; serum aminotransferase (either aspartate aminotransferase or alanine aminotransferase) greater than two and a half times the upper limit of normal; or estimated creatinine clearance (by Cockcroft formula) of less than 50 mL/min or measured glomerular filtration rate of less than 50 mL/min. Patients with another previous or current malignant disease, which, in the judgment of the treating investigator, was likely to interfere with the study treatment or assessment of response were also excluded.

After the start of the trial, data emerged to support a benefit of cetuximab only in *KRAS* wild-type cancers, which led to a protocol amendment (July 8, 2008) to exclude patients with mutated *KRAS*. All patients accrued thereafter had confirmed *KRAS* wild-type status of the primary colorectal cancer (codons 12, 13, and 61). After completion of the study, a subset of tissue specimens were analysed for expanded *RAS/RAF* mutation status (see appendix p 5).

The study was approved by the South West Research Ethics Committee. Written, informed consent was obtained from all patients before random assignment.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to chemotherapy alone or chemotherapy plus cetuximab. Treatment assignments were made over the telephone by the Medical Research Council Clinical Trials Unit with the use of randomised minimisation factors with 20% random element. The first 52 patients were randomly assigned on the basis of nine stratification factors. A protocol amendment was then implemented on April 22, 2009, to condense the stratification factors to surgical centre, poor prognostic cancer (yes *vs* no), and previous treatment with oxaliplatin as adjuvant (yes *vs* no). Poor prognostic cancer was defined as one or more of: four or more metastases; N2 disease (according to the tumour, node, and metastasis [TNM] staging system); or poor differentiation of primary cancer. The amendment was made because the trial management group thought that the initial large number of stratification factors would be less effective at achieving balance between the treatment groups, as well as being logistically complicated. There was no masking of either investigators or patients to treatment allocation.

Procedures

Patients were randomly assigned to chemotherapy with or without cetuximab for 12 weeks, followed by surgery and then a further 12 weeks of chemotherapy with or without cetuximab. Chemotherapy consisted of oxaliplatin 85 mg/m² administered intravenously over 2 h, *l*-folinic acid (175 mg flat dose administered intravenously over 2 h) or *d*,*l*-folinic acid (350 mg flat dose administered intravenously over 2 h), and 5-fluorouracil bolus 400 mg/m² administered intravenously over 5 min, followed by a 46-h infusion of fluorouracil 2400 mg/m² repeated every 2 weeks (regimen one), or oxaliplatin 130 mg/m² administered intravenously over 2 h and oral capecitabine 1000 mg/m² twice daily on days 1–14 repeated every 3 weeks (regimen two). Patients who had received adjuvant oxaliplatin could receive irinotecan 180 mg/m² intravenously over 30 min with fluorouracil instead of oxaliplatin (regimen three). Choice of regimen was determined according to previous oxaliplatin exposure and clinician and patient choice. Cetuximab was given as an intravenous dose of 500 mg/m² every 2 weeks with regimens one and three or a loading dose of 400 mg/m² followed by a weekly infusion of 250 mg/m² with regimen two. Detailed dose reduction schedules are in the protocol (appendix pp 34–127). Briefly, 20% dose reductions of chemotherapy were made for haematological or gastrointestinal toxic effects and dose delays of 2 weeks or longer were made for cetuximab toxic effects.

There were several protocol changes throughout the duration of the study (appendix pp 17, 18). The most important ones related to the restriction of recruitment to patients with *KRAS* wild-type cancers and the change in the sample size based on the predicted effect size from other studies.

All surgery was done in high-volume liver centres in the UK with expertise in complex liver resections. The protocol stipulated that all sites of metastatic disease (including those responding to neoadjuvant therapy) were resected. In the original trial protocol, written in 2006, it was suggested that a resection margin of 10 mm should be achieved when possible. In the past decade, the consensus on the need for such a large margin has changed, but the protocol was not amended. Staged resection was allowed, as was synchronous resection of the primary cancer. Treatment with ablation was not permitted by the protocol.

All patients were followed up every 3 months for the first 2 years and every 6 months for a further 3 years until progression or death. At these visits, patients underwent a clinical examination, chest–abdomen–pelvis CT, and laboratory investigations, and completed quality-of-life assessments. CT or MRI scans were done to assess Response Evaluation Criteria In Solid Tumors (RECIST; version 1.0) before systemic treatment. The multidisciplinary team managing the patient established

disease progression; external radiological review was not done. Adverse events and safety were assessed using the Common Terminology Criteria for Adverse Events version 3 before each cycle unless there was a presentation earlier.

Criteria for treatment to be discontinued were: progression while on therapy, unacceptable toxicity, intercurrent illness preventing further treatment, withdrawal of consent for treatment by the patient, or any alterations in the patient's condition that justified the discontinuation of treatment in the investigator's opinion.

After Nov 1, 2012, when the predefined futility criteria were met (using a method proposed by Freidlin and colleagues[10] when the lower limit of the 95% CI for the progression-free survival HR was >1), the trial steering committee, on advice from the independent data monitoring committee, requested that cetuximab administration was stopped. Treatment defaulted to standard of care, which, for most patients, was continuation of chemotherapy alone. Data collection to inform outcomes was continued.

Outcomes

The primary outcome was progression-free survival, which was defined as the time from randomisation to disease progression or death from any cause, whichever occurred first, and has been previously reported.[5] Patients without disease progression or death were censored at the date of the last assessment. The objective of this present study was to assess the secondary endpoint of overall survival, defined as the time from randomisation to death from any cause. Patients still alive were censored at the time of last follow-up. Long-term death data were obtained via patient registration with National Health Service (NHS) Digital. As such, the assumption was made that any patient not recorded as having died could be assumed alive (and censored) 2 months before the NHS Digital date of assessment of patient status (ie, this excluded the possibility of missing a death event as the death had not yet reached the NHS Digital database). For the evaluation of progression-free survival, patients lost to follow-up without progression were censored at the date of the last assessment, irrespective of whether or not the date of death was received subsequently via NHS Digital. Other secondary outcomes were preoperative response (response after the end of the preoperative treatment period, assessed using RECIST), pathological resection status (margin ≥1 cm, <1 cm, or cancer on cut surface), safety, quality of life, and cost-effectiveness. Quality-of-life and cost-effectiveness analyses were not done because the trial was negative. Other prespecified exploratory outcomes were post-progression survival in the primary analysis population who progressed and progression-free survival and overall survival in: patients treated with oxaliplatin, fluorouracil, and folinic acid; patients who responded to preoperative chemotherapy; patients with left-sided cancers; and patients with right-sided cancers. All analyses presented were prespecified in the statistical analysis plan that was updated for this mature analysis (appendix pp 196–291).

