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NCRI

New EPOC

A prospective randomised open label trial of Oxaliplatin / Irinotecan plus Fluorouracil versus Oxaliplatin / Irinotecan plus Fluorouracil and Cetuximab pre and post operatively in patients with resectable colorectal liver metastases requiring chemotherapy

CLINICAL PROTOCOL
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Developed on behalf of the NCRI Upper Gastrointestinal Clinical Studies Groups

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Signature: Date: 11th October 2017

NCRI UPPER GI STUDIES GROUP

This document describes the New EPOC trial, and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care was taken in its drafting, however corrections or amendments may be necessary. These will be circulated to the known investigators in the trial, but centres entering patients for the first time are advised to contact the University of Southampton Clinical Trials Unit (UoSCTU) to confirm that they have the most up to date version of the protocol in their possession. Clinical problems relating to this study should be referred to the Chief Investigator or one of the co-investigators or advisors for the study either directly or via UoSCTU.

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Glossary and abbreviations

AE	Adverse event	MAP	Mitogen-activated protein
ALT	Alanine aminotransferase	MdG	Modified de Gramont
AR	Adverse reaction	MHRA	Medicines and Healthcare Products Regulatory Agency
ASCO	American Society of Clinical Oncology	MI	Myocardial infarction
AST	Aspartate aminotransferase	MRC	Medical Research Council
bd	Twice daily	MREC	Multi-centre Research Ethics Committee
C225	Mouse monoclonal antibody C225	MRI	Magnetic resonance imaging
CAPOX	Xeloda (Capecitabine) plus Oxaliplatin	NCI	National Cancer Institute (America)
CEA	Carcino-embryonic antigen	NICE	National Institute of Clinical Excellence
CRF	Case Report Form	NCRI	National Cancer Research Institute
CRUK	Cancer Research UK	od	Once daily
CT	Computed Tomography	ONS	Office of National Statistics
CTA	Clinical Trials Authorisation	OS	Overall survival
CTU	Clinical Trials Unit	OxMdG	Oxaliplatin in combination with Modified de Gramont
dG	de Gramont	PFS	Progression-free survival
DMEC	Data Monitoring and Ethics Committee	PI	Principal investigator
DNA	Deoxyribonucleic acid	prn	pro re nata; when necessary
DPA	Data protection act	PS	Performance Status
DPD	Dihydropyrimidine dehydrogenase	Pt	Platinum
EDTA	Ethylene diamine tetraacetic acid	QALY	Quality Adjusted Life-Years
EGFR	Epidermal growth factor eeceptor	qds	quarter in die; 4 times daily
FA	Folinic acid (a.k.a. leucovorin)	QoL	Quality of Life
FBC	Full blood count	kRAS-mt	kRAS mutant
FFS	Failure-free survival	kRAS-wt	kRAS wildtype
FOLFIRI	Folinic acid, 5-Fluorouracil and Irinotecan chemotherapy	RECIST	Response Evaluation Criteria In Solid Tumours
Fp	Fluoropyrimidine	SA	Surface Area
5FU	5-Fluorouracil	SAE	Serious Adverse Event
GFR	Glomerular filtration rate	SAR	Serious Adverse Reaction
HR	Hazard ratio	SOP	Standard Operating Procedure
HRQL	Health-related quality of life	SpC	Summary of product Characteristics
IBW	Ideal body weight	SSA	Site Specific Assessment
IgG	Immunoglobulin gamma	SUSAR	Suspected Unexpected Serious Adverse Reaction
IHC	Immunohistochemistry	tds	ter die sumeudum, three times daily
IrMdG	Irinotecan + modified de Gramont	TGFα	Transforming growth factor alpha
ITT	Intention-to-treat	TMA	Tissue microarray
IV	Intravenous	TSC	Trial Steering Committee
LFTs	Liver function tests	UAR	Unexpected Adverse Reaction
LREC	Local research ethics committee	U&Es	Urea & Electrolytes
m2	Metre squared	ULN	Upper limit of normal
mg	Milligram	UoSCTU	University of Southampton Clinical Trials Unit
ml	Millilitre	WHO	World Health Organisation

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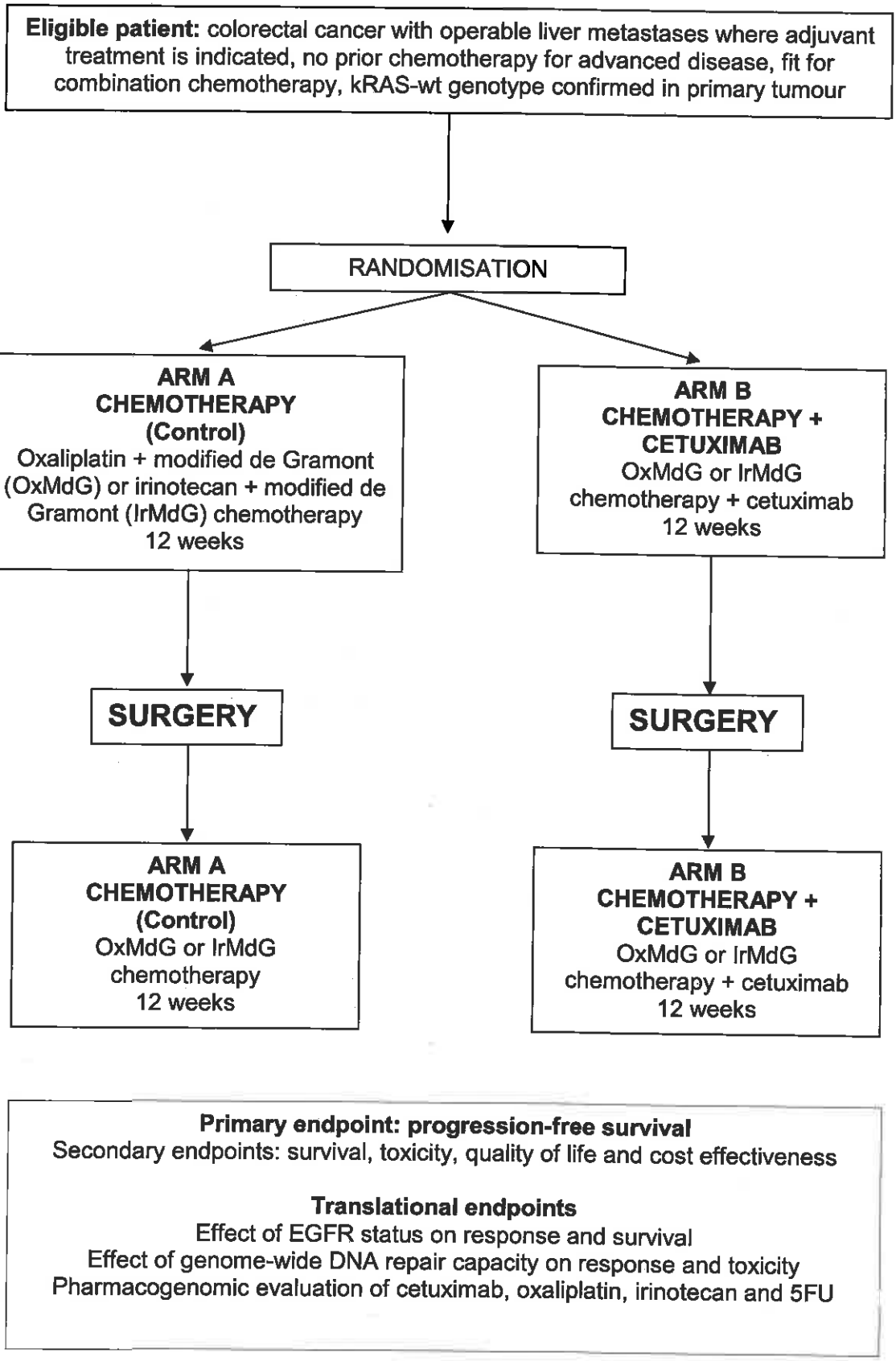
1. Trial design



2. Summary

Title	
	New EPOC: an open-label randomised trial, comparing OxMdG / IrMdG chemotherapy versus OxMdG / IrMdG chemotherapy plus Cetuximab.
Study population	
	Two hundred and eighty eight colorectal cancer patients with liver metastases deemed resectable in whom the oncologist feels chemotherapy would be beneficial, who are fit for combination chemotherapy, and possess the kRAS-wt genotype confirmed in primary tumour by laboratory analysis.
Study regimen	
	Patients will be randomised at the start of chemotherapy to receive **either**: **Arm A:** OxMdG / IrMdG chemotherapy **Arm B:** OxMdG / IrMdG chemotherapy with **Cetuximab** **OxMdG**: *l*-folinic acid (175 mg flat dose IV over 2 h) or *d,l*-folinic acid (350 mg flat dose IV over 2 h), concurrent administration of Oxaliplatin (85 mg/m^2 IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m^2) followed by a 46 h IV infusion of 5FU 2400 mg/m^2 repeated every 2 weeks as used in the FOCUS trial or **IrMdG**: Irinotecan 180 mg/m^2 IV over 30 minutes, *l*-folinic acid (175 mg flat dose IV over 2 h) or *d,l*-folinic acid (350 mg flat dose IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m^2) followed by a 46 h IV infusion of 5FU 2400 mg/m^2 repeated every 2 weeks as used in the FOCUS trial in patients intolerant of Oxaliplatin. **Cetuximab** will be given as a fortnightly dose of 500 mg/m^2 with OxMdG and IrMdG. Patients will receive 12 weeks of chemotherapy, undergo surgery and then complete a further 12 weeks of chemotherapy.
Study objectives/endpoints	
	The primary endpoint is progression-free survival. Secondary endpoints include pre-operative response rate, overall survival, quality of life and cost effectiveness.
Supplementary studies	
	Patients will be asked for separate consent to use a blood sample and a proportion of their stored pathology samples for translational research projects. These include analyses of EGFR expression, biomarkers of response, DNA repair capacity and other pharmacogenomic studies.

3. Summary of interventions (treatment phase)

	Screen	Baseline	Week ... 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
ALL PATIENTS																																		
Check inclusion / exclusion criteria	X																																	
Informed consent	X																																	
Optional blood sample (check consent)	X																																	
Request stored pathology samples (check consent)	X																																	
Offer OxMdG or IrMdG	X																																	
Send sample of primary cancer for kRAS analysis	X																																	
Randomisation		X																																
Calculate GFR (if < 50 ml/min, measure GFR)		X																																
QoL questionnaire	X								X						X													X					X
CT scan (Chest, abdo, pelvis or equiv.)	X*	X*													X																			X
Tumour marker (CEA or other)	X*	X*						X¶							X¶																			X¶
Liver resection surgery																		X																
Collect pathology samples (check consent)																		X																
OxMdG and IrMdG PATIENTS																																		
Check adverse events			X		X		X		X		X		X		X			X				X		X		X		X		X		X		X
Clinical evaluation	X	X	X		X		X		X		X		X		X			X				X		X		X		X		X		X		X
RECIST response	X														X																			X
NCI CTC scores			X		X		X		X		X		X									X		X		X		X		X		X		
WHO PS		X	X		X		X		X		X		X									X		X		X		X		X		X		
FBC, U&Es, LFTs, magnesium**	X		X		X		X		X		X		X									X		X		X		X		X		X		
Chemotherapy - folinic acid			X		X		X		X		X		X									X		X		X		X		X		X		
Chemotherapy - Oxaliplatin (OxMdG) or Irinotecan (IrMdG)			X		X		X		X		X		X									X		X		X		X		X		X		
Chemotherapy - 5FU			X		X		X		X		X		X									X		X		X		X		X		X		
Chemotherapy - Cetuximab (if applic.)			X		X		X		X		X		X									X		X		X		X		X		X		
Return data to UoSCTU		X	X		X		X		X		X		X									X		X		X		X		X		X		

Results from FBC, U&Es, LFTs required before patient attends baseline visit; delay between baseline visit to week 1 visit must be < 3 weeks if clinically acceptable; * = procedure may be performed at screening or baseline but must be within 6 weeks prior to chemotherapy; ¶ = if raised at baseline; ** = measure in all patients showing possible symptoms of hypomagnesemia; QoL = quality of life; NCI CTC = national cancer institute common toxicity criteria; WHO PS = world health organisation performance status; follow-up schedule (including CT scans) described section 11 should be followed after the treatment phase

4. Introduction

Background

Over 16,000 people die of colorectal cancer per annum in the UK (CR-UK Cancer Statistics, http://info.cancerresearchuk.org/cancerstats/reports/), most of whom die with metastatic disease. However the treatment of metastatic colorectal cancer is improving. The median survival has improved from about 6 months with best supportive care alone, through 10-12 months with 5FU regimens[1], up to 16-20 months in recent randomised trials including Irinotecan and/or Oxaliplatin[2-11] and up to 27 months in other recent studies using targeted monoclonal antibodies[12]. Recent data (Table 1) demonstrate increased response rates (31-56%), median progression-free survival (PFS, 6.5-9.0 months) and median overall survival (OS, 14.5-21.4 months) achieved with combination chemotherapy in first line therapy[2-10]. The CR08 [FOCUS] trial compared 5 different schedules of administration of 5FU (using the modified de Gramont regimen) in combination with Irinotecan or Oxaliplatin in either first or second line therapy[11] and has demonstrated the efficacy of first line combination chemotherapy.

Table 1. Results of combination chemotherapy in the first line treatment of metastatic colorectal cancer from recent clinical trials (5FU based regimens including Oxaliplatin or Irinotecan or Irinotecan plus Oxaliplatin)

Author, reference	Combination Regimen	Response rate (%)	Median PFS (months)	Median OS (months)
De Gramont, 2000[2]	FOLFOX	51	9.0	16.2
Giacchetti, 1999[3]	FOLFOX	34	8.7	19.4
Douillard, 2000[4]	FOLFIRI	41	6.7	17.4
Saltz, 2000[5]	IFL	39	7.0	14.8
Goldberg, 2003[6]	IFL	31	6.9	14.8
Goldberg, 2003[6]	FOLFOX	45	8.7	19.5
Goldberg, 2003[6]	IROX	34	6.5	17.4
Grothey, 2002[7]	FUFOX	48	7.8	20.4
Kohne, 2003[8]	FUFIRI	54	8.5	20.1
Tournigand, 2000[9]	FOLFOX	54	Na	21.4
Tournigand, 2000[9]	FOLFIRI	56	Na	20.4
Braun, 2003[10]	OxMdG	53	8.3	14.5

Irinotecan is an active agent in advanced colorectal cancer used in combination with Fluorouracil[5, 13]. Data suggest a hepatic resection rate of between 5-9% in unselected series[8-9, 14-16] to 12%[17] in series of liver metastases only patients. Hepatosteatosis[18] confers significantly greater morbidity but not mortality at surgery.

Following the acceptance of Oxaliplatin as standard adjuvant treatment in node positive resected colorectal cancer[19], a significant proportion of patients developing metachronous metastasis will not be able to tolerate further Oxaliplatin because of neurotoxicity. These patients may be offered neoadjuvant Irinotecan and 5FU with or without Cetuximab as part of the New EPOC study as it reflects standard practice despite a potentially less favourable prognosis[20] and the lack of efficacy of Irinotecan as adjuvant[21-22].

Cetuximab

Since 2003, biological targeted therapies have been shown to have activity in colorectal cancer, in particular two monoclonal antibodies Bevacuzimab, a humanised monoclonal against the vascular endothelial growth factor receptor and Cetuximab, an epidermal growth factor receptor (EGFR) targeted chimeric monoclonal antibody. The EGFR family of growth factor receptors (EGFR 1-4) are the entry point to a complex signal transduction network that affect cell proliferation, migration, survival and adhesion[23]. They bind several ligands, notably EGF, transforming growth factor-α (TGF-α) and amphiregulin, which result in phosphorylation of the tyrosine kinase, and subsequent signalling through the Mitogen-activated protein (MAP) kinase pathway. EGF is the principal mitogenic stimulus for epithelium and is frequently deranged in epithelial tumours. Data on the correlation of EGFR with prognosis are limited in colorectal cancer with series reporting an association between EGFR, her2 and TGF-α expression with grade, stage, relapse-free survival and overall survival[24]. EGFR is detectable in up to 75-86% of colorectal cancer[23-25] but there is little evidence that expression is required for antibody efficacy and in the MRC COIN study using Cetuximab, EGFR expression on tumour was not a pre-requisite for study entry.

Cetuximab was chimerized from the mouse monoclonal antibody C225, which blocks the ligand binding site of the EGFR, and a human immunoglogulin IgG constant region gene segment[26]. It has a binding affinity one log higher than endogenous ligand, preventing their binding, inducing receptor internalisation and inhibiting downstream signal transduction[27]. Preclinical studies showed activity in chemotherapy resistant colorectal cancer xenografts and synergy with both radiation and Irinotecan chemotherapy[27].

Data from a phase II trial in 329 patients has confirmed this preclinical promise showing that in EGFR positive, Irinotecan refractory, metastatic colorectal cancer, Cetuximab and Irinotecan combination chemotherapy produced a response rate of 22% and Cetuximab alone produced a response rate of 11%[28]. The median survivals were 8.6 months in the combination arm and 6.9 months in the monotherapy arm. The efficacy of Cetuximab was confirmed in another Phase II study in 57 Irinotecan refractory patients[29]. On this basis the FDA have licensed Cetuximab for Irinotecan refractory EGFR positive metastatic colorectal cancer in the USA and a UK license for this indication was given in June 2004. A 42 patient Phase II trial of Cetuximab plus FOLFOX, the ACROBAT study, was reported at ASCO 2004 and showed a 81% response rate with no unexpected toxicities from the combination[30]. The mature data from ACROBAT[31] and more recent phase 2 studies support this high response rate. Pharmacokinetic data demonstrate that fortnightly Cetuximab at dose of 500 mg/m^2 is equivalent to a weekly dose of 250 mg/m^2 [32].

Skin reactions may develop in more than 80% of patients and mainly present as acne-like rash and/or, less frequently, as pruritus, dry skin, desquamation, hypertrichosis, or nail disorders (e.g. paronychia). Approximately 15% of the skin reactions are severe, including single cases of skin necrosis. Mild or moderate infusion-related reactions may occur (≥ 1/10) comprising symptoms such as fever, chills, nausea, vomiting, headache, dizziness, or dyspnoea that occur in a close temporal relationship mainly to the first Cetuximab infusion[33]. Severe infusion-related reactions may occur (≥ 1/100, < 1/10), in rare cases with fatal outcome. They usually develop during or within 1 hour of the initial Cetuximab infusion and may include symptoms such as rapid onset of airway obstruction (bronchospasm, stridor, hoarseness, difficulty in speaking), urticaria, hypotension, or loss of consciousness; in rare cases, angina pectoris, myocardial infarction or

cardiac arrest have been observed[33]. Other side effects observed in patients receiving Cetuximab monotherapy include asthenia, dyspnoea, mucositis, nausea, pain, fever and headache. Progressively decreasing serum magnesium levels have been observed leading to severe hypomagnesaemia in some patients.

Cetuximab is a targeted therapy and, to date, trials have excluded patients with apparently EGFR negative tumours. EGFR is detectable on immunohistochemistry (IHC) in 72-86% of tumours from colorectal cancer[25], but the intensity of expression has shown no correlation with response. However, the IHC test has a limit of detection at 35,000 receptors per cell, therefore in tumours where EGFR is undetectable on IHC there is still likely to be some expression of the target. In this trial, therefore, all patients will be entered irrespective of EGFR status an approach supported by recent phase 2 data[34]. Tumour samples will be collected (following patient consent) and will be analysed retrospectively for detection of the EGFR and other potential markers which may correlate with response.

k-RAS testing, the NICE recommendation and the preliminary COIN dataData recently presented at the ASCO 2008 meeting demonstrated that patients with the kRAS-mt genotype do not benefit from treatment with Cetuximab[35-38]. Following meetings of the TMG, DMEC and TSC it has been decided that based on these data patients with the kRAS-mutant genotype will be excluded from this trial. Other ongoing trials within the NCRN portfolio have adopted a similar approach.

In September 2009, the National Institute of Clinical Excellence (NICE) approved the use of Cetuximab for patients with k-RAS wild type tumours who have INOPERABLE liver only metastases. It is a further requirement that the patients' images are reviewed by a hepatic surgeon to formally determine inoperability. The NICE decision is appropriate as there is some evidence of Cetuximab benefit for this group of patients.

The New EPOC trial is studying patients with OPERABLE colorectal liver metastases. These patients are specifically EXCLUDED from the latest NICE approval and consequently funding of Cetuximab from Primary Care Trusts is unlikely to be approved. This is because there are no data on the benefit of Cetuximab in patients with OPERABLE disease therefore the question being addressed by the trial remains critically important.

The initial design of the New EPOC study was based on the COIN protocol and a combined analysis of these data was planned. The chemotherapy backbone comprised Oxaliplatin and Fluoropyrimidine: 5FU or Capecitabine. A protocol amendment was made to permit Irinotecan instead of Oxaliplatin if patients had previously had Oxaliplatin as adjuvant. The first analysis of the COIN study arm A vs B comparison, that is, Oxaliplatin and Fluoropyrimidine with or without Cetuximab was presented in September 2009. Surprisingly, there was no difference in overall or progression free survival in the k-RAS wild-type population. Although the data deserve further careful analysis, it appears that patients receiving Capecitabine and Cetuximab do less well because of greater toxicity and inferior dose intensity. Patients receiving 5FU potentially benefit more and this pattern appears to be reflected in the series of EGFR inhibition studies (CRYSTAL49OPUS50) CAIRO-251 Second-line Panitumumab and PRIME studies (ESMO 2009)). The CRYSTAL study survival data were also updated consequent on 93% of all samples being k-RAS tested. These data demonstrate a significant survival advantage for k-RAS wild type patients receiving Irinotecan, Cetuximab and 5FU compared to those receiving chemotherapy only (20 vs 23.5 months, HR 0.79 p<0.0094).

In view of these data, we have proposed that, in principle, Capecitabine NO LONGER BE USED in the New EPOC study. Clinicians are also be given the option of using IRINOTECAN or OXALIPLATIN as a partner with 5FU. These changes take account of the COIN and other data but do not significantly affect the integrity of the ongoing study. We emphasise that these changes are precautionary in the context of a clinical trial and do not represent standard practice. Cetuximab should be maintained as the experimental agent to determine its importance with respect to response rate and progression free survival in this cohort of patients.

Surgery for liver metastasis

Surgical resection of liver metastases (LM) from colorectal cancer is at present the only treatment currently offering long-term survival which is estimated from uncontrolled surgical series at 25 to 30%[39-40]. The treatment is now well-accepted and large datasets have been published. Initially, only solitary deposits were considered to be resectable. This was progressively extended to multiple but unilobar metastases, and later also to bilobar metastases as long as technically feasible. The good results that were observed in some patients have encouraged surgeons to develop more aggressive surgical approaches. Following hepatectomy, recurrences are observed in 2/3 of patients, half of them occurring in the liver. If technically feasible these can be further resected with similar expected benefits[40]. Furthermore, concurrent liver and lung metastases can be resected with a significant survival improvement.

Prognostic factors associated with survival and risk of recurrence after surgery of LM have been identified and have been incorporated into a simple scoring system allowing preoperative grouping of patients into risk groups with different 2 year survival rates[12]. This scoring system allows stratification of patients in order to evaluate and to compare the results of treatment of resectable liver metastases. Unfortunately at the present time not more than 10 to 15% of LM are considered resectable. This proportion may increase in the near future due to more aggressive surgical approaches on one hand and the use of preoperative chemotherapy on the other. Pre-operative chemotherapy has been shown in some cases to cause reduction of tumour size, thus allowing previously unresectable metastases to become resectable[41]. New methods are also now available for local destruction of liver metastases such as cryotherapy, radiofrequency ablation and laser hyperthermia, but their benefit has not yet been clearly validated and these methods are reserved for non-resectable liver deposits.

In 2005 the European Organization for Research and Treatment of Cancer (EORTC) Gastro-Intestinal Tract Cancer Cooperative Group completed a phase III study of pre- and post-operative chemotherapy with Oxaliplatin/5FU/LV versus surgery alone in resectable liver metastases from colorectal origin. 364 patients were recruited over 5 years and the primary endpoint was disease free survival which was positive[42]. The majority of these patients had metachronous metastasis. The regimen was safe in a neoadjuvant setting and the UK was the largest contributor to this study. The advantage in disease free survival was +8.1% (28.1% to 36.2%) with a hazard ratio of 0.77 (0.60-1.00) and a p = 0.041. These data strongly support the rationale for further developing neoadjuvant biochemotherapy in the context of modern imaging and surgery. The planned EORTC study BOSS-2 will randomise patients with operable liver metastasis with wild type k-RAS to receive chemotherapy alone, chemotherapy with Panitumumab or chemotherapy with Bevacizumab. A meta-analysis between these data and the New EPOC data is planned.

We feel that this study will be successful and valuable because:

1. It reflects and develops current UK practice as well as recent trial data.
2. It will target a population (patients primarily with synchronous liver metastasis) currently not addressed by the advanced disease studies.
3. It will be able to evaluate the overall benefit of modern multidisciplinary treatment in advanced colorectal cancer in both operable and inoperable groups.

Choice of trial regimen
The Oxaliplatin or Irinotecan regimens used in the trial can be selected on a per patient basis, but prior to knowledge of the treatment randomisation. The regimen will be **either:**

OxMdG: a combination of *l*-folinic acid (175 mg flat dose IV over 2 h) or *d,l*-folinic acid (350 mg flat dose IV over 2 h), concurrent administration of Oxaliplatin (85 mg/m^2 IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m^2; may also be given as a short 5 minute infusion or 15-30 minute infusion where this reflects local practice) followed by a 46 h IV infusion of 5FU 2400 mg/m^2 repeated every 2 weeks as used in FOCUS trial[10].

or

IrMdG: Irinotecan 180 mg/m^2 IV over 30 minutes, *l*-folinic acid (175 mg flat dose IV over 2 h) or *d,l*-folinic acid (350 mg flat dose IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m^2) followed by a 46 h IV infusion of 5FU 2400 mg/m^2 repeated every 2 weeks as used in the FOCUS trial.

This protocol has been evaluated in a large phase III trial including patients with metastatic colorectal cancer[12]. Please see appendices I-IV for details of the chemotherapy regimens.

5. Aims

The **primary aim** of the New EPOC trial is to determine whether the addition of Cetuximab to Oxaliplatin plus modified de Gramont or Irinotecan plus modified de Gramont combination chemotherapy results in improved progression free survival when compared with combination chemotherapy alone in patients who do not possess a kRAS mutant genotype confirmed by laboratory analysis.

Secondary aims
1. To evaluate overall survival.
2. To evaluate quality of life.
3. To compare the experimental arm in terms of cost effectiveness in a UK treatment setting
4. To determine whether the addition of Cetuximab to combination chemotherapy as above results in improved progression free survival when compared with combination chemotherapy alone in patients who possess the kRAS-wt genotype confirmed by laboratory analysis

Translational research aims

1. To assess the difference in progression free survival with chemotherapy plus Cetuximab for all patients irrespective of EGFR detectability in tumour tissue on IHC; for patients with detectable EGFR and for those with undetectable EGFR.
2. To determine, from DNA extracted from peripheral blood, the impact of individual variance in DNA repair capacity on tumour response, progression free survival and grade 3/4 toxicities.
3. To determine, from DNA extracted from peripheral blood, whether variance in the enzymes involved in the metabolism, transport and cellular targets of the drugs used affects tumour response, progression free survival and grade 3/4 toxicities.
4. To determine the effect of Cetuximab on the expression profile of hepatic metastases.

6. Outcome measures

Primary: progression-free survival.
Secondary: pre-operative response, pathological resection status, peri-operative safety findings, overall survival, EQ-5D, EORTC QLQ-C30, EORTC QLQ-LMC21, measures for cost effectiveness.

Definitions

Progression-free survival (PFS) is defined as the time from randomisation to first recurrence/disease progression or death, whichever occurs first. Patients not experiencing recurrence/progression/death will be censored at the date of the last follow-up examination. PFS will be assessed as follows:

In patients with resected metastases (R0 or R1 or R2), PFS will be considered to be the time from randomisation to the first of the following events:

- Recurrence/disease progression after surgery
- Death

In patients with unresected metastases, PFS will be considered as the time from randomisation to the first of the following events:

- Disease progression (whenever it occurs, before or after the planned surgery date)
- Death

Overall survival is defined as the time interval between the date of randomisation and the date of death. Patients who are still alive when last traced will be censored at the date of last follow-up.

Pre-operative response: evaluation of the activity of study treatment on hepatic metastases will be done according to the RECIST criteria (see Appendix V), after the end of the pre-operative treatment period by abdominopelvic computed tomography (CT) scan or magnetic resonance imaging (MRI) ideally within 1 week but not longer than 2 weeks. As patients will undergo surgery

within 2 to 4 weeks of CT scanning at the end of the pre-operative period, the 4 week confirmation does not apply for patients who achieve their first response at this time point.

A pre-operative safety finding will be if >6 weeks delay of surgery due to study treatment-related toxicity, with the delay being measured between the end of pre-operative chemotherapy (last day of last cycle) and surgery.

Pathological resection rate: following surgery, the pathologist will assess the resection as R0, R1 or R2. The rates of R0, R1 and R2 resections will be presented.

Peri-operative safety findings: any of the following events provided they are due to a severe surgery-related complication (i.e. wound infection, intra-abdominal infection, severe sepsis.):

- Prolongation of hospitalisation (discharge >20 days after surgery)
- Re-hospitalisation within 30 days of surgery
- Re-operation under general anaesthesia within 30 days of surgery (excluding secondary surgery after R1 resection)
- Death during surgery or within 30 days of surgery
- Other severe pre- or post-operative complications within 30 days of surgery:
- Surgery-associated bleeding with replacement ≥4 units of erythrocyte concentrates
- Biliary fistula for more than 10 days with a discharge of >100 mL/day
- Transient liver failure, defined as a bilirubin level >10 mg/dL lasting >7 days
- Renal failure requiring dialysis
- Respiratory failure with renewed necessary mechanical ventilation or >26 h necessary mechanical ventilation
- Deep venous thromboembolism
- Cardiac failure
- Major impaired wound healing necessitating re-operation, delaying the start of the post-operative study treatment by more than 8 weeks (delay being measured between surgery and start of post-operative study treatment) or prolonging hospitilisation (discharge >20 days after surgery)
- >8 weeks delay of the start of post-operative study treatment due to complications; delay being measured between surgery and start of post-operative study treatment
- Severe pre- or post-operative toxicity of study treatment leading to treatment discontinuation (all drugs discontinued) or death
  Note: the occurrence of minor surgery and minor impaired wound healing are not part of the endpoint definition but will be collected on the CRFs for descriptive purposes.

7. Centre and investigator selection

In order to participate in the New EPOC trial, investigators/centres must fulfill a set of basic criteria and witness this by signature of the New EPOC Commitment Form. This form will be sent to centres as soon as they express an interest in the trial. Criteria are:

- Ethical approval to participate in the trial according to their national and, for European centres, European rules and regulations
- Identification of an investigator responsible for the institution's participation in New EPOC who fulfills the legal requirements for investigators in biomedical research of the country in which the institution is situated
- Local infrastructure sufficient to guarantee that the investigations and treatment measures required by the protocol can be performed without undue delay
- Local infrastructure sufficient to guarantee follow-up
- Willingness to allow monitoring (source data verification)
- Willingness to comply with the protocol in all aspects of patient care, specimen handling and data management, as witnessed by signature(s) on the commitment form
- Familiarity with the chemotherapy agents under investigation, and the standard of supportive care required for these patients
- Familiarity with hepatic resection centre for hepatic metastases or part of a network with established links with a centre

The commitment form is signed by the Principal Investigator on behalf of all staff at their centre who will be working on the New EPOC trial.

In addition and in compliance with ICH GCP all centres participating in the trial will complete a delegation log and forward this to UoSCTU. Each person working on the New EPOC trial must complete a section of this log and indicate their responsibilities. The UoSCTU must be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the investigator file held at the participating centre and also at UoSCTU.

Finally, prior to entering patients into the trial UoSCTU must receive full contact details for all centre personnel. This must be updated whenever there are changes to trial staff or their contact details. The Clinical Trial Authorisation (CTA) for the New EPOC trial requires that the Medicines and Healthcare Products Regulatory Agency (MHRA) be supplied with the names and addresses of all participating investigators/centres. Trial staff at UoSCTU will perform this task hence it is vital full contact details for all investigators are provided.