Statistical analysis

The accrual target of the study was revised on Jan 16, 2012, at the suggestion of the trial steering committee after a reconsideration of the potential effect of *KRAS* wild-type restriction. The revised sample size needed 268 patients (and 212 disease progression events) in patients with wild-type *KRAS* (codons 12, 13, and 61), under the assumptions of a log-rank test HR of 0·68, 80% power, 5% two-sided significance level, 5% loss to follow-up, 3-year recruitment, 5 years of follow-up, and progression-free survival in the chemotherapy alone group of 67% at 1 year, 46% at 2 years, and 35% at 3 years. There was no correction of the p value to adjust for the previous analysis.

An a-priori statistical analysis plan was devised for all analyses of these long-term data. Survival was described using Kaplan-Meier curves and compared using Cox proportional hazards models. The efficacy analyses were done on the primary analysis population (composed of the intention-to-treat population including all patients with known *KRAS* [codons 12, 13, and 61] wild-type status who had data available for the analysis being done), with HRs (95% CIs) and 2-sided p values being calculated. Safety analyses included all randomly assigned patients and involved calculating frequencies and percentages. There was no adjustment for multiple comparisons. The primary analysis used an unadjusted Cox proportional hazards model, but a sensitivity analysis was also done, adjusting the model for the minimisation factors. For all Cox proportional hazards models fitted, the assumption of proportional hazards was checked by visually inspecting the complementary log-log (event times) versus log (time) plot.

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Prespecified exploratory interaction subgroup analyses assessed whether the effect of cetuximab on progression-free survival and overall survival was different depending on backbone treatment, concentration of carcinoembryonic antigen at diagnosis, lymph node-positive primary cancer, poor differentiation at biopsy, number and size of liver metastases, extrahepatic involvement, previous treatment with oxaliplatin, synchronous versus non-synchronous presentation of disease, performance status, resection status of primary cancer at study entry, updated *RAS*/*RAF* mutation status, number of weeks of postoperative chemotherapy received by the patient, and preoperative response.

To test for consistencies in the size of any effect of chemotherapy and cetuximab, a χ^2 test for interaction was done.

STATA (version 15.1) and SAS (version 9.4) were used for all analyses. Data were reviewed by the Data Monitoring and Ethics Committee.

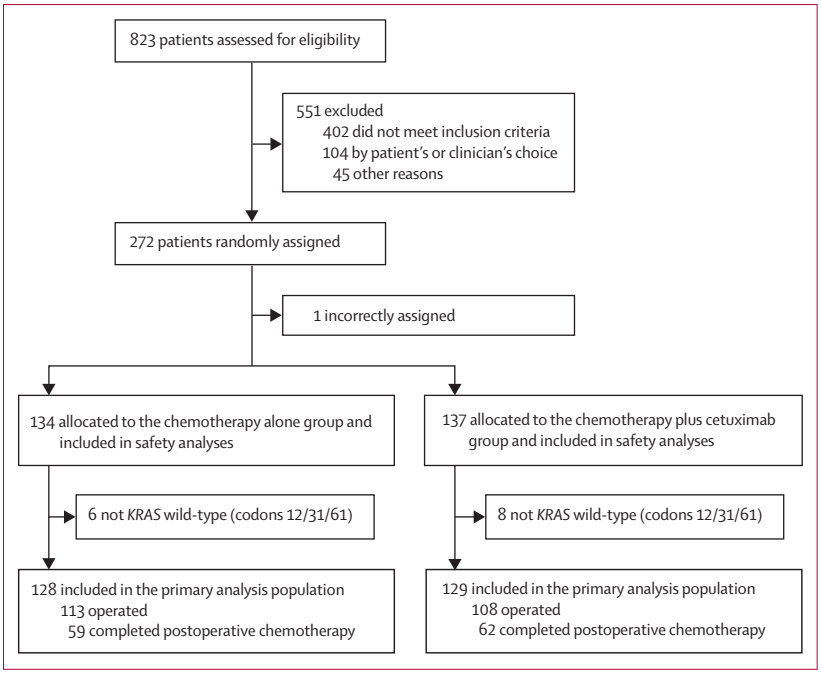

Figure 1: **Trial profile**

	Chemotherapy alone group (n=128)	Chemotherapy plus cetuximab group (n=129)
Age (years)*	65 (59–70)	64 (59–69)
Sex		
Female	47 (37%)	37 (29%)
Male	81 (63%)	92 (71%)
WHO performance status 0 or 1	128 (100%)	126 (98%)
Primary cancer		
T3 or T4†	107 (84%)	109 (84%)
N1 or N2†	83 (65%)	78 (60%)
Poorly differentiated	10 (8%)	15 (12%)
Unresected‡	9 (7%)	18 (14%)
1–3 liver metastases	103 (80%)	97 (75%)
One metastasis >3 cm	63 (49%)	75 (58%)
Synchronous metastases‡	73 (57%)	88 (68%)
Carcinoembryonic antigen >30 ng/mL	31 (24%)	34 (26%)
Extrahepatic disease	3 (2%)	6 (5%)

Data are median (IQR) or n (%). *In the previous publication, age was reported as mean (IQR).[5] †According to the tumour, node, metastasis (TNM) staging system. ‡Data updated since the previous publication, which reported unresected primary cancer at trial entry in 13 (10%) patients in the chemotherapy alone group and 18 (14%) patients in the chemotherapy plus cetuximab group and synchronous metastases in 60 (47%) patients in the chemotherapy alone group and 68 (53%) patients in the chemotherapy plus cetuximab group.[5]

Table 1: **Baseline characteristics (primary analysis population)**

This study is registered with the International Standard Randomised Controlled Trial registry (number 22944367), with ClinicalTrials.gov (number 00482222), and with the UK Clinical Research Network (number 2068).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. TM, AW, and LS had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Results

272 patients were recruited from 39 institutions in the UK between Feb 26, 2007, and Oct 12, 2012, and randomly assigned to treatment. One patient was incorrectly assigned by mistake (ie, the patient was eligible but the centre was asked to proceed with the opposite treatment to the one they had been assigned to), and was excluded from all analyses. An additional 14 patients (six in the chemotherapy alone group and eight in the chemotherapy plus cetuximab group), who were randomly assigned before the amendment necessitating *KRAS* status testing and were retrospectively shown to have a *KRAS* mutation or indeterminate *KRAS* status, were also excluded from all analyses, except safety analyses. As such, the primary analysis population consisted of 257 patients, of whom 128 patients were randomly assigned to received chemotherapy alone and 129 to receive chemotherapy plus cetuximab (figure 1). One patient assigned to the chemotherapy plus cetuximab group was lost to follow-up. Table 1 shows the baseline characteristics, similar to those published previously.[5]

87 (68%) of 128 patients in the chemotherapy alone group versus 89 (69%) of 129 patients in the chemotherapy plus cetuximab group received oxaliplatin, 5-fluorouracil, and folinic acid backbone treatment (regimen 1). Smaller proportions of patients received capecitabine and oxaliplatin (regimen 2; 27 [21%] of 128 *vs* 24 [19%] of 129) or irinotecan, 5-fluorouracil, and folinic acid (regimen 3; 11 [9%] of 128 *vs* 15 [12%] of 129). The patients who had previous oxaliplatin adjuvant therapy or another contra-indication to oxaliplatin were treated using regimen 3. Data on relative dose intensity are in the appendix (pp 19–24).