8. Eligibility criteria

Inclusion criteria

- Confirmed colorectal adenocarcinoma:
  - previous or current histologically confirmed primary adenocarcinoma of colon or rectum, together with clinical or radiological evidence of advanced and / or metastatic disease.

- Presence of potentially resectable colorectal cancer liver metastases without detectable extra-hepatic distant metastatic disease. Patients with intra-abdominal loco regional recurrence which in the opinion of the surgeon is easily resectable may be included. Appendix The following patients are eligible:

- Patients with rectal cancer who would be suitable for short course radiotherapy as an adjuvant treatment.
- Patients who have had long course chemoradiation and R0 surgery for rectal cancer.
- Patients with metachronous metastases having undergone complete resection of the primary tumour without gross or microscopic evidence of residual disease (R0).
- Patients with synchronous metastases who have undergone R0-resection of the primary tumour more than one month before randomisation.
- Patients with synchronous metastases for whom there is sufficient evidence (for example by CT scan or diagnostic laparoscopy) that both the primary tumour and the liver metastases can be completely resected during the same procedure and that resection of primary cancer can be delayed for 3 to 4 months.
- Patients who are thought by the hepatic surgeon to be suboptimally resectable are included. This will normally include patients, for instance, who have potentially resectable disease but in whom compromise of the resection margins is likely. These patients are currently normally treated with pre-operative chemotherapy under NICE guidance. This decision will be at the surgeons discretion.
- Unidimensionally measurable disease (RECIST criteria, see AAppendix V) to measure pre-operative response.
- Patients with previously resected liver metastases for whom surgery was performed ≥ 1 year previously.
- No previous systemic chemotherapy for metastatic disease.
- adjuvant chemotherapy with 5FU +/- FA, Capecitabine or Oxaliplatin may have been given, if completed > 6 months prior to trial entry.
- rectal chemoradiotherapy with 5FU +/- FA may have been given, if completed > 1 month prior to trial entry.

- WHO performance status (PS) 0, 1 or 2 (see AAppendix VII) and considered by responsible consultant to be fit to undergo combination chemotherapy.
- Baseline laboratory tests (within 1 week prior to randomisation):
  - neutrophils ≥ 1.5 x10^9/l and platelet count ≥ 100 x10^9/l
  - serum bilirubin ≤ 1.25 x upper limit of normal (ULN), alkaline phosphatase ≤ 5 x ULN, and serum transaminase (either AST or ALT) ≤ 2.5 x ULN
  - estimated creatinine clearance (Cockcroft; Appendix VIII) >50ml/min **or** measured GFR (EDTA clearance) >50 ml/min.

- All patients must be aged 18 years or older.
- For women of childbearing potential, negative pregnancy test and adequate contraceptive precautions. Adequate contraception for men.
- Written informed consent.
- Consent to allow surplus pathological material to be analysed for translational research projects *(patients may decline participation in this supplementary component and still participate in the main trial).*

Exclusion criteria

- Patients who are unfit for the chemotherapy regimens in this protocol, e.g.:
  - severe uncontrolled concurrent medical illness (including poorly-controlled angina or very recent MI, i.e. in previous 3 months) likely to interfere with protocol treatments.
  - Any psychiatric or neurological condition which is felt likely to compromise the patient's ability to give informed consent or to comply with oral medication.
  - Partial or complete bowel obstruction.
  - Pre-existing neuropathy (> grade 1).

- Patients requiring ongoing treatment with a contraindicated concomitant medication.
- Patients with another previous or current malignant disease which, in the judgement of the treating investigator, is likely to interfere with New EPOC treatment or assessment of response.
- Patients with known hypersensitivity reactions to any of the components of the study treatments.
- Patients with distant metastases outside the liver.
- Female patients who are lactating.
- Patients with a personal or family history suggestive of dihydropyrimidine dehydrogenase (DPD) deficiency or with known DPD deficiency.
- Patients who possess the kRAS-mt genotype or whose kRAS genotype status is unknown in the primary tumour.
- Partial or complete bowel obstruction.
- Chronic diarrhoea or inflammatory bowel disease.
- Gilbert's syndrome or other congenital abnormality of biliary transport (e.g. Crigler-Najjar syndrome, Dubin-Johnson syndrome).
- Previous transplant surgery, requiring immunosuppressive therapy (due to interaction of cyclosporin-A with irinotecan).
- Patients with ≥ grade 1 residual neurotoxicity following Oxaliplatin as adjuvant may be offered Irinotecan and 5FU instead of Oxaliplatin and Fluoropyrimidine as neoadjuvant[45].

9. Treatment of patients

9.a Starting chemotherapy

- Prior to randomisation (i.e. at screening) the chemotherapy regimen to be used (OxMdG or IrMdG) should be selected either according to patient choice or centre policy.
- Following randomisation, patients must start treatment within three weeks (if clinically acceptable) but ideally as soon as possible.
- Appendices I-IV contains protocols for the trial regimens. It is the responsibility of the treating consultant to ensure that these protocols are followed. In particular:
  - Renal, hepatic and bone marrow function must be monitored carefully, and dose-adjustments made as indicated (see AAppendix IV).

- Dose modifications should only be made after consulting appendices I-IV (if in doubt, please discuss with UoSCTU).
- Note that overweight patients are dosed using 1.15 x ideal body weight (see AAppendix II) for all chemotherapy drugs. Cetuximab doses should not however be capped to 1.15 x ideal body weight, please dose according to the patients actual body weight.
- Magnesium levels should be measured in all patients at screening, prior to each chemotherapy cycle and in patients displaying symptoms of hypomagnesemia.

- The ambulatory technique for OxMdG and IrMdG is described in AAppendix III. These regimens may also be given on an inpatient basis, but investigators are urged to use outpatient ambulatory treatment whenever possible.

9.b Treatment duration and breaks

- **Arm A (Control, OxMdG / IrMdG):** These patients will receive 12 weeks of pre-operative and 12 weeks of post-operative chemotherapy dependent on cumulative toxicity, post-surgical performance status or because of patient choice to stop chemotherapy. Patients in this arm should continue on treatment with no more than a three week interval off treatment for any reason although the post surgical interval can be 6 weeks. *The cumulative toxicity that is most likely to occur is the neuropathy associated with Oxaliplatin, which increases in incidence from about 12 weeks duration of therapy. If this occurs, patients may continue on the fluorouracil component of the regimen with dose increment as indicated in Appendix I.* If the neuropathy resolves to < grade 1 the Oxaliplatin may be reintroduced cautiously at the investigator's discretion.
- **Arm B: OxMdG / IrMdG plus Cetuximab:** These patients will receive chemotherapy as Arm A above plus Cetuximab. Patients in this arm should continue on treatment with no more than a three week interval off treatment for any reason although the post surgical interval can be 6 weeks. Cetuximab will be continued if chemotherapy is stopped because of toxicity or patient choice, but should be discontinued on recurrence or unacceptable Cetuximab toxicity. Full details of Cetuximab administration and dose reduction and delays are given in Appendix I.

9.c Surgery

The liver resection is carried out **at the earliest 4 weeks** after the last administration of chemotherapy and Cetuximab, and within 2 to 6 weeks of CT scanning at the end of the pre-operative period. Patients who progress during the first 12 weeks of chemotherapy and who are still operable should be considered for surgery. However these patients are unlikely to be salvaged with surgery and consideration should be given to second-line chemotherapy. In addition, the patient must have completely recovered from side effects, the general condition according to WHO grade must be $\leq$ 1 and liver function must be adequate for liver surgery.

The type and extent of liver resection should be decided at time of randomisation and should include all the areas that have contained tumour even when there is marked tumour shrinkage or a complete radiological response. It is accepted by most liver surgeons that the benefit of neoadjuvant chemotherapy is that it may increase the surgeons ability to achieve clear margins. When previously undetected deposits are discovered at surgery or if the tumour is larger than expected, liver resection should be adapted to ensure complete tumour resection wherever possible.

Before the beginning of the liver resection (after abdominal incision), extrahepatic involvement of the abdomen must be excluded by inspection and palpation and frozen section histological examination of suspicious lesions. Intra-operative ultrasonography is suggested to detect and localize any additional metastases but is not mandatory.

A curative resection of the metastases with a clearance of ≥ 1 cm of normal parenchyma should be the aim. However metastases will be considered resectable even if the clearance is less than 1 cm provided complete macroscopic resection of liver metastases is possible. Whether anatomical liver resection or wedge resection or a combination of the two is carried out depends on the localization of the metastases. The surgical technique, including vascular isolation, use of technology is left to each surgeon's discretion. The technique used should be noted on the correct form and blood loss and extent of resection detailed. Post-operative follow up will be recorded and serious complications will be reported within one month after surgery to allow a direct comparison.

Post-operative study treatment should **start 4 weeks** after surgery (not earlier); however, post-operative study treatment may be delayed until 8 weeks after surgery, at the latest. The rationale for any delays must be documented in the CRF.

9.d Other anticancer treatment modalities

If, in the opinion of the treating investigator, an alternative treatment modality becomes indicated at any stage, it may be offered (e.g. radiofrequency ablation, palliative radiotherapy, bypass surgery). Patients may be offered surgery to resect their primary cancer if appropriate. Patients with rectal cancer who are suitable for short course radiotherapy as an adjuvant may receive this treatment after the first 12 weeks of chemotherapy, prior to resection of the rectal tumour and subsequent resection of metastases. Patients expected to be candidates for other modalities at randomisation are not eligible for this trial.

9.e Follow-up

Once randomised, patients remain evaluable for the intent-to-treat analysis regardless of their subsequent course and treatment. Follow-up data on all patients, including details of other treatments given, is therefore important.

Patients enrolled from the UK will be registered with The Health and Social Care Information Centre in order to obtain long term follow-up information on survival, in the event that patients are lost to follow-up in the clinical centres.

10. Trial drugs

10.a Drug supplies

Details of the procedures for obtaining drugs within the trial will be sent to centres when they express an interest in participating in the trial. Study medication will be stored and dispensed by the trial centre pharmacy department in accordance with Good Clinical Practice and Good Manufacturing Practice. Cetuximab is not licensed for this first line indication. Cetuximab stocks will

be provided by Merck and will be special trial stock. Cetuximab is provided in ready use vials containing 5 mg/ml. Once removed from the vial, Cetuximab must be used within 8 hours if stored at room temperature. All other drugs and other products used in this trial are commercially available and are being used within NICE guidance. No special arrangements are required for Oxaliplatin, Irinotecan or Fluorouracil but should be in accordance with EU regulation. The guidelines in this protocol are in line with manufacturers' recommendations at the time of writing, but Summaries of Product Characteristics (SpCs) are updated from time to time. Up-to-date SpCs are posted on the Medicine Guides Website (http://www.medicines.org.uk).

10.b Prescribing and compliance

Chemotherapy prescriptions should conform to local best practice including computerised prescribing systems where available.

10.c Concomitant medications

There are no specific drug interactions documented with Cetuximab. However, any agent that may interfere with the immune system of the patient should preferably be avoided except the indicated study regimen and necessary supportive treatment (including Corticosteroids, Antiemetics etc).

St John's Wort is contraindicated for concomitant use with irinotecan. St John's Wort induces the cytochrome P450 isoform CYP3A4 which leads to reduced plasma levels of the active Irinotecan metabolite SN-38.

The following medications may interact with chemotherapy in New EPOC. These medications are not contraindicated but should be avoided unless there is no reasonable alternative:

1. **Allopurinol**: may potentially reduce the effectiveness of 5FU.

11. Trial procedures

11.a Centre approval process

The following documentation must be received by UoSCTU in order for a centre to become an approved New EPOC centre:

- Confirmation of ethics approval (site-specific assessment);
- A copy of the most recent version of the patient information sheets and consent form on local headed paper;
- Confirmation from the MHRA that centres/investigators have been added to the New EPOC CTA;
- Completed delegation log (signature list and delegation of responsibilities);
- Full contact details for all centre personnel;

Once all of this documentation has been received, confirmation of centre approval will be sent to the Principal Investigator at each centre by the trial team at UoSCTU.

11.b Within the week prior to randomisation

- The patient should have a minimum of 24 hours after the initial invitation to participate before being asked to sign the main trial consent form.
- Ensure that the patient understands that they are free to give or withhold permission for the translational studies (single blood sample and use of resected primary colorectal cancer and liver metastases) without affecting their participation in the clinical study.
- History and examination.
- Assessment of performance status.
- Full blood count and biochemistry. Calculate GFR using Cockcroft formula (see Appendix VIII). If the Cockcroft estimate is < 50 ml/min, a measured GFR is required (e.g. by EDTA clearance). Magnesium levels & C Reactive Protein (CRP) should also be recorded.
- Ensure patient has measurable disease (RECIST criteria, Appendix V) and that a baseline CT scan (chest, abdomen, pelvis) has been (or will be) performed **within 4-6 weeks prior to the planned start date for chemotherapy.**
- Check all other inclusion and exclusion criteria in protocol section 8.

kRAS genotyping

- During the initial clinic visit where the main trial patient information sheet is provided, also provide the patient with the kRAS patient information sheet and answer any questions the patient has regarding the kRAS genotyping.
- Seek appropriate informed consent to conduct kRAS genotyping and ask the patient to sign the kRAS consent form.
- If consent to conduct kRAS genotyping is obtained, request a sample from the patients' primary cancer (paraffin block or biopsy) from the relevant pathology laboratory and send with a copy of the histology report and kRAS genotype request form for kRAS analysis (see Appendix XIV). Any reports sent may only identify patients by their initials, year of birth and the New EPOC site ID number where the patient consented to participate in the trial. Package the sample in the safebox provided according to the requirements described by the University of Southampton Clinical Trials Unit in the investigator information sheet, mark as '**urgent clinical sample**' and send to:

  Molecular Genetics Laboratory
  Institute of Medical Genetics
  Cardiff & Vale NHS Trust
  Heath Park
  Cardiff CF14 4XW

- kRAS genotype will be reported by the Molecular Genetics Laboratory in Cardiff within one working week to the University of Southampton Clinical Trials Unit which will subsequently forward results to the relevant trial site.

- Patients who have already been kRAS genotyped locally, and are confirmed as wild -type, please send a copy of the kRAS result to the University of Southampton Clinical Trials Unit prior to randomisation.
- Please also send a tumour block before or after randomisation to Cardiff using the procedures outlined above, in order for quality assurance purposes.

After obtaining written consent to the main trial:

- Patient to complete first QoL forms (see appendices IX and X).
- Confirm with the patient whether they are to receive OxMdG or IrMdG chemotherapy regimen.

11.c Randomisation

Enrolment will only be accepted if current eligibility criteria have been checked, written consent obtained, chemotherapy choice decided (OxMdG or IrMdG) and the current baseline QoL form has been completed.

- Patients will be randomised to the control or experimental arm by telephone to the MRC Clinical Trials Unit. Randomisation will utilise minimisation and the stratification factors are surgical centre, poor prognostic tumour (yes or no) and prior treatment with Oxaliplatin as adjuvant (yes vs. no). A poor prognostic tumour is defined as having any one or more of the following ≥4 metastases (yes or no), N2 disease (yes or no) or poor differentiation at biopsy (if available, if not available the tumour is considered to be not poorly differentiated).
- Complete the first page of the Baseline and Randomisation Form and telephone the MRC CTU on **020 7670 4777** (9am – 5pm, Mon-Fri).
- Details will be taken and the patient will be allocated a treatment and trial number. At that point, complete the remainder of the Randomisation Form and fax it to UoSCTU on **0844 7740621**, together with the baseline QoL form and a copy of the signed Consent Form.
- Also at this point, provided the patient has not withheld consent for the translational studies:
    1. Ensure that the patient's pathology details are recorded on the **Randomisation and pre-treatment Form and request the pathology block from the relevant local pathology laboratory using the pathology request form.**
    2. Request stored pathology samples (normal and tumour tissue) from previous resection surgery of the patients' primary colorectal cancer and take 20 ml blood in an EDTA tube (2 tubes required if 10 ml size). Label each sample with the **date of collection and patient details**. Seal the tube(s) in a plastic bag, place in a Royal Mail 'safeBox' provided by UoSCTU and post first-class with a copy of the patient consent form and any histology information available. The address for posting is:

        New EPOC Trial Sample laboratory
        Cancer Sciences Tissue Bank
        Somers Research Building
        MP 824, Southampton General Hospital
        Tremona Road
        Southampton SO16 6YD

11.d Start of chemotherapy

Treatment should start as soon as possible after randomisation. However, a delay of up to 3 weeks from randomisation to start of treatment (e.g. for venous line insertion) may elapse if clinically acceptable. Patients should still be treated within 4-6 weeks of the cross sectional imaging scan used to assess their disease. If the patient will receive infused 5FU in OxMdG or IrMdG but the line cannot be fitted sufficiently quickly, give the first cycle of treatment as an inpatient.