In this updated analysis, the median follow-up time was 66·7 months (IQR 58·0–77·5): 66·9 months (58·3–77·5) for patients in the chemotherapy alone group and 65·0 months (57·0–77·5) in the chemotherapy plus cetuximab group. For the progression-free survival updated analysis there were 180 events (89 in the chemotherapy alone group and 91 in the chemotherapy plus cetuximab group; since the preliminary analysis in 2013, 57 additional events had occurred [33 in the chemotherapy alone group and 24 in the chemotherapy plus cetuximab group]). The unadjusted HR for progression-free survival was 1·17 (95% CI 0·87–1·56; p=0·304) for chemotherapy without versus with cetuximab, with an observed median progression-free survival of 22·2 months (95% CI 18·3–26·8) in the chemotherapy alone group and 15·5 months (13·8–19·0) in the chemotherapy plus cetuximab group (figure 2A).

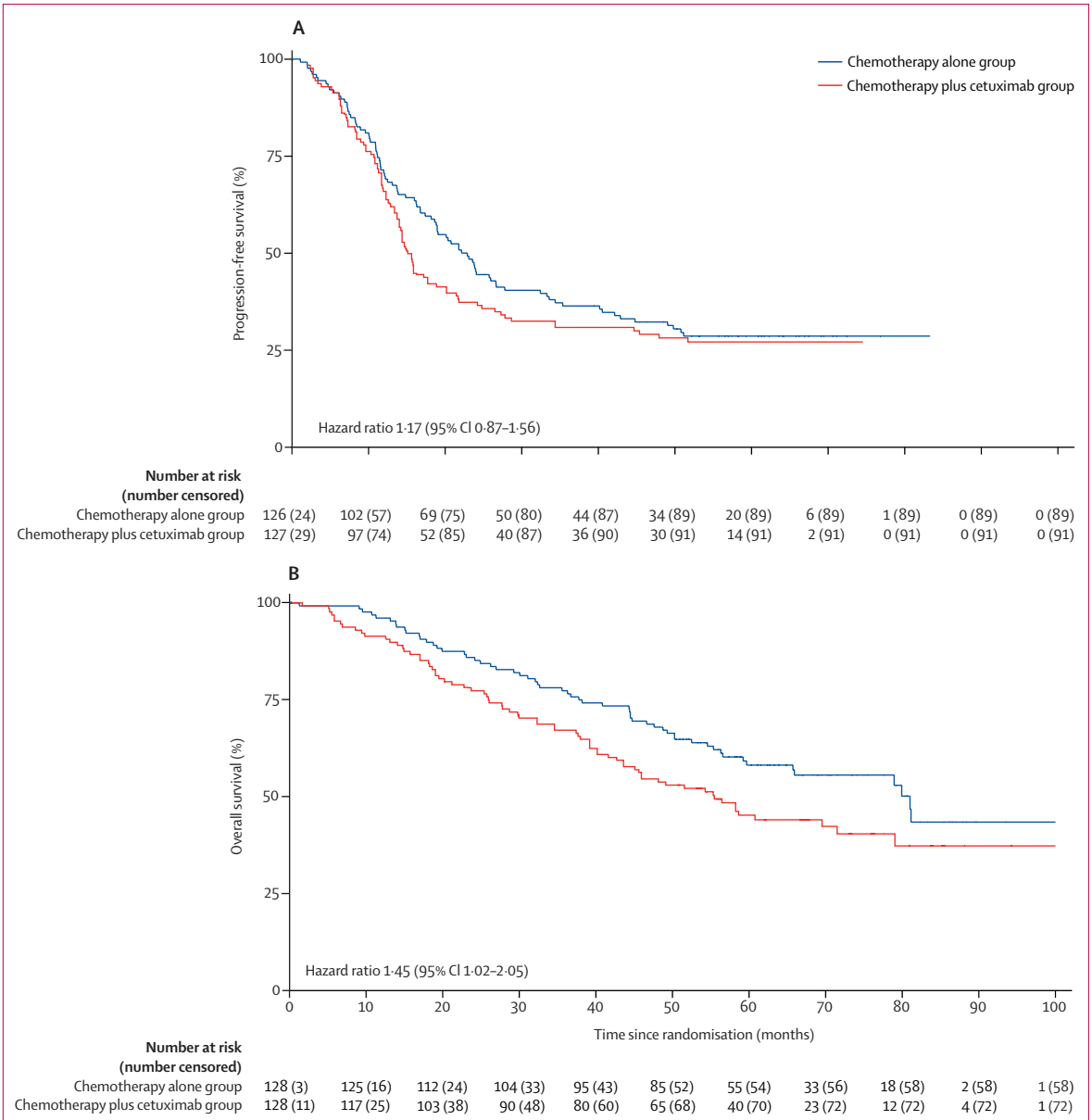

Figure 2: **Progression-free survival (A) and overall survival (B) in the primary analysis population**

The sensitivity analysis adjusting for the minimisation factors gave a similar result (HR 1·13, 0·84–1·52; p=0·401; appendix p 27).

130 patients died and most deaths were disease-related, accounting for 54 (93%) of 58 deaths in the chemotherapy alone group and 67 (93%) of 72 deaths in the chemotherapy plus cetuximab group. The remaining nine (7%) deaths were due to other causes (four [7%] in the chemotherapy alone group and five [7%] in the chemotherapy plus cetuximab group; appendix p 29). The addition of cetuximab to chemotherapy resulted in an unadjusted HR for overall survival of 1·45 (95% CI 1·02–2·05; p=0·036), with an observed median overall survival of 81·0 months (59·6–not reached) in the chemotherapy alone group and 55·4 months (43·5–71·5) in the chemotherapy plus cetuximab group (figure 2B). The sensitivity analysis adjusting for the minimisation factors gave a similar result (HR 1·44, 1·02–2·05; p=0·040; appendix p 27).

The response to preoperative chemotherapy is shown in the appendix (p 25). Complete or partial response occurred in 78 (61%) of 128 patients receiving chemotherapy alone and in 93 (72%) of 129 patients receiving chemotherapy plus cetuximab. There was no significant difference in the proportion of patients achieving a response between treatment groups (p=0·383).