11.e Every chemotherapy cycle (day 1, or up to 3 working days before)

1. Clinical evaluation (doctor/nurse), to include NCI toxicity scores from previous cycle (see Appendix XI) and current WHO PS (see Appendix VII)
2. Check FBC, U&Es, and LFTs (see regimen details in Appendix I for critical values).
3. Measure and record magnesium levels.
4. Recalculate drug doses if patients' weight has changed by more than 10%, or follow local policy.
5. Record Cetuximab administration details for patients in Arm B.
6. These data should be collated on the **Treatment Form** which is returned to UoSCTU every 6 weeks (i.e. after every 3 cycles of OxMdG or IrMdG)

Patients should also complete QoL questionnaires during both pre- and post-operative chemotherapy at the beginning of cycle 4 with OxMdG and IrMdG.

11.f Surgery

Surgical data will be recorded on the surgery form and returned to UoSCTU within four weeks of the date of surgery. Investigators should make local arrangements to ensure that facilities to snap-freeze samples are available during surgery (if possible). Pathology samples (normal and tumour tissue) obtained following liver resection surgery should be requested and sent to the Cancer Sciences Tissue Bank, Southampton (see section 11c) for those patients who have given consent.

11.g After the end of treatment

After completion of study treatment patients will be followed up with the following tests and procedures every 3 months for 2 years, and every 6 months thereafter until progression for a further 3 years and/or death, using the **Progress report & follow-up form:**

1. Clinical examination.
2. Chest, abdomen and pelvis CT scan (or equivalent imaging). Chest x-ray only to be performed if chest CT not available.
3. A QoL form should also be completed every 3 months for the first year and every 6 months thereafter.
4. Magnesium levels should be measured 6-8 weeks after the last dose of Cetuximab and at intervals until hypomagnesaemia has resolved.
5. Documentation of survival status and further anticancer treatments will be done. All deaths should be reported to UoSCTU using the Death CRF.

Patients who progress whilst in follow-up should come off protocol follow-up but treatment and care outcome data should still be collected. The follow-up only form should be completed at the same study time points.

Patients enrolled from the UK will be registered with The Health and Social Care Information Centre in order to obtain long term follow-up information on survival, in the unlikely event that patients are lost to follow-up in the clinical centres.

Subjects who undergo all protocol CT scans will receive a total effective dose of 476mSv detrimental radiation. The rounded risk of fatal cancer (adult) is 1 in 70. For adults under 50 years of age this level of exposure would be classed as level III (moderate) risk. This level of exposure will be standard care in some centres and only a percentage above standard of care in others, at maximum 100%. Whilst the subjects recruited into this study may receive up to this level of detrimental radiation as part of their normal care, the survival of this patient group is 30% at 5 years and 20% at 10 years. Any centre unable to comply with this dose constraint should contact the University of Southampton Clinical Trials Unit.

Please refer to section 3 (summary of interventions) for details of the expected timing of the trial procedures during the treatment phase.

12. Safety reporting

The Amended Medicines for Human Use (Clinical Trials) Regulations 2006 gives the following definitions:

Adverse event (AE): any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse reaction (AR): any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected adverse reaction (UAR): an adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SpC) for that product (for products with a marketing authorisation), or the Investigator's Brochure (IB) relating to the trial in question (for any other investigational product).

Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction (USAR): any adverse event, adverse reaction or unexpected adverse reaction, respectively that results in death is life-threatening, required hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or consists of a congenital anomaly or birth defect.

12.a Reporting responsibilities

All SAEs must be reported immediately by the Investigator (Consultant responsible for the patient) to UoSCTU UNLESS the SAE is specified in section 12.b. Investigators should notify UoSCTU of all SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration. SUSARs occurring after this 30 day period must be reported to UoSCTU following the same procedure. A completed SAE form for all events requiring immediate reporting should be faxed to the UoSCTU within 24 hours or identification of the event. This should be followed by further reports giving additional relevant information as required. Other adverse events should be recorded on the appropriate CRF.

Death as a result of disease progression and other events that are primary or secondary outcome measures are not considered to be SAEs and should be reported in the normal way, on the appropriate CRF.

SAEs will be recorded in the medical notes and the CRF returned to UoSCTU in a timely manner. UoSCTU is responsible for, and will report SUSARs (Suspected Unexpected Serious Adverse Reactions) and other suspected SARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states in which the trial is taking place) and the relevant ethics committees as follows:

- SUSARs which are fatal or life-threatening reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information reported within a further 8 days.
- SUSARs that are not fatal or life-threatening reported within 15 days of the sponsor first becoming aware of the reaction.
- Suspected SARs (expected and unexpected) listed and reported annually.

All serious adverse drug reactions will also be reported by the clinician caring for the affected patient to the MHRA Committee on Safety of Medicines using the yellow card scheme.

12.b SAEs not requiring immediate reporting

The most recent version of an agent SpC should be accessed at www.medicines.org.uk. A file note detailing this process is filed in the investigator site file. SAEs that are expected with these agents and do not require immediate reporting in this trial are documented in the SpC.

12.c Evaluation of SAEs

The Investigator should assess each SAE for the likelihood that it is a response to the investigational medicines. The SAE will also be evaluated by an allocated Clinical Reviewer at the request of UoSCTU for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities. The causality assessment given by the Investigator cannot be overruled and in the case of disagreement, both opinions will be provided to the authorities with the report.

All SUSARs reported to UoSCTU will be forwarded to Merck kGaA.

13. Protocol deviations and withdrawal of patients

All protocol deviations should be reported to University of Southampton Clinical Trials Unit at the earliest opportunity.

In consenting to the trial, patients are consenting to trial treatment, trial follow-up and data collection. If a patient wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes. If the patient explicitly states their wish not to contribute further data to the study, UoSCTU should be informed in writing and an End of Study form completed.

13.a Withdrawal from trial intervention

A patient may withdraw, or be withdrawn, from trial treatment for the following reasons:

- Progression whilst on therapy
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Withdrawal of consent for treatment by patient
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the investigator's opinion.

The patient should however remain in the trial for the purposes of follow-up and data analysis.

14. Trial closure

We plan to recruit 288 patients which we anticipate we will reach at the end of December 2012. We will then follow-up all patients for 5 years after the trial closes to patient entry.

For the purposes of regulatory requirements the end of the trial will be the final date on which data was (or is expected to be) collected'.

15. Quality of life

15.a QoL timing

QoL assessments will be performed at screening (prior to randomisation), mid pre- and post-operative chemotherapy and following each 12 week chemotherapy treatment. Further assessments will be performed every 3 months for the first year and every 6 months thereafter during follow-up. The primary QoL endpoint will be analysed immediately after the post-operative chemotherapy treatment.

15.b QoL instruments and endpoints

The EORTC QLQ-C30 and QLQ-LMC21 have been chosen (see Appendix IX). It has been used in previous MRC and NCRI trials (CR05, CR06, FOCUS and COIN). In addition, a number of trial-specific questions have been added (see Appendix IX). The primary QoL endpoints are toxicity, functional scales and global QoL.

The EuroQol (EQ)-5D questionnaire (see Appendix X) will also be administered[27]. This is a preference-based generic measure of health-related quality of life that is necessary to measure quality-adjusted life-years (QALYs) for use in cost-effectiveness analysis.

15.c Administration of the QoL questionnaires

The initial QoL questionnaire must be completed in the clinic before randomisation (at screening), and thereafter, in order to fit in with treatment schedules and protocol assessments. When the QoL questionnaire coincides with a treatment cycle (including the mid-chemotherapy QoL measures) it should be completed in the clinic before treatment is given.

A window of 2 weeks around each follow-up QoL assessment time-point will be accepted. At least one person in each centre must be nominated to take responsibility for the administration, collection and checking of the QoL forms. High levels of compliance throughout will be required in order to pick up cumulative toxicity and to assess duration of palliation.

The patients without conferring with friends or relatives should complete the questionnaires, and all questions should be answered even if the patient feels them to be irrelevant. Patients should always be asked to complete questionnaires even if they declined to complete a previous assessment.

An explanation for patients is given in Appendix IX and more details about QoL administration. Please note that once randomised all patients remain in the trial and QoL questionnaires are required even if patients do not complete protocol treatment.

16. Economic evaluation

Given the high cost per patient of the antibody treatment at an estimated £20k, economics is important and will be included in the trial as follows:

The incremental cost per life year and per QALY will be estimated, initially at 3 years but also at 5 years and 10 years. Longer term survival will be modelled using time to event analysis, supplemented eventually by actual survival data (using The Health and Social Care Information Centre tagging of patients). Differences in the quality of life of treated patients compared to controls will be estimated by use of EQ5D, the standard instrument. Costs will be from the societal perspective and besides the cost of antibody treatment will include use of all hospital resources, NHS non-hospital resources and subject travel costs. See Appendix XII for more details.

17. Molecular pathological research

New EPOC will parallel and complement COIN in its translational intention. Three parallel translational studies will be undertaken.

The first is a focused, in depth study investigating the relationship between DNA repair capacity and chemotherapy response and side effects. This will increase the power to detect differences between the effect of SNPs in the DNA repair genes on response and toxicity (as per COIN trial protocol).

Secondly, this study uses Cetuximab without prior exclusion of patients whose tumours do not express EGFR on immunohistochemistry. We will therefore collect tumour samples from redundant stored paraffin embedded tissue to evaluate the presence of the EGFR and other downstream markers, in an attempt to define molecular correlates with response to Cetuximab (as per COIN trial protocol).

Thirdly, the trial provides a unique opportunity to collect fresh tumour tissue in order to undertake cDNA microarray analysis and further analyses related to EGFR pathway functions and response to therapy.

17.a Blood and tumour sample collection

- Patients will be asked for consent to obtain blood, tumour and normal tissue samples for translational research projects. These include redundant formalin fixed samples of their primary cancer and normal colorectal tissue from the pathology laboratories which were surgically resected during a previous operation (where available). New specimens to be collected during this study include liver metastases, normal liver tissue and 20 ml blood. Samples of liver metastases and normal liver tissue should be both formalin fixed and snap-frozen in liquid nitrogen where this facility is available. Any subject who undergoes resection of their primary cancer during their enrolment in the trial will also have samples of normal and tumour colorectal tissue taken for translational work (fresh frozen and formalin fixed). In the *FOCUS* trial, over 95% of patients gave separate consent for surplus pathological material to be used in molecular research[10] and we anticipate a similar acceptance rate for this study.
- All samples (blood and tissue) will be sent for storage at the Cancer Sciences Tissue Bank, Southampton (see section 11c) and subsequently anonymised.
- 20 ml blood will be collected in EDTA tubes (1 x 20 ml or 2 x 10 ml) and stored at ambient temperature.
- Research staff in the investigator centres will request formalin fixed paraffin blocks of the primary cancer, metastases and normal tissue from these centres from the relevant pathologist. On receipt, the sample will be forwarded to the tissue bank in Southampton and then anonymised. Tumour tissue microarrays (TMAs) will be constructed which may be performed by a laboratory in collaboration with the tissue bank in Southampton.
- Fresh normal and tumour liver tissue should be collected during liver resection surgery and stored by the local pathologist at -80°C. Tissue blocks should be snap-frozen prior to storage where this facility is available.
- Investigator centres should contact the University of Southampton Clinical Trial Unit to ensure that the correct storage and shipping procedures are followed.
- The custodian of the samples will be the Trial Management Group (TMG). Proposals for translational research projects involving the material will be considered by the TMG for approval. Full ethical approval by an NHS research ethics committee must also have been

given before the TMG will authorise release of the samples from the trial tissue bank for any translational study.

18. Analysis plan and statistics

This 2 arm trial will compare the experimental arm (OxMdG-C/IrMdG-C, ARM B) against the control (OxMdG/IrMdG, ARM A).

Sample Size Calculation

The original EPOC trial (EORTC 40983) compared patients having surgery alone to patients being treated with pre and post operative chemotherapy with FOLFOX[42]. It assumed that chemotherapy may increase the median progression free survival by 40% from 16 months to 22.4 months. The power calculation study required 330 patients (165 in each arm) and 364 were actually recruited. The study demonstrated that peri-operative FOLFOX improved PFS and is compatible with major liver surgery[42]. This trial studied a group of patients with favourable liver metastases (4 lesions or less, mainly metachronous presentation). The group being studied in the current proposal has a considerably worse prognosis[1-10, 46] as it includes patients with synchronous presentation and with sub optimal operability. An open study of such a group of patients treated with FOLFOX chemotherapy and surgery revealed a median progression free survival of around 17 months[47]. The current proposal will also recruit a cohort of patients with metachronous disease who have received adjuvant Oxaliplatin. The survival of this group is less good than those patients treated with 5FU alone. However, metachronous disease patients suitable for FOLFOX have improved PFS compared to synchronous disease patients. Considering published data and the target patient population for this trial the expected median PFS for the control group is 15 months.The Crystal study[49] randomly assigned 599 patients with epidermal growth factor receptor-positive colorectal cancer with unresectable metastases to receive FOLFIRI either alone or in combination with Cetuximab. The results found the overall hazard ratio observed for progression free survival among 348 patients with wild-type-KRAS tumours was 0.68 (95% CI, 0.5 to 0.94). The results from the Crystal study have been used to power the New EPOC trial because it is internationally accepted as the best demonstration of Cetuximab in advanced colorectal cancer and if in New EPOC an effect less than this is observed it would be questionable as to whether it would be considered clinically meaningful. Further, bearing in mind the cost of antibody treatment, a hazard ratio greater than this would not justify its routine use. Using a hazard ratio of 0.68, assuming 80% power, a 5% 2-sided significance level and 5% loss to follow up by 2 years the total number of patients required with kRAS wild type genotype in the primary tumour is 268 (134 in each arm). This means the total sample size required for New EPOC is 288. This ensures the 20 patients for whom their kRAS status is unknown as they were recruited before the protocol amendment are replaced. The total sample size 268 patients with kRAS wild type genotype in the primary tumour is powered to detect 212 target events (disease progression). The sample size calculation was performed using ART version 1.07 in STATA and assumed recruitment would take place over 3 years with 5 years of follow up. Baseline survival probabilities from EPOC were also used in the calculation. This assumed progression free survival at 1 year, 2 years and 3 years was 67%, 46% and 35% respectively.

Initial analysis plan

The primary outcome measure is progression free survival. The two treatment groups will be compared on an intention to treat basis. Comparison of survival between the two treatment groups will be performed using Cox regression. The hazard ratio and 95% confidence interval will be reported. The primary analysis will be unadjusted and will include only patients whose primary tumour has been confirmed as kRAS wild type genotype. Sensitivity analyses may be adjusted for any confounding variables if, by chance, there are imbalances between the groups. The primary analysis will be repeated including only patients whose primary tumour has been confirmed as kRAS wild type genotype and who were not treated with CAPOX. The DMEC will also regularly review the trial data. Serial analyses will not be performed, except by the DMEC.

There will also be a planned combined analysis with arms A and B of the COIN study to evaluate the intention to treat effect of Cetuximab on all patients with advanced disease. In this combined analysis consideration for confirmed kRAS status in the primary tumour will be made. Comparison of survival between the two treatment groups will be performed using Cox regression, adjusted for stratification factors. The hazard ratio and 95% confidence interval will be reported. The analyses will be adjusted for any confounding variables if, by chance, there are imbalances between the groups. The DMEC will also regularly review the trial data.

19. Patient confidentiality

The University of Southampton is registered under the Data Protection Act to hold data as required for trial purposes. Patients will be allocated a unique trial number that will be used in all correspondence with the participating centres. At no point in the presentation or publication of trial data will individual patients be identified. Each patient's GP will be notified of their enrolment in this clinical trial using the associated GP letter (if consent is provided).

20. Monitoring and quality assurance

20.a Monitoring at UoSCTU

The study will be monitored and audited in accordance with University Hospital Southampton NHS Foundation Trust (UHS) procedures. All trial related documents will be made available on request for monitoring and audit by UHS, the relevant REC and for inspection by the MHRA or other licensing body.

20.b Direct access to data

Collaborating centres should be aware that direct access to patient data by UoSCTU staff will be required for trial-related monitoring or audit. Patient consent for access to patient medical records and for a copy of the consent form to be sent to UoSCTU will be obtained as part of the general trial consent process.

20.c Visits to investigator centres

Each centre will be visited at least once during the course of the New EPOC trial.

The purpose of these visits is:

- to verify that the rights and well-being of human subjects are protected
- to verify accuracy, completion and validity of reported trial data from the source documents
- to evaluate the conduct of the trial within the institution with regard to compliance with the currently approved protocol, GCP and with the applicable regulatory requirements

UoSCTU will give the responsible investigator adequate notice of the monitoring visit to allow adequate time, space and staff for these visits.

After the monitoring visit the trial co-ordinator or monitor from UoSCTU will complete a visit report. This report may be circulated to the TMG for comment. A copy of the report will be sent to the Principal Investigator (PI) at the centre. A copy will also be filed in the UoSCTU New EPOC Trial Master File.

21. Ethical considerations and approval

21.a Ethical considerations

This is a randomised controlled trial. Therefore neither the patients nor their physicians will be able to choose the patient's treatment. Treatment will be allocated randomly using a computer-based algorithm. This is to ensure that the groups of patients receiving each of the different treatments are similar.

21.b Ethical approval

The study will be performed subject to regulatory approval, Research Ethics Committee (REC) approval, including any provision of Site Specific Assessment (SSA.

The protocol has Multi-Centre Research Ethics Committee (MREC) approval but the Local Research Ethics Committee (LREC) must give each Principal Investigator (PI) /additional centre Site Specific Assessment (SSA) approval before patients are entered at that centre. SSA approval letters will be sent by MREC to UoSCTU who will then liaise directly with the local investigator/s to advise. Copies of the SSA approval will be sent to the PI and must be maintained in the local Investigator File.

The patient's consent to participate in the trial should be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. Patients should be given sufficient time after being given the trial patient information sheet to consider and discuss participation in the trial with friends and family. A contact number should be given to the patient should they wish to discuss any aspect of the trial. Following this, the randomising investigator should determine that the patient is fully informed of the trial and their participation, in accordance with ICH GCP guidelines and the EU Commission Directive 2005/628/EC. Patients should always be asked to sign a consent form. One copy should be given

to the patient, one copy should be kept with patient's hospital notes and the original filed in the local investigator's file.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the patient must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

21.c Research governance

The study will be conducted in accordance with The Medicines for Human Use (Clinical Trial) Amended Regulations 2006 and subsequent amendments; the International Conference for Harmonisation of Good Clinical Practice (ICH-GCP) guidelines; and the Research Governance Framework for Health and Social Care.

22. Sponsorship and indemnity

The sponsor of the trial is University Hospital Southampton NHS Foundation Trust (UHS). For NHS sponsored research HSG(96)48 reference no.2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

23. Finance

New EPOC will be coordinated at the UoSCTU. The trial is funded by Cancer Research UK (CRUK) via the Clinical Trials Advisory and Awards Committee (CTAAC). The CRUK grant award reference number is C317/A7275.

Merck have agreed to support this trial by providing free Cetuximab for the 170 patients randomised to the chemotherapy plus Cetuximab arm.

24. Trial management and trial committees

This trial is being undertaken in accordance with the International Conference on Harmonisation (ICH) note for Guidance on GCP (ICH, Topic E6, 1995) approved July 17th, 1996. The trial will be conducted in accordance with the recommendations for physicians involved in research on human

subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. Responsibilities of the trial personnel and committees are as follows:

The **Chief Investigator** (CI) and UoSCTU are responsible for the day-to-day running of the trial as detailed in GCP Guidelines. The UoSCTU will in addition prepare data reports for the TSC and DMEC, including interim analyses, and will make safety and progress reports to the Multicentre Research Ethics Committee (MREC) and Medicines and Healthcare products Regulatory Agency (MHRA).

The **Trial Management Group** (TMG) usually meets at least once every 6 months (but may convene more often or by other means) to advise the CI and UoSCTU in the promotion and running of the trial. TMG members include active trial investigators and members with specific interests.

The **Trial Steering Committee** (TSC) is an independent committee providing overall supervision of the trial. It will meet at least annually, and will receive reports from UoSCTU, CI and DMEC.

The **Data Monitoring and Ethics Committee** (DMEC) is also independent. The group will meet at least annually, with interim analysis reports from the UoSCTU, to give advice on continuing recruitment. A recommendation to discontinue recruitment (in all patients or in selected subgroups) will be made only if the result is likely to convince a broad range of investigators including participants in the trial and the general clinical community. If a decision is made to continue, the DMEC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The DMEC will make recommendations to the TSC as to the continuation of the trial.

25. Publication and intellectual property

All publications and presentations relating to the trial will be authorised by the TMG. The first publication of the trial results from all centres will be in the name of the TMG. Members of the TMG will be listed as authors and other significant contributors will be cited by name if published in a journal where this does not conflict with the journal policy. Surgeons and oncologists at the highest recruiting centres will also be acknowledged. The ISRCTN number allocated to this trial (ISRCTN22944367) will be attached to any publications resulting from this trial.

Participating centres may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. Ownership of intellectual property resulting from the trial will be governed in accordance with the relevant agreements and the CRUK terms and conditions for research grants and awards.

26. Protocol amendments

Please check with UoSCTU that you are using the most recent version of the New EPOC clinical trial protocol.

The protocol was amended on the 16 January 2012 to update the analysis plan and statistics which resulted in reducing the sample size to 288 patients.

The protocol was amended on the 08 December 2010 to correct an administration error regarding infusion rates of subsequent doses of Cetuximab. Clarification was also made to information relating to chemotherapy delivery following Cetuximab infusion. An update was also made to the radiation risk assessment

The protocol was amended on 28 July 2010 to remove Capecitabine and permit first line use of Irinotecan as treatment options.

An amendment to the protocol was completed on 22 April 2009 to update the randomisation stratification factors. Patient information sheets, consent forms and GP information sheets were also removed from the appendices.

The protocol was amended on 16 September 2008 to offer Irinotecan and Fluorouracil based chemotherapy to patients previously treated with Oxaliplatin.

The protocol was amended on 4 July 2008 to introduce kRAS genotyping for all patients, in order to exclude patients with a confirmed kRAS-mutant genotype in the primary cancer from the trial due to a lack of efficacy of Cetuximab in this patient group (data presented at ASCO 2008).

The protocol was amended on 14 March 2008 to change the formulation of Cetuximab used in this trial from 2 mg/ml to 5 mg/ml.

A minor amendment to the protocol was completed on 16 January 2008, to update the randomisation stratification factors.

The protocol was amended on 3 January 2008 to clarify the study treatment regimens, tissue bank details, and other items to ensure efficient management of the trial.

The protocol was amended on 24 July 2007 to reduce the dose of Capecitabine from 1000 to 850 mg/m^2 in subjects receiving CAPOX + Cetuximab following an interim analysis of the COIN trial where a significantly increased prevalence of grade 3/4 diarrhoea was shown with this regimen. Additional information was included in the Appendix to describe the dose adjustments to be followed for subjects with diarrhoea.

This protocol was amended on the 11 October 2017 to amend the end of study date and correct changes to study personnel both at the University of Southampton CTU and the Trial TMG.

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Appendix I – Chemotherapy regimens

Regimen	Arm using regimen	Page
OxMdG (Oxaliplatin + MdG schedule)	A	42
IrMdG (Irinotecan + MdG schedule)	A	45
OxMdG + Cetuximab	B	49
IrMdG + Cetuximab	B	58

Investigators may find it helpful to copy the relevant schedule from this Appendix and keep it with the patients' notes.

The OxMdG regimen

Treatment is given in two-weekly schedules as follows:

Day 1 of treatment schedule (14 day cycle)

0:00	IV bolus GGranisetron 3 mg (or equivalent)
	IV bolus DDexamethasone 8 mg
	Flush line with 5% DDextrose
0:00-2:00	*l*-folinic acid (175 mg flat dose) or *d,l*-folinic acid (350 mg flat dose) IV infusion, 2 hrs, 250 ml 5% Dextrose concurrently with:
0.00-2:00	Oxaliplatin 85 mg/m^2 IV infusion, 2 hrs, 250 ml 5% DDextrose
2:00	Flush line with 5% DDextrose again
2:00-2:05	5-Fluorouracil 400 mg/m^2 IV bolus over 5 minutes
2:05-48:00	5-Fluorouracil 2400 mg/m^2 IV infusion over 46 hours
48:00	Disconnect pump and flush line (5 ml heparinised saline)
Day 3-14	No treatment

Notes:

- Bolus 5FU is recommended to be given over 5 minutes but may be administered as a 15 or 30 minute infusion where this reflects local practice.
- Because of a potential in vitro chemical reaction between Oxaliplatin and chloride ions, care is taken to avoid contact with normal saline in the drip-tubing etc.
- Oxaliplatin may cause vein pain, which is helped by applying an electric heat pad over the vein throughout the 2-hour infusion. Suitable therapeutic heat pads are available from Winterwarm® (38x30cm, model HP5/LT) or Dimplex® (38x28cm) each costing under £20. If this fails, extending the infusion time to 4-6 hours may be helpful.
- Do not use injection equipment containing aluminium.
- The use of pre-packed 'minibags' of 5FU is acceptable.
- Please check with the UoSCTU if your local policy for pre-chemotherapy medication differs to that stated here to confirm if it is acceptable for use in the trial.

Oral antiemetics (starting day 2):

- Dexamethasone 4 mg tds x 1 day; 4 mg bd x 1 day; 4 mg od x 1 day.
- Domperidone or metoclopramide prn.

Note on the use of dexamethasone

- For patients at high risk of steroid side effects (e.g. diabetics) or for those who develop toxicity attributable to steroids (e.g. dyspepsia; dysphoria; etc), the oral steroid should be omitted.

Scheduled tests

- FBC and clinical assessment (NCI toxicity scores) should be performed on the day of starting each cycle (or within 3 working days before) and the results available before starting.
- Biochemistry (including creatinine, bilirubin, magnesium and either AST or ALT) is done at the same time as FBC.
- If patient is clinically jaundiced, bilirubin level must be reviewed prior to administration of Oxaliplatin.
- If patient has symptoms of possible hypomagnesemia, check magnesium level and correct as advised (see Appendix XIII).

Toxicity and dose adjustments for OxMdG

Haematological

- Myelotoxicity occured in 30% of patients treated with OxMdG in the FOCUS trial.
- Check FBC on (or up to 3 working days before) day 1 of each cycle. Delay 1 week if neutrophils < 1.5 x 10^9/l or platelets < 75 x 10^9/l. Only treat when neutrophils and platelets are above these limits. The lower limit for the day 1 platelet count for this regimen is due to the possible occurrence of mild thrombocytopenia after a number of cycles of OxMdG.
- If >1 delay, or 1 delay of ≥ 2 weeks occurs, maintain Oxaliplatin and infusional 5FU doses but omit bolus 5FU and continue without bolus 5FU for subsequent doses.
- If a further delay(s) for myelotoxicity occurs despite omitting bolus 5FU reduce the Oxaliplatin and infusional 5FU doses by 20%.
- Further dose reductions may be made, at the discretion of the treating investigator.

Neurotoxicity

- Oxaliplatin commonly causes peripheral sensory symptoms, easily distinguishable from 5FU neurotoxicity, which is uncommon, and cerebellar.
- Many patients experience transient paraesthesia of hands and feet, and some experience dysaesthesia in the throat. These symptoms are precipitated by cold and last from a few hours to a few days after each Oxaliplatin administration. They do not require treatment or dose reduction.
- If symptoms persist until the next cycle is due, and are associated with significant discomfort or loss of function (e.g. dropping objects), omit Oxaliplatin from the regimen and continue with MdG alone. Infusional 5FU should be increased from 2400mg/m^2 to 2800mg/m^2 during this time (any prior 5FU dose reductions should be taken into account). When symptoms have resolved to grade 1, Oxaliplatin should be restarted at the reduced dose of 75mg/m^2 (infusional 5FU should return to normal).

Renal function (see also Appendix IV)

- Oxaliplatin, like Carboplatin, is not nephrotoxic but is renally cleared.
- Before starting Oxaliplatin, ensure patient fulfils eligibility for renal function (estimated creatinine clearance [Cockcroft) >50ml/min or measured GFR [EDTA clearance] >50 ml/min).

- Check serum creatinine at each cycle. If this rises >25%, re-check EDTA or 24-hour urinary creatinine, and adjust Oxaliplatin and 5FU doses according to the table in Appendix IV.
- If GFR drops to below 30 ml/min, omit Oxaliplatin and reduce 5FU by 25% until recovery.

Hepatobiliary function (see also Appendix IV)

- Oxaliplatin is not principally cleared by the liver, but there is evidence of delayed clearance in patients with marked hepatic dysfunction. For this reason Oxaliplatin as well as 5FU should be reduced by 50% in patients with serum bilirubin > 3 x ULN (see Appendix IV).
- Bilirubin ≤ 1.25 x ULN is required for study entry. If bilirubin rises above this limit during treatment, discuss with treating investigator as this may indicate disease progression. If treatment is to continue, please refer to table in Appendix IV.
- Transaminase (either AST or ALT) ≤ 2.5 x ULN is required for study entry. An isolated rise in transaminase above 2.5 x ULN during treatment is likely to be treatment-related, and all treatment should be interrupted until recovery (see Appendix IV).

Respiratory

- As with other platinum drugs, rare cases of acute interstitial lung disease or lung fibrosis have been reported with Oxaliplatin. In the case of unexplained respiratory symptoms or signs, Oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease.

Stomatitis

- Routine mouthcare (e.g. Corsadyl, nystatin) is recommended, local policy on the use of these or similar drugs is acceptable.
- If mouth ulcers occur despite this, reduce the 5FU doses (bolus and infusion) by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.
- If further toxicity occurs reduce 5FU (bolus and infusion) and Oxaliplatin doses by a further 20%.

Diarrhoea

- For diarrhoea occurring between cycles, treat symptomatically initially: LLoperamide 2-4 mg qds and/or Codeine Phosphate 30-60 mg qds as required.
- If diarrhoea has not resolved by the time the next cycle is due, delay 1 week.
- If diarrhoea is a problem despite symptomatic treatment, or if more than one delay is required, reduce the Oxaliplatin and 5FU (bolus and infusion) doses by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.
- If further toxicity occurs reduce 5FU (bolus and infusion) and Oxaliplatin doses by a further 20%.

Hand-foot syndrome (HFS)

- Treat symptomatically. Pyridoxine 50 mg tds by mouth or topical corticosteroid may help.
- If HFS is still a problem, reduce the 5FU doses (bolus and infusion) by 20% for subsequent cycles.
- If further toxicity occurs reduce 5FU (bolus and infusion) and Oxaliplatin doses by a further 20%.

DPD deficiency; cardiotoxicity

- DPD is the initial and rate-limiting enzyme for 5-FU breakdown. DPD deficiency is an inherited (pharmacogenetic) disorder in which individuals with absent or significantly decreased DPD activity develop life-threatening toxicity following exposure to 5-FU (in either IV or oral form). Reduced drug clearance results in markedly prolonged exposure to 5-FU so that administration of standard doses of 5-FU results in altered 5-FU pharmacokinetics and severe toxicity including mucositis, granulocytopenia, neuropathy and death. The onset of toxicity usually occurs twice as fast in patients with low DPD activity as compared with patients with a normal DPD activity. Approximately 3-5% of the population has low DPD activity and 0.1% have absent activity. We recommend that (i) patients with a personal or family history suggestive of DPD deficiency should not be enrolled onto New EPOC, and (ii) those who experience grade 3/4 neutropenia and grade 3/4 mucositis after cycle 1 should be considered as potentially having DPD deficiency. If DPD deficiency is suspected, patients should only continue on trial after full recovery but without the further use of a Fluoropyrimidine.
- 5FU may provoke angina attacks or even MI in patients with ischaemic heart disease. Continued treatment with upgraded antianginal medication and reduced 5FU dose may be considered.