	Chemotherapy alone group (n=128)	Chemotherapy plus cetuximab group (n=129)
Operated*	113/128 (88%)	108/129 (84%)
Resected†	108/113 (96%)	100/108 (93%)
From sole resection/first resection		
One monosegmentectomy or wedge resection ‡	20/108 (19%)	29/100 (29%)
One plurisegmentectomy (major resection, two or more segments)‡	54/108 (50%)	46/100 (46%)
Multiple resections (major and minor, minor and minor, etc)‡	34/108 (31%)	25/100 (25%)
Number of patients who had staged resections‡	3/108 (3%)	6/100 (6%)
From second resection		
One monosegmentectomy or wedge resection ‡	1/108 (1%)	2/100 (2%)
One plurisegmentectomy (major resection, two or more segments)‡	1/108 (1%)	1/100 (1%)
Multiple resections (major and minor, minor and minor, etc)‡	0	3/100 (3%)
NA (ablation performed)‡	1/108 (1%)	0
Not resected†	5/113 (4%)	8/108 (7%)
Complete response§	0	2/8 (25%)
Irresectable disease§	3/5 (60%)	1/8 (13%)
Microwave ablation performed§	1/5 (20%)	0
RFA performed§	1/5 (20%)	5/8 (63%)
Not operated*	15/128 (12%)	21/129 (16%)
Inadequate future liver remnant¶	1/15 (7%)	0
Inoperable at baseline in retrospect¶	1/15 (7%)	2/21 (10%)
Patient refused surgery¶	0	1/21 (5%)
Portal vein thrombosis¶	0	1/21 (5%)
Progressive disease¶	3/15 (20%)	11/21 (52%)
Radiological complete response¶	2/15 (13%)	0
Unfit for surgery¶	4/15 (27%)	2/21 (10%)
Withdrew or died before surgery¶	4/15 (27%)	4/21 (19%)
Any ablation†	5/113 (4%)	11/108 (10%)
Cancer on specimen‡		
From sole resection or first resection		
Macroscopic‡	87/108 (81%)	81/100 (81%)
Only microscopic residual‡[3]	11/108 (10%)	9/100 (9%)
No residual cancer‡	10/108 (9%)	7/100 (7%)
Other‡	0/108 (0%)	2/100 (2%)
Missing (limited surgery information available)‡	0/108 (0%)	1/100 (1%)
From second resection		
Macroscopic‡	1/108 (1%)	5/100 (5%)
Only microscopic residual‡	0/108 (0%)	1/100 (1%)
No residual cancer‡	1/108 (1%)	0
NA (ablation performed)‡	1/108 (1%)	0
Shortest macroscopic margin between cancer and cut surface		
From sole resection or first resection		
Margin ≥1cm‡	36/108 (33%)	29/100 (29%)
Margin <1cm‡	54/108 (50%)	49/100 (49%)
No margin (cancer visible on cut surface)‡	8/108 (7%)	12/100 (12%)
NA (no residual cancer)‡	10/108 (9%)	7/100 (7%)
Missing (limited surgery information available or ablation)‡	0/108 (0%)	3/100 (3%)
From second resection		
Margin ≥1cm‡	1/108 (1%)	2/100 (2%)
Margin <1cm‡	0	3/100 (3%)
No margin (cancer visible on cut surface)‡	0	0
Not applicable (no residual cancer)‡	1/108 (1%)	0
NA (ablation performed)‡	1/108 (1%)	1/100 (1%)
At least one surgical complication	28/113 (25%)	27/108 (25%)
Death during surgery†	0	0
Postoperative death (30 days after liver resection)†	0	1/108 (1%)

Data are n/N (%). The numbers in this table represent all surgeries carried out. Patients who had their resection staged are counted twice as this information was recorded for each surgery. RFA=radiofrequency ablation. NA=not applicable. *Denominator is the number of patients in the primary analysis population. †Denominator is the number of patients in the primary analysis population who have had an operation (before disease progression). ‡Denominator is the number of patients in the primary analysis population who have had an operation (before disease progression) and had a resection. §Denominator is the number of patients in the primary analysis population who have had an operation (before disease progression), but not a resection. ¶Denominator is the number of patients in the primary analysis population who did not have an operation (before disease progression).

Table 2: **Surgical information and postoperative complications (primary analysis population)**

Surgical information is presented in table 2. 221 (86%) of 257 randomly assigned patients underwent an operation, among whom 108 (96%) of 113 patients in the chemotherapy alone group and 100 (93%) of 108 patients in the chemotherapy plus cetuximab group proceeded to resection. Most patients who underwent an operation had a R0 resection (89 [82%] of 108 in the chemotherapy alone group and 79 [79%] of 100 in the chemotherapy plus cetuximab group).

The median post-progression survival (among 167 patients, of whom 82 were in the chemotherapy alone group and 85 in the chemotherapy plus cetuximab group) was 33·5 months (95% CI 25·3–41·2) in the chemotherapy alone group compared with 23·5 months (16·0–31·3) in the chemotherapy plus cetuximab group (HR 1·55, 1·07–2·24; p=0·020; appendix p 16).

The progression-free survival and overall survival in patients in the primary analysis population treated with the chemotherapy backbone of oxaliplatin, 5-fluorouracil, and folinic acid and in the subpopulations of patients who responded to preoperative chemotherapy, who had left-sided cancers, and who had right-sided cancers were explored in prespecified analyses and are shown in

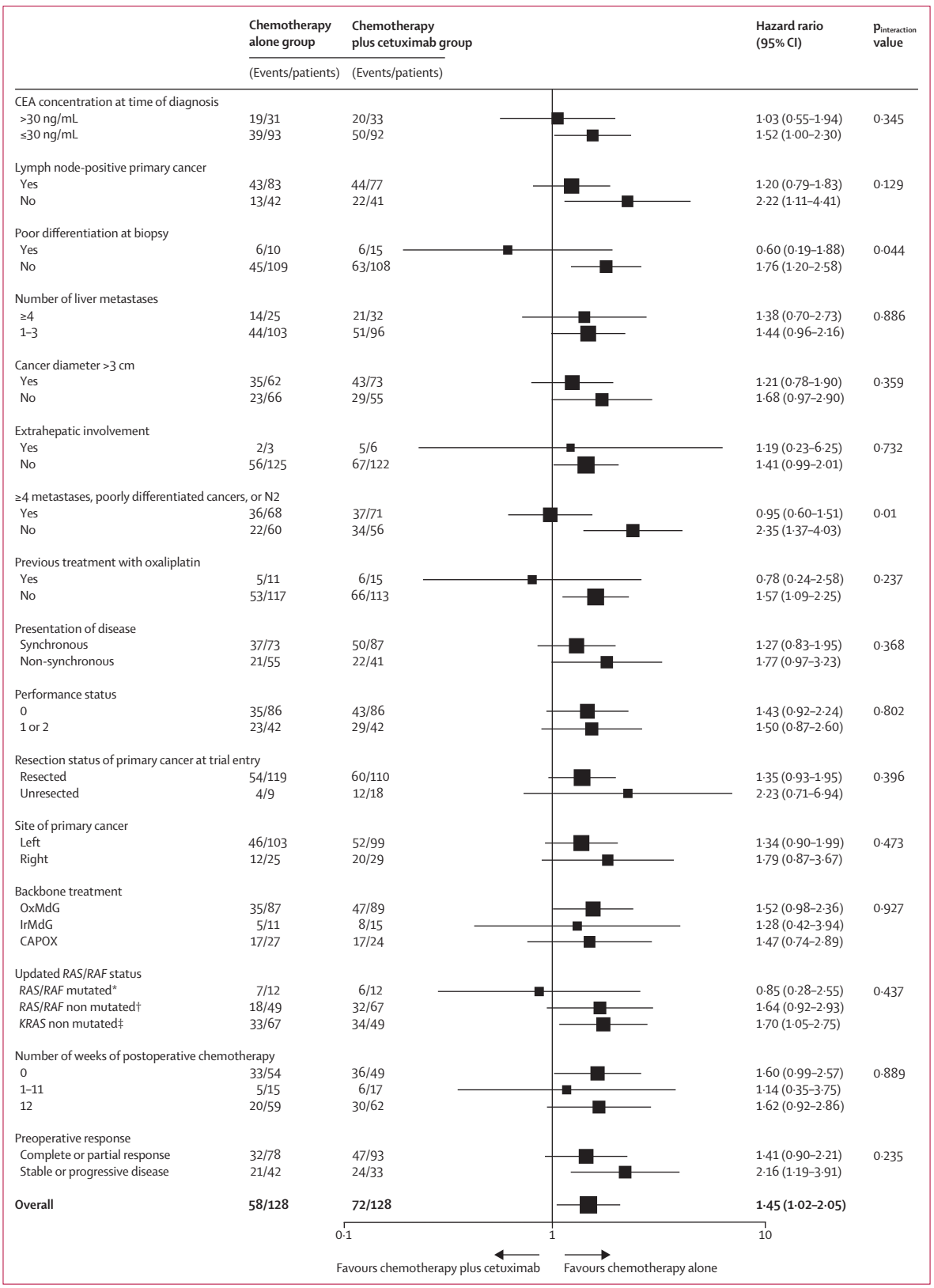

Figure 3: **Forest plot for overall survival**
CAPOX=capecitabine and oxaliplatin. CEA=carcinoembryonic antigen. IrMdG=irinotecan, 5-fluorouracil, and folinic acid. OxMdG=oxaliplatin, 5-fluorouracil, and folinic acid. *Mutation identified in primary cancer in *KRAS* (codons 12/13/61/117,146), *NRAS* (codons 12/13/61/117,146), or *BRAF* (V600E). †No mutation identified in primary cancer in *KRAS* (codons 12/13/61/117,146), *NRAS* (codons 12/13/61/117,146), or *BRAF* (V600E). ‡No mutation identified in primary cancer in *KRAS* (codons 12/13/61); no testing for remaining mutations (ie, *KRAS* [codons 117,146], *NRAS* [codons 12/13/61/117,146], or *BRAF* [V600E]).

	Chemotherapy alone group				Chemotherapy plus cetuximab group			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
During preoperative chemotherapy period*								
Blood and lymphatic system disorders								
Anaemia	64 (48%)	0	0	0	58 (42%)	1 (1%)	0	0
Febrile neutropenia	..	2 (1%)	0	0	..	0	0	0
Other (platelets)	56 (42%)	4 (3%)	0	0	39 (28%)	0	0	0
Other (white cell count low)	36 (27%)	5 (4%)	0	0	38 (28%)	4 (3%)	0	0
Cardiac disorders								
Acute coronary syndrome	..	1 (1%)	0	0	..	0	0	0
Cardiac arrest	..	0	0	0	..	0	0	1 (1%)
Cardiac chest pain	..	1 (1%)	0	0	..	0	0	0
Heart failure	..	0	0	1 (1%)	..	0	0	0
Pericarditis	..	0	1 (1%)	0	..	0	0	0
Ear and labyrinth disorders								
Hearing impaired	..	1 (1%)	0	0	..	0	0	0
Eye disorders								
Conjunctivitis	..	0	0	0	..	1 (1%)	0	0
Other (transient visual disturbance)	..	0	0	0	..	1 (1%)	0	0
Gastrointestinal disorders								
Abdominal pain	..	3 (2%)	0	0	..	0	0	0
Constipation	35 (26%)	0	0	0	41 (30%)	1 (1%)	0	0
Diarrhoea	78 (58%)	12 (9%)	0	0	81 (59%)	12 (9%)	0	0
Gastroesophageal reflux disease or dyspepsia	18 (13%)	0	0	0	27 (20%)	1 (1%)	0	0
Mucositis oral	56 (42%)	3 (2%)	0	0	90 (66%)	11 (8%)	0	0
Nausea	78 (58%)	3 (2%)	0	0	66 (48%)	3 (2%)	0	0
Obstruction gastric	..	1 (1%)	0	0	..	0	0	0
Vomiting	31 (23%)	4 (3%)	0	0	24 (18%)	4 (3%)	1 (1%)	0
General disorders and administration-site conditions								
Fever	..	1 (1%)	0	0	..	1 (1%)	0	0
Non-cardiac chest pain	..	1 (1%)	0	0	..	0	0	0
Hepatobiliary disorders								
Hepatic haemorrhage	..	0	0	0	..	1 (1%)	0	0
Immune system disorders								
Allergic reaction	..	1 (1%)	0	0	..	1 (1%)	0	0
Anaphylaxis	..	0	0	0	..	1 (1%)	0	0
Infections and infestations								
Abdominal infection	..	1 (1%)	0	0	..	0	0	0
Device-related infection	..	1 (1%)	0	0	..	4 (3%)	0	0
Infection	..	2 (1%)	0	0	..	1 (1%)	0	0
Lung infection	..	0	0	0	..	2 (1%)	0	0
Other (*Escherichia coli* infection)	..	0	0	0	..	1 (1%)	0	0
Other (infection of unknown aetiology)	..	0	0	0	..	1 (1%)	0	0
Other (*Clostridioides difficile* infection)	..	1 (1%)	0	0	..	0	0	0
Sepsis	..	0	1 (1%)	0	..	2 (1%)	1 (1%)	0
Upper respiratory tract infection	..	1 (1%)	0	0	..	0	0	0
Investigations								
Deranged liver function tests	..	0	0	0	..	3 (2%)	0	0
Neutrophil count decreased	50 (37%)	14 (10%)	7 (5%)	0	35 (26%)	12 (9%)	1 (1%)	0
Metabolism and nutrition disorders								
Anorexia	39 (29%)	3 (2%)	0	0	41 (30%)	3 (2%)	0	0
Dehydration	..	2 (1%)	0	0	..	2 (1%)	0	0
Hyperglycaemia	..	1 (1%)	0	0	..	1 (1%)	1 (1%)	0

(Table 3 continues on next page)