Allergic reactions to Oxaliplatin

- The occasional patient (approx 0.5%) develops acute hypersensitivity to Oxaliplatin, usually after more than 6 cycles have been administered. During drug administration, the patient may develop rash, fever, swollen mouth or tongue, hypo- or hypertension and other signs/symptoms of hypersensitivity. This rarely develops to full-blown anaphylaxis, even with repeated treatment.
- If acute hypersensitivity occurs, discontinue the infusion and treat with IV corticosteroid and antihistamine.
- After full recovery, the patient may continue with FA and 5FU.
- At the investigator's discretion, the patient may be rechallenged with Oxaliplatin at the next cycle. In this case, premedication is recommended as follows:
  Dexamethasone 4mg p.o. 6 hourly starting 24 hours pre-treatment, + 8mg IV 30 minutes pre-dose CChlorphenamine 10mg (or equivalent) + Ranitidine 50mg (or equivalent) IV 30 minutes pre-dose. Continue Dexamethasone, CChlorphenamine and Ranitidine for 24-48 hours after treatment with Oxaliplatin.

The IrMdG regimen (IrMdG)

Treatment is given in two-weekly schedules as follows:

Day 1 of treatment schedule (14 day cycle)

0:00	IV bolus Granisetron 3 mg (or equivalent)
	IV bolus Dexamethasone 8 mg
	Flush line with 5% Dextrose
0:00-0:30	Irinotecan 180 mg/m^2 IV infusion over 30 minutes in 250 ml normal saline
0:30-2:30	*l*-folinic acid (175 mg flat dose) or *d,l*-folinic acid (350 mg flat dose) IV infusion, 2 hrs, 250 ml 5% Dextrose
	Flush line with 5% Dextrose
2:30-2:35	5-Fluorouracil 400 mg/m^2 IV bolus over 5 minutes
2:35-48:30	5-Fluorouracil 2400 mg/m^2 IV infusion over 46 hours
48:30	Disconnect pump and flush line (5 ml heparinised saline).
Days 4-14	No treatment

Notes:

- Bolus 5FU is recommended to be given over 5 minutes but may be administered as a 15 or 30 minute infusion where this reflects local practice.
- Do not use injection equipment containing aluminium.
- The use of pre-packed 'minibags' of 5FU is acceptable.
- Please check with the UoSCTU if your local policy for pre-chemotherapy medication differs to that stated here to confirm if it is acceptable for use in the trial.

Oral antiemetics (starting day 2):

- Dexamethasone 4 mg tds x 1 day; 4 mg bd x 1 day; 4 mg od x 1 day.
- Domperidone or metoclopramide prn.
- Ensure patient has supplies of Loperamide and Ciprofloxacin, and knows how to use them.

Note on the use of dexamethasone

- For patients at high risk of steroid side effects (e.g. diabetics) or for those who develop toxicity attributable to steroids (e.g. dyspepsia; dysphoria; etc), the oral steroid should be omitted.

Scheduled tests

- FBC and clinical assessment (NCI toxicity scores) should be performed on the day of starting each cycle (or within 3 working days before) and the results available before starting.
- Biochemistry (including creatinine, bilirubin, magnesium and either AST or ALT) is done at the same time as FBC.
- If patient has symptoms of possible hypomagnesemia, check magnesium level and correct as advised (see Appendix XIII).

Toxicity and dose adjustments for IrMdG

Acute cholinergic syndrome

- Irinotecan may provoke an acute cholinergic syndrome with diarrhoea, sweating, salivation, bradycardia, etc. This may start during the drug infusion or shortly after.
- If this occurs, give atropine sulphate 0.25 mg s/c immediately. Atropine should then be given prophylactically with subsequent cycles.

Haematological

- Myelotoxicity is commoner with IrMdG than with MdG.
- Check FBC on (or up to 3 working days before) day 1 of each cycle. Delay 1 week if WBC < 3.0 x 109/l, granulocytes < 1.5 x 10^9/l or platelets < 100 x 10^9/l. Only treat when WBC and platelets are above these limits.
- If >1 delay, or 1 delay of ≥ 2 weeks occurs, reduce the Irinotecan and 5FU (bolus and infusion) doses by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.
- If a further delay(s) for myelotoxicity occurs despite a 20% dose reduction, a further dose reduction may be made, at the discretion of the treating clinician.

Neurotoxicity

- Neurotoxicity (cerebellar) is uncommon; consider changing to alternative treatment.
- Changes in treatment should be discussed with one of the clinical coordinators.

Renal function (see also Appendix IV)

- Check serum creatinine at each cycle. If this rises >25%, re-check EDTA clearance or 24-hour urinary clearance, and adjust Irinotecan and 5FU doses according to the table in Appendix IV.
- Patients with moderate renal impairment may receive irinotecan, but if GFR <30ml/min, the Irinotecan dose should be reduced by 50% and the 5FU dose should be reduced by 25% (see Appendix IV).

Hepatobiliary function (see also Appendix IV)

- Irinotecan and its metabolites are cleared by biliary excretion and patients with cholestasis have delayed clearance.
- LFTs should be checked before each treatment cycle. Patients with serum ALP >5 x ULN or serum bilirubin in the range 1.5-3 x ULN require a 50% dose reduction of irinotecan;

patients with serum bilirubin >3 x ULN should not receive Irinotecan (please refer to Appendix IV).

- 5FU should be reduced by 50% in patients with serum bilirubin >3 x ULN (see Appendix IV).
- Transaminase (either AST or ALT) ≤ 2.5 x ULN is required for study entry. An isolated rise in transaminase above 2.5 x ULN during treatment is likely to be treatment-related, and all treatment should be interrupted until recovery (see Appendix IV).
- Bilirubin ≤ 1.25 x ULN is required for study entry. If bilirubin rises above this limit during treatment, discuss with treating investigator as this may indicate disease progression. If treatment is to continue, please refer to table in Appendix IV.

Stomatitis

- Routine mouthcare (e.g. Corsadyl, Nystatin) is recommended, local policy on the use of these or similar drugs are acceptable.
- If mouth ulcers occur despite this, reduce the 5FU doses (bolus and infusion) by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.
- If further toxicity occurs reduce 5FU doses (bolus and infusion) by a further 20%.

Diarrhoea

- Irinotecan may produce delayed diarrhoea which, if untreated, may become severe. Early intervention with high-dose LLoperamide is highly effective. Patients must be carefully instructed and given the written information sheet, telephone contact numbers and supplies of LLoperamide and CCiprofloxacin. Care should be taken that out-of-hours staff answering patient queries are familiar with the protocol.
- Patients should start Loperamide at the first loose stool: 4 mg, then 2 mg every 2 hours until 12 hours after the last loose stool (up to a maximum of 48 hours).
- If diarrhoea lasts > 24 hours, Ciprofloxacin 500 mg bd should be added. If it lasts > 48 hours, or if the patient reports symptoms of dehydration, admit acutely for rehydration and further management (eg Octreotide).
- After an episode of severe diarrhoea (grade 3-4), delay chemotherapy until full recovery then resume at 20% reduced doses of Irinotecan and 5FU (bolus and infusion).
- If diarrhoea from the previous cycle, even if not severe, has not resolved by the time the next cycle is due, delay 1 week.

Hand-foot syndrome (HFS)

- Treat symptomatically. Pyridoxine 50 mg tds by mouth or topical corticosteroids may help.
- If HFS is still a problem, reduce the 5FU doses (bolus and infusion) by 20% for subsequent cycles (no need to reduce irinotecan).
- If further toxicity occurs reduce 5FU doses (bolus and infusion) by a further 20%.

DPD deficiency; cardiotoxicity

- DPD is the initial and rate-limiting enzyme for 5-FU breakdown. DPD deficiency is an inherited (pharmacogenetic) disorder in which individuals with absent or significantly decreased DPD activity develop life-threatening toxicity following exposure to 5-FU (in either IV or oral form). Reduced drug clearance results in markedly prolonged exposure to 5-FU so that administration of standard doses of 5-FU results in altered 5-FU pharmacokinetics and severe toxicity including mucositis, granulocytopenia, neuropathy

and death. The onset of toxicity usually occurs twice as fast in patients with low DPD activity as compared with patients with a normal DPD activity. Approximately 3-5% of the population has low DPD activity and 0.1% have absent activity. We recommend that (i) patients with a personal or family history suggestive of DPD deficiency should not be enrolled onto New EPOC, and (ii) those who experience grade 3/4 neutropenia and grade 3/4 mucositis after cycle 1 should be considered as potentially having DPD deficiency. If DPD deficiency is suspected, patients should only continue on trial after full recovery but without the further use of a Fluoropyrimidine.

- 5FU may provoke angina attacks or even MI in patients with ischaemic heart disease. Continued treatment with upgraded antianginal medication and reduced 5FU dose may be considered.

Cetuximab plus Oxaliplatin modified de Gramont administration

Patients will receive Cetuximab intravenous infusions at a dose of 500 mg/m^2 to be administered over 2 hours and thereafter fortnightly infusions. Cetuximab is provided in ready use vials containing 5 mg/ml. Once removed from the vial, Cetuximab must be used within 8 hours if stored at room temperature.

Please note Cetuximab must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured. Vital signs should be checked and recorded before, during, and 1 hour after the Cetuximab infusion. There must be at least one hour between completion of the Cetuximab infusion and the start of chemotherapy.

Day 1 of treatment schedule (14 day cycle)

0:00	IV Chlorphenamine 10mg, Paracetamol 1g p.o., Ranitidine 150mg p.o.
	IV bolus DDexamethasone 8 mg
	IV bolus GGranisetron 3 mg (or equivalent)
	Flush line with 0.9% saline
0:00-2:00	Cetuximab 500 mg/m^2 IV infusion, 0.5-2 hours (see below)
	Flush line with 0.9% saline
2:00-3:00	Observe for delayed hypersensitivity reaction
3:00	Flush line with 5% DDextrose
3:00-5:00	*l*-folinic acid (175 mg flat dose) or *d,l*-folinic acid (350 mg flat dose) IV infusion, 2 hrs, 250 ml 5% Dextrose
	Concurrently with:
3.00-5:00	Oxaliplatin 85 mg/m^2 IV infusion, 2 hrs, 250 ml 5% Dextrose
5:00	Flush line with 5% DDextrose
5:00-5:05	5-Fluorouracil 400 mg/m^2 IV bolus over 5 minutes
5:05-51:00	5-Fluorouracil 2400 mg/m^2 IV infusion over 46 hours
51:00	Disconnect pump and flush line (5 ml heparinised saline)
Day 4-14	No treatment

Notes:

- The **1st dose** of Cetuximab (500 mg/m ^{2}) should be administered by i.v. infusion **over 120 minutes**. There must be at least one hour between completion of Cetuximab and the start of chemotherapy.
- The **2nd dose** of Cetuximab (500 mg/m ^{2}) should be administered by i.v. infusion **over 90 minutes**. There must be at least one hour between completion of Cetuximab and the start of chemotherapy.

- **Subsequent doses** of Cetuximab (500 mg/m ²) should be administered by i.v. infusion **over 60 minutes**. There must be at least one hour between completion of Cetuximab and the start of chemotherapy.
- Bolus 5FU is recommended to be given over 5 minutes but may be administered as a 15 or 30 minute infusion where this reflects local practice.
- Because of a potential in vitro chemical reaction between Oxaliplatin and chloride ions, care is taken to avoid contact with normal saline in the drip-tubing etc.
- Oxaliplatin may cause vein pain, which is helped by applying an electric heat pad over the vein throughout the 2-hour infusion. Suitable therapeutic heat pads are available from Winterwarm® (38x30cm, model HP5/LT) or Dimplex® (38x28cm) each costing under £20. If this fails extending the infusion time to 4-6 hours may be helpful.
- Do not use injection equipment containing aluminium.
- The use of pre-packed 'minibags' of 5FU is acceptable.
- Please check with the UoSCTU if your local policy for pre-chemotherapy medication differs to that stated here to confirm if it is acceptable for use in the trial.

Oral antiemetics (starting day 2):

- Dexamethasone 4 mg tds x1 day; 4 mg bd x1 day; 4 mg od x1 day.
- Domperidone or Metoclopramide prn.

Note on the use of dexamethasone

- For patients at high risk of steroid side effects (e.g. diabetics) or for those who develop toxicity attributable to steroids (e.g. dyspepsia; dysphoria; etc), the oral steroid should be omitted.

Scheduled tests

- FBC and clinical assessment (NCI toxicity scores) should be performed on the day of starting each cycle (or within 3 working days before) and the results available before starting.
- Biochemistry (including creatinine, bilirubin, magnesium and either AST or ALT) is done at the same time as FBC.
- If patient is clinically jaundiced bilirubin level must be reviewed prior to administration of Oxaliplatin.
- If patient has symptoms of possible hypomagnesemia, check magnesium level and correct as advised (see Appendix XIII).

Toxicity and dose adjustments for OxMdG plus Cetuximab

Allergic/hypersensitivity reactions - Cetuximab

- Severe grade 3/4 hypersensitivity reactions have occurred in 2.2% of patients treated with Cetuximab. One death from angio-oedema has been reported.

- Signs include rapid onset of airway obstruction, urticaria and/or hypotension. 80% occur during or within one hour of the first infusion, but reactions can occur with later infusions.
- **Cetuximab must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured.**
- Treatment depends on the grade or severity of the reaction, as follows:

CTC Grade Allergic/hypersensitivity reaction	**Treatment**
Grade 1 Transient flushing or rash, drug fever <38°C	Decrease the Cetuximab infusion rate by 50% and monitor closely for any worsening. The total infusion time for Cetuximab should not exceed 240 minutes (4 hours).
Grade 2 Rash; flushing; urticaria; dyspnea; drug fever ≥ 38°C	Stop Cetuximab infusion. Administer bronchodilators, oxygen etc. as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related oedema/angioedema; hypotension Grade 4: Anaphylaxis	Stop Cetuximab infusion immediately and disconnect infusion tubing from the patient. Administer adrenaline, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen etc., as medically indicated. Patients have to be withdrawn immediately from treatment and must not receive any further Cetuximab treatment.

- Once the infusion rate has been slowed for an allergic reaction, it should remain at the slower rate for all subsequent infusions.
- If the patient has a second allergic/hypersensitivity reaction on the slower infusion rate, the infusion should be stopped and no further Cetuximab administered.

- If a patient receives a grade 3 or 4 allergic/hypersensitivity reaction at any time, Cetuximab must be discontinued, but remaining chemotherapy treatment should be continued as normal.
- If there is any doubt whether a reaction is an allergic/hypersensitivity reaction of Grades 1-4, the trial principal co-investigator Dr John Bridgewater should be contacted immediately to discuss and grade the reaction.