	Chemotherapy alone group				Chemotherapy plus cetuximab group			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Hypokalaemia	..	1 (1%)	0	0	..	0	1 (1%)	0
Hypomagnesaemia	..	0	0	0	21 (15%)	1 (1%)	0	0
Hyponatraemia	..	0	0	0	..	2 (1%)	0	0
Musculoskeletal and connective tissue disorders								
Pain	53 (40%)	5 (4%)	0	0	49 (36%)	4 (3%)	0	0
Nervous system disorders								
Dizziness	..	1 (1%)	0	0	..	0	0	0
Dysgeusia	20 (15%)	0	0	0	19 (14%)	0	0	0
Lethargy	99 (74%)	5 (4%)	0	0	110 (80%)	8 (6%)	0	0
Peripheral neuropathy	115 (86%)	7 (5%)	0	0	100 (73%)	1 (1%)	0	0
Stroke	..	0	0	0	..	0	1 (1%)	0
Syncope	..	0	0	0	..	1 (1%)	0	0
Psychiatric disorders								
Agitation	..	1 (1%)	0	0	..	0	0	0
Anxiety	..	1 (1%)	0	0	..	0	0	0
Confusion	..	0	0	0	..	1 (1%)	0	0
Renal and urinary disorders								
Acute kidney injury	..	0	1 (1%)	0	..	1 (1%)	0	0
Respiratory, thoracic, and mediastinal disorders								
Hiccups	..	0	0	0	..	1 (1%)	0	0
Laryngospasm	..	0	0	0	..	1 (1%)	0	0
Skin and subcutaneous tissue disorders								
Alopecia	31 (23%)	1 (1%)	0	0	31 (23%)	0	0	0
Nail changes	..	0	0	0	24 (18%)	2 (1%)	1 (1%)	0
Palmar-plantar erythrodysesthesia syndrome	28 (21%)	1 (1%)	0	0	66 (48%)	4 (3%)	0	0
Pruritus	..	0	0	0	..	1 (1%)	0	0
Skin rash	26 (19%)	1 (1%)	0	0	124 (91%)	18 (13%)	0	0
Vascular disorders								
Peripheral ischaemia	..	0	0	0	..	1 (1%)	0	0
Phlebitis	..	1 (1%)	0	0	..	1 (1%)	2 (1%)	0
Thromboembolic event	..	3 (2%)	5 (4%)	0	..	6 (4%)	2 (1%)	0
During postoperative chemotherapy period†								
Blood and lymphatic system disorders								
Anaemia	35 (30%)	0	1 (1%)	0	37 (32%)	0	0	0
Febrile neutropenia	..	0	0	0	..	1 (1%)	0	0
Other (platelets)	35 (30%)	0	0	0	32 (28%)	0	0	0
Other (white cell count low)	18 (16%)	2 (2%)	0	0	23 (20%)	0	0	0
Ear and labyrinth disorders								
Tinnitus	..	1 (1%)	0	0	..	0	0	0
Gastrointestinal disorders								
Abdominal pain	..	1 (1%)	0	0	..	0	0	0
Constipation	18 (16%)	1 (1%)	0	0	28 (24%)	0	0	0
Diarrhoea	39 (34%)	2 (2%)	0	0	49 (43%)	2 (2%)	0	0
Mucositis oral	29 (25%)	0	0	0	49 (43%)	3 (3%)	0	0
Nausea	39 (34%)	1 (1%)	0	0	38 (33%)	1 (1%)	0	0
Vomiting	..	3 (3%)	0	0	16 (14%)	2 (2%)	0	0
General disorders and administration-site conditions								
Non-cardiac chest pain	..	1 (1%)	0	0	..	0	0	0
Immune system disorders								
Allergic reaction	..	0	0	0	..	1 (1%)	1 (1%)	0

(Table 3 continues on next page)

	Chemotherapy alone group				Chemotherapy plus cetuximab group			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Infections and infestations								
Device-related infection	..	2 (2%)	0	0	..	1 (1%)	0	0
Lung infection	..	1 (1%)	0	0	..	1 (1%)	0	0
Sepsis	..	0	0	0	..	1 (1%)	0	0
Investigations								
Deranged liver function tests	..	0	0	0	..	1 (1%)	0	0
Neutrophil count decreased	29 (25%)	6 (5%)	1 (1%)	0	26 (23%)	6 (5%)	3 (3%)	0
Metabolism and nutrition disorders								
Anorexia	17 (15%)	1 (1%)	0	0	22 (19%)	0	0	0
Dehydration	..	1 (1%)	0	0	..	1 (1%)	0	0
Hyperglycaemia	..	1 (1%)	0	0	..	0	0	0
Hypokalaemia	..	0	0	0	..	1 (1%)	1 (1%)	0
Musculoskeletal and connective tissue disorders								
Back pain	..	1 (1%)	0	0	..	0	0	0
Generalised muscle weakness	..	0	0	0	..	1 (1%)	0	0
Pain	30 (26%)	2 (2%)	0	0	33 (29%)	2 (2%)	0	0
Nervous system disorders								
Dysgeusia	17 (15%)	0	0	0	..	0	0	0
Lethargy	55 (47%)	5 (4%)	0	0	63 (55%)	2 (2%)	0	0
Peripheral neuropathy	58 (50%)	3 (3%)	0	0	61 (53%)	5 (4%)	0	0
Skin and subcutaneous tissue disorders								
Nail changes	12 (10%)	0	0	0	20 (17%)	1 (1%)	0	0
Palmar-plantar erythrodysesthesia syndrome	16 (14%)	1 (1%)	0	0	40 (35%)	3 (3%)	0	0
Skin rash	..	0	0	0	64 (56%)	6 (5%)	0	0
Vascular disorders								
Phlebitis	..	1 (1%)	0	0	..	0	0	0
Thromboembolic event	..	3 (3%)	1 (1%)	0	..	1 (1%)	2 (2%)	1 (1%)

Data are n (%), where n is the number of patients who experienced that adverse event and grade combination. Grade 1–2 adverse events reported in 10% or more patients and all grade 3–5 events are shown. *The preoperative chemotherapy period includes all randomised patients: n=134 in the chemotherapy alone group, n=137 in the chemotherapy plus cetuximab group; the preoperative chemotherapy period lasted from the start of cycle 1 to the start of the last preoperative cycle plus 3 weeks for patients receiving chemotherapy regimen 1 or 3 or plus 4 weeks for patients receiving chemotherapy regimen 2. †Only patients who had surgery and postoperative chemotherapy are included in the postoperative chemotherapy period, n=116 in the chemotherapy alone group, n=115 in the chemotherapy plus cetuximab group; the postoperative chemotherapy period lasted from the start of the first postoperative chemotherapy cycle to the start of the last postoperative cycle plus 3 weeks for patients receiving chemotherapy regimen 1 or 3 or plus 4 weeks for patients receiving chemotherapy regimen 2.

Table 3: **Adverse events during the preoperative and postoperative chemotherapy periods**

the appendix (pp 6–9, 12–15). The results from the interaction subgroup analysis of overall survival and progression-free survival are in figure 3 and the appendix (pp 10, 11).

Extended *RAS/RAF* testing was successfully completed on primary colorectal cancer samples from 140 patients in the trial previously classified as *KRAS* wild-type (codons 12, 13, and 61). 24 (17%) of these 140 patients had mutations identified, comprising 13 patients with *KRAS* mutations, four patients with *NRAS* mutations, and seven patients with *BRAF* mutations. These mutations were balanced between the groups of the study with 12 in the chemotherapy alone group (eight *KRAS*, one *NRAS*, three *BRAF*) and 12 in the chemotherapy plus cetuximab group (5 *KRAS*, 3 *NRAS*, 4 *BRAF*). All mutations were mutually exclusive. Restriction to an all *RAS/RAF* wild-type population revealed a HR for overall survival of 1·64 (95% CI 0·92–2·93), with an observed median overall survival not reached (47·5–not reached) in the chemotherapy alone group and of 79·0 months (29·9–not reached) in the chemotherapy plus cetuximab group.

Treatment-related adverse events are in table 3. 99 (77%) of 128 patients in the chemotherapy alone group and 103 (80%) of 129 patients in the chemotherapy plus cetuximab group completed 12 weeks of preoperative chemotherapy; 59 (52%) of 113 patients in the chemotherapy alone group and 62 (57%) of 108 patients in the chemotherapy plus cetuximab group completed 12 weeks of postoperative therapy. The proportion of patients requiring at least one dose modification was similar between the chemotherapy alone group (58 [45%] of 128 in the preoperative period and 49 [43%] of 113 in the postoperative period) and the chemotherapy plus cetuximab group (60 [47%] of 129 in the preoperative

period and 48 [44%] of 108 in the postoperative period). The proportion of patients requiring at least one dose delay was also similar between the chemotherapy alone group (65 [51%] of 128 in the preoperative period and 38 [34%] of 113 in the postoperative period) and the chemotherapy plus cetuximab group (63 [49%] of 129 in the preoperative period and 39 [36%] of 108 in the postoperative period). There were 14 premature withdrawals from study treatment due to toxicity, six (4%) of 134 in the chemotherapy alone group and eight (6%) of 137 in the chemotherapy plus cetuximab group.

The proportion of patients having at least one preoperative grade 3 or worse toxicity and any postoperative grade 3 or worse toxicity was similar between the chemotherapy alone group (63 [47%] of 134 in the preoperative period and 26 [22%] of 116 in the postoperative period) and the chemotherapy plus cetuximab group (72 [53%] of 137 in the preoperative period and 34 [30%] of 115 in the postoperative period; table 3).

The most common grade 3–4 adverse events reported were neutrophil count decreased (26 [19%] of 134 in the chemotherapy alone group *vs* 21 [15%] of 137 in the chemotherapy plus cetuximab group), diarrhoea (13 [10%] *vs* 14 [10%]), skin rash (one [1%] *vs* 22 [16%]), thromboembolic events (ten [7%] *vs* 11 [8%]), lethargy (ten [7%] *vs* nine [7%]), oral mucositis (three [2%] *vs* 14 [10%]), vomiting (seven [5%] *vs* seven [5%]), peripheral neuropathy (eight [6%] *vs* five [4%]), and pain (six [4%] *vs* six [4%]). The most common serious adverse events reported of any grade were diarrhoea (nine [7%] *vs* seven [5%]), thromboembolic events (nine [7%] *vs* seven [5%]), vomiting (seven [5%] *vs* five [4%]), fever (six [4%] *vs* three [2%]), sepsis (two [1%] *vs* five [4%]), and device-related infection (two [1%] *vs* five [4%]).

There were 26 drug-related serious adverse events in the chemotherapy alone group and 32 in the chemotherapy plus cetuximab group (appendix pp 30, 31) There were five deaths potentially related to treatment (appendix p 29). Three of these related to systemic treatment, one in the chemotherapy alone group (heart failure) and two in the chemotherapy plus cetuximab group (one pulmonary embolism and interstitial lung disease and one pulmonary embolism). One patient died of bronchopneumonia within 30 days of surgery in the chemotherapy plus cetuximab group. Another patient died of cardiac arrest within 90 days of surgery in the same treatment group and, although outside the protocol definition, this death might have been related to surgery. Surgical complications were reported in 28 (25%) of 113 patients in the chemotherapy alone group and 27 (25%) of 108 patients in the chemotherapy plus cetuximab group (table 2). Protocol violations are recorded in the appendix (pp 32, 33).

Discussion

The interim analysis of the primary endpoint of the New EPOC study showed a significantly shorter progression-free survival when cetuximab was added to perioperative chemotherapy, for patients with resectable colorectal liver metastasis.[5] Although progression-free survival has accepted validity as a surrogate endpoint, in the context of such an unexpected finding, the overall survival assumes a greater importance, despite being a secondary endpoint. This mature analysis found that the detriment in progression-free survival is no longer significant, although median overall survival was 26 months shorter for patients receiving cetuximab and chemotherapy than for those receiving chemotherapy alone. This finding suggests that the premature closure of the trial, its primary limitation but mandated by the trial steering committee, did not influence the outcome. If the study were to be repeated, translational endpoints would be prioritised. However, such a choice was neither standard nor technically feasible in 2005, when the study started.

The baseline characteristics of the chemotherapy plus cetuximab group are prognostically less favourable, with more patients having synchronous disease and a metastasis larger than 3 cm. However, these differences are small and not significant. Furthermore, review of the predefined subgroup analyses reveals the detriment with cetuximab in this present study occurred in patients with favourable characteristics (not poorly differentiated, not N2 disease, fewer than four metastases). The subset with unfavourable prognostic features (poorly differentiated histology, N2 disease, or four or more metastases) did not benefit from addition of cetuximab to chemotherapy, but were not disadvantaged. As such, there is no evidence to suggest that any difference in the baseline variables contributed to the poor outcome of the cetuximab group.

The quality of surgery following systemic therapy might have affected study outcome. At the time of the first publication it was not possible to present complete surgical data since not all patients had, at that time, undergone protocol-defined surgery. These data are now complete. More patients in the chemotherapy plus cetuximab group than in the chemotherapy alone group did not undergo an operation, in most cases because of progressive disease. Of the patients who underwent an operation, some were treated with ablation with or without surgery. This choice was not permitted in the protocol, but patient management was always at the discretion of the clinician. Additional protocol violations included the two patients in the chemotherapy alone group who were not operated on during the period allowed by the protocol, because of a complete radiological response, and the two patients in the chemotherapy plus cetuximab group who were operated on, but not resected, because of a complete response.