Skin toxicity - Cetuximab

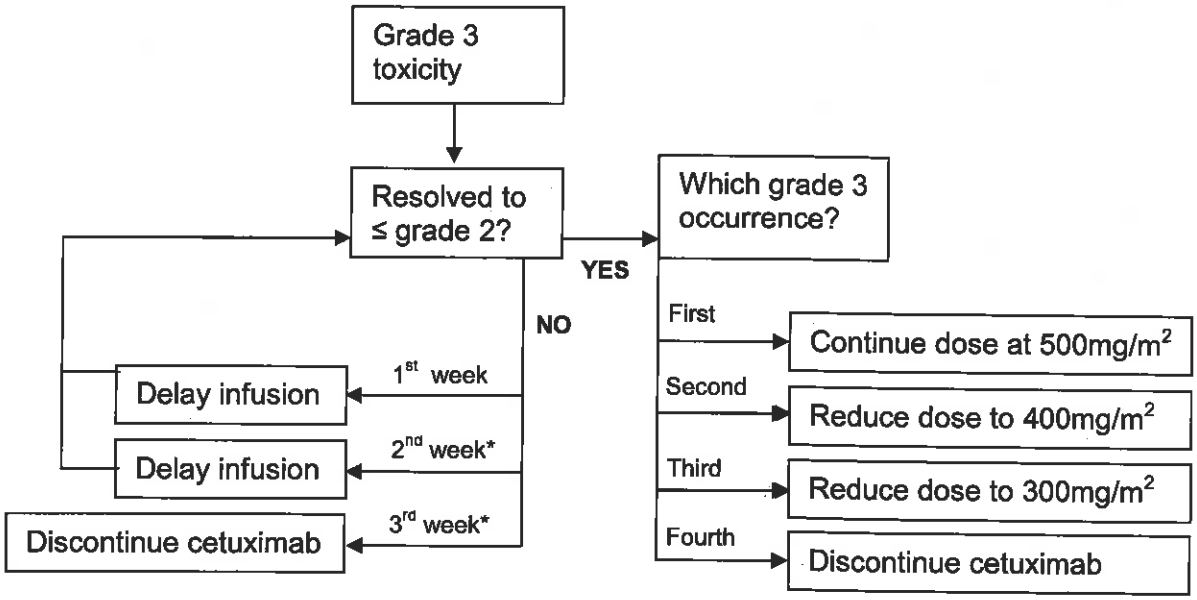
- The acneiform skin rash associated with Cetuximab occurs in over 70% of patients. About 12% have grade ≥ 3 reactions. On longer-term therapy, paranychia occurs in about 10% of patients and can be painful.
- Discussion with a local dermatologist prior to study initiation would be helpful to agree local plans of management and mechanisms for rapid referral in case of severe skin toxicity.
- The occurrence of the rash has been correlated with an increased likelihood of response to treatment, though this information needs to be used with caution, as it is not a direct correlation.
- The rash usually occurs on the face, upper chest and back with multiple follicles and pustules. The onset is usually within the first 3 weeks of treatment and many cases improve by 12 weeks on treatment.
- Dose modifications for grade 3 toxicity are summarised on the algorithm below. For CTC grade 1 or 2: continue treatment with Cetuximab. If a patient experiences grade 3 skin toxicity (rash effects > 50% of body surface area), Cetuximab therapy may be delayed for up to 14 days without changing the dose level. If grade 3 skin toxicity occurs for a second and third time, Cetuximab therapy may again be delayed for up to 14 days with concomitant dose reductions to 400 mg/m^2 and then 300 mg/m^2. Cetuximab dose reductions are permanent. Patients must discontinue Cetuximab if more than 2 consecutive infusions are withheld or grade 3 skin toxicity occurs for a fourth time despite appropriate dose reduction. If the toxicity resolves to grade 2 or less by the following treatment period, treatment may be resumed.
- The investigator should also consider concomitant treatment with topical and oral antibiotics. Grade 1 acneiform eruption: consider treatment with topical antibiotics (e.g. Topical Metronidazole or Erythromycin). Systemic antibiotics (e.g. a second generation tetracycline such as Doxycycline 100mg po daily) should be considered for grade 2 acneiform eruption, and are mandatory for grade ≥ 3 reactions. The threshold for referral to the dermatology clinic should be planned locally but all patients with grade ≥ 3 reactions and probably all with grade 2 reactions should be referred for advice and management. If pruritus occurs an oral antihistamine is advised. Dry skin often occurs (and may contribute to pruritus) general advice on replacing soap with oil for washing, avoidance of hot water for baths or showers and use of emollient creams are beneficial; topical corticosteroids can be used according to local practice. Fissures may occur in dry skin and topical dressings (e.g. hydrocolloid dressings and as advised by your dermatologist) are helpful.

- Colloidal oatmeal preparations (Aveeno, Nature's Gate) can be effective if applied at least 3 times daily[48]. These are available at chemists or on the internet.
- Nail toxicities occur in 8% of patients with Cetuximab, characterised by a paronychial inflammation with associated swelling of the lateral skin folds of toes and fingers, especially great toes and thumbs, which may be painful. It may persist for up to three months after cessation of Cetuximab therapy. Dermatological advice should be sought. Use of daily salt baths and local antiseptic / astringent ointments have been found to be helpful. Anti-inflammatory drugs may help to ease the pain.

Hypomagnesaemia - Cetuximab

- Hypomagnesaemia has been reported in up to 65% of patients following Cetuximab therapy. Patients should have magnesium concentration monitored at baseline, prior to each cycle of chemotherapy and for up to 8 weeks after the last dose of chemotherapy, or until magnesium has normalised, whichever is the longer.
- Fatigue, malaise, tremor, ataxia, carpopedal spasm, hyperreflexia, confusion, hallucinations, convulsions and arrhythmias may occur.
- Hypomagnesemia should be corrected by intravenous supplementation if grade 3 (<0.4 mmol/l) or symptomatic. If lesser degrees of hypomagnesemia are detected, oral supplementation may be considered (see Appendix XIII for details).
- Dose modifications for grade 3 toxicity are summarised in the algorithm below. For CTC grade 1 or 2: continue treatment with Cetuximab. If a patient experiences grade 3 toxicity, Cetuximab therapy may be delayed for up to 14 days without changing the dose level. If grade 3 toxicity occurs for a second and third time, Cetuximab therapy may again be delayed for up to 14 days with concomitant dose reductions to 400 mg/m^2 and then 300 mg/m^2. Cetuximab dose reductions are permanent. Patients must discontinue Cetuximab if more than 2 consecutive infusions are withheld or grade 3 toxicity occurs for a fourth time despite appropriate dose reduction. If the toxicity resolves to grade 2 or less by the following treatment period, treatment may be resumed.

Dose modifications for Cetuximab-related skin toxicity and hypomagnesaemia:



* These refer to the second and third consecutive week of non-resolving grade 3 toxicity.

Haematological

- Myelotoxicity is similar in frequency as with OxMdG alone. Leucopenia has been reported and attributed to Cetuximab in 8% of patients treated with chemotherapy plus Cetuximab.
- Check FBC on (or up to 3 working days before) day 1 of each cycle. Delay 1 week if neutrophils < 1.5 x 10^9/l or platelets < 75 x 10^9/l. Only treat when neutrophils and platelets are above these limits. The lower limit for the day 1 platelet count for this regimen is due to the possible occurrence of mild thrombocytopenia after a number of cycles of OxMdG.
- If >1 delay, or 1 delay of ≥ 2 weeks occurs, maintain Oxaliplatin and infusional 5FU doses but omit bolus 5FU and continue without bolus 5FU for subsequent doses.
- If a further delay(s) for myelotoxicity occurs despite omitting bolus 5FU reduce Oxaliplatin and infusional 5FU doses by 20%.
- Further dose reductions may be made, at the discretion of the treating investigator.

Neurotoxicity

- Oxaliplatin commonly causes peripheral sensory symptoms, easily distinguishable from 5FU neurotoxicity, which is uncommon, and cerebellar.
- Many patients experience transient paraesthesia of hands and feet, and some experience dysaesthesia in the throat. These symptoms are precipitated by cold and last from a few hours to a few days after each Oxaliplatin administration. They do not require treatment or dose reduction.
- If symptoms persist until the next cycle is due, and are associated with significant discomfort or loss of function (e.g. dropping objects), omit Oxaliplatin from the regimen and continue with MdG plus Cetuximab. Infusional 5FU should be increased from 2400mg/m^2 to 2800mg/m^2 during this time (any prior 5FU dose reductions should be taken into account). When symptoms have resolved to grade 1, Oxaliplatin should be restarted at the reduced dose of 75mg/m^2 (infusional 5FU should return to normal).

Renal function (see also Appendix IV)

- Oxaliplatin, like Carboplatin, is not nephrotoxic but is renally cleared.
- Before starting Oxaliplatin, ensure patient fulfils eligibility for renal function (estimated creatinine clearance [Cockcroft) >50ml/min or measured GFR [EDTA clearance] >50 ml/min).
- Check serum creatinine at each cycle. If this rises >25%, re-check EDTA clearance or 24-hour urinary clearance, and adjust Oxaliplatin and 5FU doses according to the table in Appendix IV.
- If GFR drops to below 30 ml/min, omit Oxaliplatin and reduce 5FU by 25% until recovery.
- There is little experience of administering Cetuximab in patients with renal insufficiency. Physicians should exercise caution and consider a dose reduction. No specific guidelines are available.

Hepatobiliary function (see also Appendix IV)

- Oxaliplatin is not principally cleared by the liver, but there is evidence of delayed clearance in patients with marked hepatic dysfunction. For this reason Oxaliplatin as well

as 5FU should be reduced by 50% in patients with serum bilirubin >3 x ULN (see Appendix IV).

- Bilirubin ≤ 1.25 x ULN is required for study entry. If bilirubin rises above this limit during treatment, discuss with treating investigator as this may indicate disease progression. If treatment is to continue, please refer to table in Appendix IV.
- Transaminase (either AST or ALT) ≤ 2.5 x ULN is required for study entry. An isolated rise in transaminase above 2.5 x ULN during treatment is likely to be treatment-related, and treatment should be interrupted until recovery (see Appendix IV).
- There is little experience of administering Cetuximab in patients with hepatic insufficiency. Physicians should exercise caution and consider a dose reduction. No specific guidelines are available.

Respiratory

- As with other platinum drugs, rare cases of acute interstitial lung disease or lung fibrosis have been reported with Oxaliplatin. In the case of unexplained respiratory symptoms or signs, Oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease.

Interstitial pneumonitis

- A syndrome of severe acute interstitial pneumonitis has been reported recently with another EGFR targeted therapy, gefitinib.
- Should a patient develop severe dyspnoea and/or hypoxia, seek urgent assistance from a chest physician. A high resolution CT scan of thorax, bronchoscopy plus transbronchial biopsies for pathology and relevant cultures should be considered.
- Cetuximab should be withheld until complete resolution of the toxicity.

Stomatitis

- Routine mouthcare (e.g. Corsadyl, Nystatin) is recommended, local policy on the use of these or similar drugs are acceptable.
- If mouth ulcers occur despite this, reduce the 5FU doses (bolus and infusion) by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.
- If further toxicity occurs reduce 5FU (bolus and infusion) and Oxaliplatin doses by a further 20%.
- Stomatitis occurs in about 10% of patients treated with Cetuximab. It has not been considered an indication for dose reduction in previous trials. However, if stomatitis continues despite 5FU dose reduction, Cetuximab dose reduction to 400mg/m^2 should be considered.

Diarrhoea

- Diarrhoea grade 3/4 has been reported in 6% of patients treated with Cetuximab plus chemotherapy and 4 serious adverse events due to diarrhoea were reported in the phase 2 trial of Cetuximab plus FOLFOX.
- For diarrhoea occurring between cycles, treat symptomatically initially: Loperamide 2-4 mg qds and/or codeine phosphate 30-60 mg qds as required.
- If diarrhoea has not resolved by the time the next cycle is due, delay 1 week.

- If diarrhoea is a problem despite symptomatic treatment, or if more than one delay is required, reduce the Oxaliplatin and 5FU (bolus and infusion) doses by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.
- If further toxicity occurs reduce 5FU (bolus and infusion) and Oxaliplatin doses by a further 20%.
- If diarrhoea persists despite this dose reduction, Cetuximab dose reduction to 400mg/m^2 should be considered.

Hand-foot syndrome (HFS)

- Treat symptomatically. Pyridoxine 50 mg tds by mouth or topical corticosteroids may help.
- If HFS is still a problem, reduce the 5FU doses (bolus and infusion) by 20% for subsequent cycles.
- If further toxicity occurs reduce 5FU (bolus and infusion) and Oxaliplatin doses by a further 20%.

DPD deficiency; cardiotoxicity

- DPD is the initial and rate-limiting enzyme for 5-FU breakdown. DPD deficiency is an inherited (pharmacogenetic) disorder in which individuals with absent or significantly decreased DPD activity develop life-threatening toxicity following exposure to 5-FU (in either IV or oral form). Reduced drug clearance results in markedly prolonged exposure to 5-FU so that administration of standard doses of 5-FU results in altered 5-FU pharmacokinetics and severe toxicity including mucositis, granulocytopenia, neuropathy and death. The onset of toxicity usually occurs twice as fast in patients with low DPD activity as compared with patients with a normal DPD activity. Approximately 3-5% of the population has low DPD activity and 0.1% have absent activity. We recommend that (i) patients with a personal or family history suggestive of DPD deficiency should not be enrolled onto New EPOC, and (ii) those who experience grade 3/4 neutropenia and grade 3/4 mucositis after cycle 1 should be considered as potentially having DPD deficiency. If DPD deficiency is suspected, patients should only continue on trial after full recovery but without the further use of a Fluoropyrimidine.
- 5FU may provoke angina attacks or even MI in patients with ischaemic heart disease. Continued treatment with upgraded antianginal medication and reduced 5FU dose may be considered.

Allergic reactions to Oxaliplatin

- The occasional patient (approx 0.5%) develops acute hypersensitivity to Oxaliplatin, usually after more than 6 cycles have been administered. During drug administration, the patient may develop rash, fever, swollen mouth or tongue, hypo- or hypertension and other signs/symptoms of hypersensitivity. This rarely develops to full-blown anaphylaxis, even with repeated treatment.
- If acute hypersensitivity occurs, discontinue the infusion and treat with IV corticosteroid and antihistamine.
- After full recovery, the patient may continue with Cetuximab, FA and 5FU.

- At the investigator's discretion, the patient may be rechallenged with Oxaliplatin at the next cycle. In this case, premedication is recommended as follows:

  Dexamethasone 4mg p.o. 6 hourly starting 24 hours pre-treatment, + 8mg IV 30 minutes pre-dose; CChlorphenamine 10mg (or equivalent) + Ranitidine 50mg (or equivalent) IV 30 minutes pre-dose. Continue Dexamethasone, CChlorphenamine and Ranitidine for 24-48 hours after treatment with Oxaliplatin.

Cetuximab plus Irinotecan modified de Gramont administration

Patients will receive Cetuximab intravenous infusions at a dose of 500 mg/m^2 to be administered over 2 hours and thereafter fortnightly infusions. Cetuximab is provided in ready use vials containing 5 mg/ml. Once removed from the vial, Cetuximab must be used within 8 hours if stored at room temperature.

Please note Cetuximab must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured. Vital signs should be checked and recorded before, during, and 1 hour after the Cetuximab infusion. There must be at least one hour between completion of Cetuximab and the start of chemotherapy.

Day 1 of treatment schedule (14 day cycle)

0:00	IV Chlorphenamine 10mg, Paracetamol 1g p.o., ranitidine 150mg p.o.
	IV bolus Dexamethasone 8 mg
	IV bolus Granisetron 3 mg (or equivalent)
	Flush line with 0.9% saline
0:00-2:00	Cetuximab 500 mg/m^2 IV infusion, 2 hours
	Flush line with 0.9% saline
2:00-3:00	Observe for delayed hypersensitivity reaction
	Flush line with 5% Dextrose
3:00-3:30	Irinotecan 180 mg/m^2 IV infusion over 30 minutes in 250 ml normal saline
3:30-5:30	*l*-folinic acid (175 mg flat dose) or *d,l*-folinic acid (350 mg flat dose) IV infusion, 2 hrs, 250 ml 5% Dextrose
	Flush line with 5% Dextrose
5:30-5:35	5-Fluorouracil 400 mg/m^2 IV bolus over 5 minutes
5:35-51:30	5-Fluorouracil 2400 mg/m^2 IV infusion over 46 hours
51:30	Disconnect pump and flush line (5 ml heparinised saline)
Day 4-14	No treatment

Notes:

- The **1st dose** of Cetuximab (500 mg/m ^{2}) should be administered by i.v. infusion **over 120 minutes**. There must be at least one hour between completion of Cetuximab and the start of chemotherapy.
- The **2nd** dose of Cetuximab (500 mg/m ^{2}) should be administered by i.v. infusion **over 90 minutes**. There must be at least one hour between completion of Cetuximab and the start of chemotherapy.

- **Subsequent doses** of Cetuximab (500 mg/m ²) should be administered by i.v. infusion **over 60 minutes**. There must be at least one hour between completion of Cetuximab and the start of chemotherapy.

- Observations continue as on day 1 and the one hour gap between Cetuximab and chemotherapy should be maintained.
- Bolus 5FU is recommended to be given over 5 minutes but may be administered as a 15 or 30 minute infusion where this reflects local practice.
- Do not use injection equipment containing aluminium.
- The use of pre-packed 'minibags' of 5FU is acceptable.
- Please check with the UoSCTU if your local policy for pre-chemotherapy medication differs to that stated here to confirm if it is acceptable for use in the trial.