Although it is natural to focus on the unexpected outcome in the experimental group of the trial, the survival achieved in the chemotherapy alone group should not be overlooked. Indeed, the 5-year survival in this group is comparable to the best of any case series,[1] despite the

inclusion of borderline resectable patients. Furthermore, there was only one 30-day mortality in the 221 patients that underwent surgery, attesting to the quality of care in high-volume liver surgery centres in the UK.

Post-hoc analyses of other trials in advanced colorectal cancer have shown inferior survival outcomes with the addition of anti-EGFR therapies to chemotherapy for *KRAS*-mutated and all *RAS*-mutated cancers,[7,11–13] and all *RAS* wild-type testing before EGFR therapy is now mandatory. Now, patients with any *RAS* or *BRAF* mutation would not be given cetuximab.[14] Accordingly, extended *RAS/RAF* testing was done on all available New EPOC samples. The HR point estimate for detriment with cetuximab in the all *RAS/RAF* wild-type population was almost identical to that in the whole trial population, although it was not significant. This finding was not observed in the patients who had additional *RAS/RAF* pathway mutations discovered in the primary cancer on further testing, but the numbers are insufficient to make any definite conclusion.

Data to support a biological explanation for this unexpected trial outcome are accumulating. High expression of the microRNA miR-31–3p in primary colorectal cancer of patients with metastatic disease treated with cetuximab or panitumumab has been shown to be associated with resistance to EGFR and disease progression.[15] In the New EPOC cohort, it was not possible to identify a patient subgroup in which miR-31–3p expression levels were associated with an improvement in outcomes when cetuximab was added to chemotherapy.[16] It is nevertheless interesting to observe that the poorer outcomes associated with the addition of cetuximab to chemotherapy were limited to patients with high miR-31–3p expression in the primary cancer. This detrimental effect was not observed in patients with low miR-31–3p expression levels.[16]

Previous studies have suggested a predictive role for the expression of the EGFR ligands amphiregulin (AREG) and epiregulin (EREG). In 2016, survival benefit from the use of panitumumab in advanced colorectal cancer was observed in patients with high AREG or EREG expression, or both, but not in those with low expression.[17] By contrast, in New EPOC, high ligand expression was associated with a decreased progression-free survival with the addition of cetuximab, whereas patients with low ligand expression had a similar progression-free survival irrespective of treatment allocation.[18] Rationalising these results with those of other studies is challenging,[17,19–21] but serves to highlight the importance of biology, and possibly of an intact EGFR signalling pathway, to the detriment in outcomes with the addition of cetuximab. Mismatch repair status was not routinely measured during the period of study recruitment and cannot be reliably reported. This will be assessed in the translational analysis.

Although studies of anti-EGFR therapies in advanced disease have mostly been positive, those in the adjuvant setting have not,[22,23] with a trend towards detrimental outcomes in older patients.[23] In the New EPOC study, most patients were upfront operable and, therefore, the predominant effect of systemic intervention was likely to be on micrometastatic disease; as such, these results are consistent with the adjuvant anti-EGFR therapy data. Furthermore, and as discussed above, the survival of patients with poorer prognostic features did not seem to be affected by the addition of cetuximab. This trial, therefore, does not preclude the possibility that there might be benefit from the addition of cetuximab in patients with more advanced and inoperable disease.[6,7] The translational studies currently underway will hopefully provide an understanding of this possibility, thereby further informing the appropriate selection of patients for anti-EGFR therapies.

In the advanced disease setting, right-sided metastatic colon cancer has been reported to be less responsive to EGFR inhibition,[24] the biology of which is currently being interrogated. In the New EPOC trial, survival of patients with liver metastases from right-sided cancers was affected more than that of patients with left-sided cancers by the addition of cetuximab, although there were relatively few right-sided cancers and the difference was not significant. Therefore, the biology underlying the right versus left phenomenon seen in advanced disease with EGFR inhibition in the neoadjuvant setting should be investigated in future trials.

Further interrogation of the progression events in the New EPOC population has revealed some informative observations.[25] First, additional data collected after the interim analysis showed that there were numerically more multisite progressions in the chemotherapy plus cetuximab group than in the chemotherapy alone group. Second, this updated analysis shows post-progression survival to be shorter for the chemotherapy plus cetuximab group. Therefore, the addition of cetuximab seems to have not only accelerated disease progression, but also might have led to the development of a more aggressive disease genotype and phenotype. Visual inspection of the survival curves suggests that progression was associated with early death in the chemotherapy plus cetuximab group, but not in the chemotherapy alone group. These early deaths were mainly attributable to disease progression. The translational studies that are underway will be crucial to explaining these complex observations.

Overall, we have shown that survival in patients with operable colorectal liver metastases is significantly worse with the use of cetuximab in combination with chemotherapy in the perioperative setting than with chemotherapy alone. This finding is robust, with no apparent confounding variables, and suggests that biological intervention in molecularly complex cancers might have unintended consequences. Cetuximab should not be used as neoadjuvant therapy in patients with operable colorectal liver metastases.

Contributors

JNP and JAB conceived the study, designed the protocol, supervised the conduct and analysis of the trial. TSM designed the protocol with JNP and JAB, and was a member of the trial management group and as such supervised the conduct of the trial. OJG, DC, and SAP were members of the trial management group and as such supervised the conduct of the trial. SF, JWV, DO'R, AKS, JH, MyR, TJI, and TH recruited patients and oversaw the conduct of the trial at participating centres. SAP, JM, and ZE were involved in the day-to-day running of the trial. MiR was responsible for data management. AW, TM, and LS were responsible for the statistical analysis and writing of the statistical analysis plan. SAP, JNP, JAB, and TM were responsible for preparing the manuscript. All authors have contributed to, seen, and approved the final draft.

Declaration of interests

JAB has received speakers' fees from Merck Serono. JWV reports grants from Cancer Research UK during the conduct of the study; personal fees from Ipsen, Novartis, AstraZeneca, Merck, Delcath, Agios, Pfizer, PCI Biotech, Incyte, Keocyt, QED, Pieris Pharmaceuticals, Genoscience Pharma, Mundipharma EDO, Wren Laboratories, Nucana, and Imaging Equipment Limited outside the submitted work; and travel grants from Celgene and Nucana. TH is a medical director for iQHealth Tech, has received research funding (to institution) from Pfizer, Pierre Fabre and has attended advisory boards for Lilly and Sobi. DC reports research funding from Amgen, Sanofi, Merrimack, AstraZeneca, Celgene, MedImmune, Bayer, 4SC, Clovis, Eli Lilly, Janssen and Merck. All other authors declare no competing interests.

Data sharing

The anonymised derived data from this study including all fields will be made available to any investigator by application to the trial management group thorough the Southampton Clinical Trials Unit (ctu@soton.ac.uk) from the time of publication and thereafter. The trial protocol and statistical analysis plans will also be made available as will a data fields dictionary. These data are available for any analysis with or without support of the investigators.

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