Oral antiemetics (starting day 2):

- Dexamethasone 4 mg tds x1 day; 4 mg bd x1 day; 4 mg od x1 day.
- Domperidone or metoclopramide prn.
- Ensure patient has supplies of Loperamide and Ciprofloxacin, and knows how to use them.

Note on the use of dexamethasone

- For patients at high risk of steroid side effects (e.g. diabetics) or for those who develop toxicity attributable to steroids (e.g. dyspepsia; dysphoria; etc), the oral steroid should be omitted.

Scheduled tests

- FBC and clinical assessment (NCI toxicity scores) should be performed on the day of starting each cycle (or within 3 working days before) and the results available before starting.
- Biochemistry (including creatinine, bilirubin, magnesium and either AST or ALT) is done at the same time as FBC.
- If patient is clinically jaundiced bilirubin level must be reviewed prior to administration of Oxaliplatin.
- If patient has symptoms of possible hypomagnesemia, check magnesium level and correct as advised (see Appendix XIII).

Toxicity and dose adjustments for IrMdG plus Cetuximab

Allergic/hypersensitivity reactions - Cetuximab

- Severe grade 3/4 hypersensitivity reactions have occurred in 2.2% of patients treated with Cetuximab. One death from angio-oedema has been reported.

- Signs include rapid onset of airway obstruction, urticaria and/or hypotension. 80% occur during or within one hour of the first infusion, but reactions can occur with later infusions.
- **Cetuximab must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured.**
- Treatment depends on the grade or severity of the reaction, as follows:

CTC Grade Allergic/hypersensitivity reaction	**Treatment**
Grade 1 Transient flushing or rash, drug fever <38°C	Decrease the Cetuximab infusion rate by 50% and monitor closely for any worsening. The total infusion time for Cetuximab should not exceed 240 minutes (4 hours).
Grade 2 Rash; flushing; urticaria; dyspnea; drug fever ≥ 38°C	Stop Cetuximab infusion. Administer bronchodilators, oxygen etc. as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related oedema/angioedema; hypotension Grade 4: Anaphylaxis	Stop Cetuximab infusion immediately and disconnect infusion tubing from the patient. Administer adrenaline, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen etc., as medically indicated. Patients have to be withdrawn immediately from treatment and must not receive any further Cetuximab treatment.

- Once the infusion rate has been slowed for an allergic reaction, it should remain at the slower rate for all subsequent infusions.
- If the patient has a second allergic/hypersensitivity reaction on the slower infusion rate, the infusion should be stopped and no further Cetuximab administered.

- If a patient receives a grade 3 or 4 allergic/hypersensitivity reaction at any time, Cetuximab must be discontinued.
- If there is any doubt whether a reaction is an allergic/hypersensitivity reaction of Grades 1-4, the trial principal co-investigator Dr John Bridgewater should be contacted immediately to discuss and grade the reaction.

Skin toxicity - Cetuximab

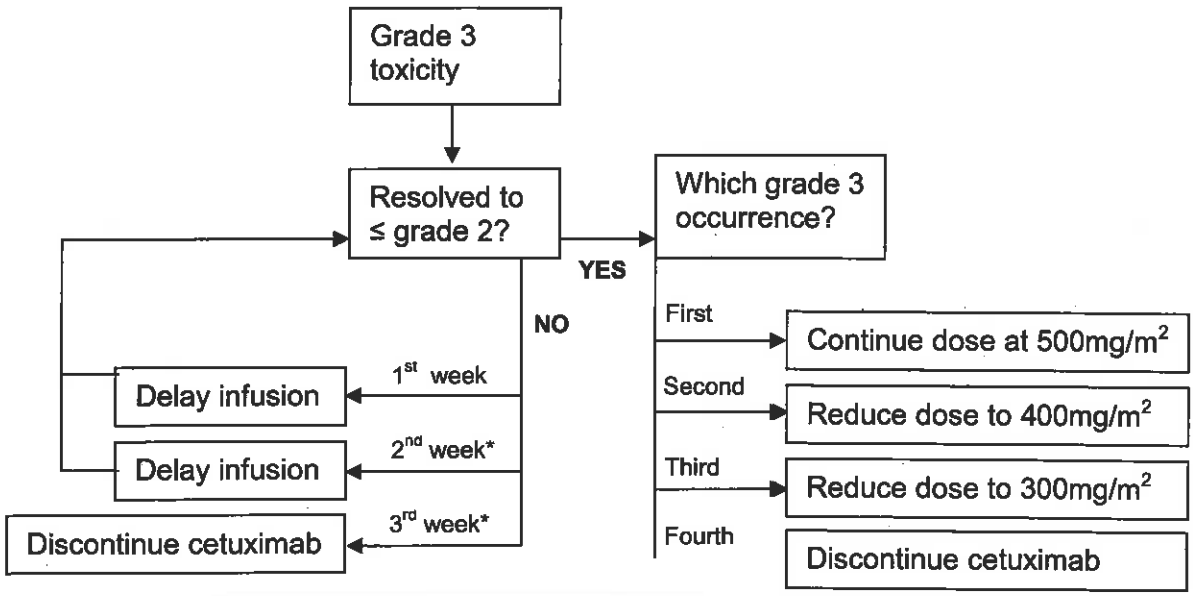
- The acneiform skin rash associated with Cetuximab occurs in over 70% of patients. About 12% have grade ≥ 3 reactions. On longer-term therapy, paranychia occurs in about 10% of patients and can be painful.
- Discussion with a local dermatologist prior to study initiation would be helpful to agree local plans of management and mechanisms for rapid referral in case of severe skin toxicity.
- The occurrence of the rash has been correlated with an increased likelihood of response to treatment, though this information needs to be used with caution, as it is not a direct correlation.
- The rash usually occurs on the face, upper chest and back with multiple follicles and pustules. The onset is usually within the first 3 weeks of treatment and many cases improve by 12 weeks on treatment.
- Dose modifications for grade 3 toxicity are summarised on the algorithm below. For CTC grade 1 or 2: continue treatment with Cetuximab. If a patient experiences grade 3 skin toxicity (rash effects > 50% of body surface area), Cetuximab therapy may be delayed for up to 14 days without changing the dose level. If grade 3 skin toxicity occurs for a second and third time, Cetuximab therapy may again be delayed for up to 14 days with concomitant dose reductions to 400 mg/m^2 and then 300 mg/m^2. Cetuximab dose reductions are permanent. Patients must discontinue Cetuximab if more than 2 consecutive infusions are withheld or grade 3 skin toxicity occurs for a fourth time despite appropriate dose reduction. If the toxicity resolves to grade 2 or less by the following treatment period, treatment may be resumed.
- The investigator should also consider concomitant treatment with topical and oral antibiotics. Grade 1 acneiform eruption: consider treatment with topical antibiotics (e.g. topical metronidazole or erythromycin). Systemic antibiotics (e.g. a second generation tetracycline such as doxycycline 100mg po daily) should be considered for grade 2 acneiform eruption, and are mandatory for grade ≥ 3 reactions. The threshold for referral to the dermatology clinic should be planned locally but all patients with grade ≥ 3 reactions and probably all with grade 2 reactions should be referred for advice and management. If pruritus occurs an oral antihistamine is advised. Dry skin often occurs (and may contribute to pruritus) general advice on replacing soap with oil for washing, avoidance of hot water for baths or showers and use of emollient creams are beneficial; topical corticosteroids can be used according to local practice. Fissures may occur in dry skin and topical dressings (e.g. hydrocolloid dressings and as advised by your dermatologist) are helpful.

- Colloidal oatmeal preparations (Aveeno, Nature's Gate) can be effective if applied at least 3 times daily[48]. These are available at chemists or on the internet.
- Nail toxicities occur in 8% of patients with Cetuximab, characterised by a paronychial inflammation with associated swelling of the lateral skin folds of toes and fingers, especially great toes and thumbs, which may be painful. It may persist for up to three months after cessation of Cetuximab therapy. Dermatological advice should be sought. Use of daily salt baths and local antiseptic / astringent ointments have been found to be helpful. Anti-inflammatory drugs may help to ease the pain.

Hypomagnesaemia - Cetuximab

- Hypomagnesaemia has been reported in up to 65% of patients following Cetuximab therapy. Patients should have magnesium concentration monitored at baseline, prior to each cycle of chemotherapy and for up to 8 weeks after the last dose of chemotherapy, or until magnesium has normalised, whichever is the longer.
- Fatigue, malaise, tremor, ataxia, carpopedal spasm, hyperreflexia, confusion, hallucinations, convulsions and arrhythmias may occur.
- Hypomagnesemia should be corrected by intravenous supplementation if grade 3 (<0.4 mmol/l) or symptomatic. If lesser degrees of hypomagnesemia are detected, oral supplementation may be considered (see Appendix XIII for details).
- Dose modifications for grade 3 toxicity are summarised in the algorithm below. For CTC grade 1 or 2: continue treatment with Cetuximab. If a patient experiences grade 3 toxicity, Cetuximab therapy may be delayed for up to 14 days without changing the dose level. If grade 3 toxicity occurs for a second and third time, Cetuximab therapy may again be delayed for up to 14 days with concomitant dose reductions to 400 mg/m^2 and then 300 mg/m^2. Cetuximab dose reductions are permanent. Patients must discontinue Cetuximab if more than 2 consecutive infusions are withheld or grade 3 toxicity occurs for a fourth time despite appropriate dose reduction. If the toxicity resolves to grade 2 or less by the following treatment period, treatment may be resumed.

Dose modifications for Cetuximab-related skin toxicity and hypomagnesaemia:



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* These refer to the second and third consecutive week of non-resolving grade 3 toxicity.

Acute cholinergic syndrome

- Irinotecan may provoke an acute cholinergic syndrome with diarrhoea, sweating, salivation, bradycardia, etc. This may start during the drug infusion or shortly after.
- If this occurs, give atropine sulphate 0.25 mg s/c immediately. Atropine should then be given prophylactically with subsequent cycles.

Haematological

- Myelotoxicity is commoner with IrMdG than with MdG. Leucopenia has been reported and attributed to Cetuximab in 8% of patients treated with chemotherapy plus Cetuximab.
- Check FBC on (or up to 3 working days before) day 1 of each cycle. Delay 1 week if WBC < 3.0 x 109/l, granulocytes < 1.5 x 10^9/l or platelets < 100 x 10^9/l. Only treat when WBC and platelets are above these limits.
- If >1 delay, or 1 delay of ≥ 2 weeks occurs, reduce the Irinotecan and 5FU (bolus and infusion) doses by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.
- If a further delay(s) for myelotoxicity occurs despite a 20% dose reduction, a further dose reduction may be made, at the discretion of the treating clinician.

Neurotoxicity

- Neurotoxicity (cerebellar) is uncommon; consider changing to alternative treatment.
- Changes in treatment should be discussed with one of the clinical coordinators.

Renal function (see also Appendix IV)

- Check serum creatinine at each cycle. If this rises >25%, re-check EDTA clearance or 24-hour urinary clearance, and adjust Irinotecan and 5FU doses according to the table in Appendix IV.
- Patients with moderate renal impairment may receive irinotecan, but if GFR <30ml/min, the Irinotecan dose should be reduced by 50% and the 5FU dose should be reduced by 25% (see Appendix IV).
- There is little experience of administering Cetuximab in patients with renal insufficiency. Physicians should exercise caution and consider a dose reduction. No specific guidelines are available.

Hepatobiliary function (see also Appendix IV)

- Irinotecan and its metabolites are cleared by biliary excretion and patients with cholestasis have delayed clearance.
- LFTs should be checked before each treatment cycle. Patients with serum ALP >5 x ULN or serum bilirubin in the range 1.5-3 x ULN require a 50% dose reduction of irinotecan; patients with serum bilirubin >3 x ULN should not receive Irinotecan (please refer to Appendix IV).

- 5FU should be reduced by 50% in patients with serum bilirubin >3 x ULN (see Appendix IV).
- Transaminase (either AST or ALT) ≤ 2.5 x ULN is required for study entry. An isolated rise in transaminase above 2.5 x ULN during treatment is likely to be treatment-related, and treatment should be interrupted until recovery (see Appendix IV).
- Bilirubin ≤ 1.25 x ULN is required for study entry. If bilirubin rises above this limit during treatment, discuss with treating investigator as this may indicate disease progression. If treatment is to continue, please refer to table in Appendix IV.
- There is little experience of administering Cetuximab in patients with hepatic insufficiency. Physicians should exercise caution and consider a dose reduction. No specific guidelines are available.

Interstitial pneumonitis

- A syndrome of severe acute interstitial pneumonitis has been reported recently with another EGFR targeted therapy, gefitinib.
- Should a patient develop severe dyspnoea and/or hypoxia, seek urgent assistance from a chest physician. A high resolution CT scan of thorax, bronchoscopy plus transbronchial biopsies for pathology and relevant cultures should be considered.
- Cetuximab should be withheld until complete resolution of the toxicity.

Stomatitis

- Routine mouthcare (e.g. Corsadyl, nystatin) is recommended, local policy on the use of these or similar drugs is acceptable.
- If mouth ulcers occur despite this, reduce the 5FU doses (bolus and infusion) by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.
- If further toxicity occurs reduce 5FU doses (bolus and infusion) by a further 20%.
- Stomatitis occurs in about 10% of patients treated with Cetuximab. It has not been considered an indication for dose reduction in previous trials. However, if stomatitis continues despite 5FU dose reduction, Cetuximab dose reduction to 400mg/m^2 should be considered.

Diarrhoea

- Irinotecan may produce delayed diarrhoea which, if untreated, may become severe. Early intervention with high-dose Loperamide is highly effective. Patients must be carefully instructed and given the written information sheet, telephone contact numbers and supplies of Loperamide and Ciprofloxacin. Care should be taken that out-of-hours staff answering patient queries are familiar with the protocol.
- Patients should start Loperamide at the first loose stool: 4 mg, then 2 mg every 2 hours until 12 hours after the last loose stool (up to a maximum of 48 hours).
- If diarrhoea lasts > 24 hours, Ciprofloxacin 500 mg bd should be added. If it lasts > 48 hours, or if the patient reports symptoms of dehydration, admit acutely for rehydration and further management (eg octreotide).
- After an episode of severe diarrhoea (grade 3-4), delay chemotherapy until full recovery then resume at 20% reduced doses of Irinotecan and 5FU (bolus and infusion).

- If diarrhoea from the previous cycle, even if not severe, has not resolved by the time the next cycle is due, delay 1 week.
- If diarrhoea persists, Cetuximab dose reduction to 400mg/m^2 should be considered.

Hand-foot syndrome (HFS)

- Treat symptomatically. Pyridoxine 50 mg tds by mouth or topical corticosteroids may help.
- If HFS is still a problem, reduce the 5FU doses (bolus and infusion) by 20% for subsequent cycles (no need to reduce irinotecan).
- If further toxicity occurs reduce 5FU doses (bolus and infusion) by a further 20%.

DPD deficiency; cardiotoxicity

- DPD is the initial and rate-limiting enzyme for 5-FU breakdown. DPD deficiency is an inherited (pharmacogenetic) disorder in which individuals with absent or significantly decreased DPD activity develop life-threatening toxicity following exposure to 5-FU (in either IV or oral form). Reduced drug clearance results in markedly prolonged exposure to 5-FU so that administration of standard doses of 5-FU results in altered 5-FU pharmacokinetics and severe toxicity including mucositis, granulocytopenia, neuropathy and death. The onset of toxicity usually occurs twice as fast in patients with low DPD activity as compared with patients with a normal DPD activity. Approximately 3-5% of the population has low DPD activity and 0.1% have absent activity. We recommend that (i) patients with a personal or family history suggestive of DPD deficiency should not be enrolled onto New EPOC, and (ii) those who experience grade 3/4 neutropenia and grade 3/4 mucositis after cycle 1 should be considered as potentially having DPD deficiency. If DPD deficiency is suspected, patients should only continue on trial after full recovery but without the further use of a Fluoropyrimidine.
- 5FU may provoke angina attacks or even MI in patients with ischaemic heart disease. Continued treatment with upgraded antianginal medication and reduced 5FU dose may be considered.

Appendix II – Dose calculations and banding

Overweight patients:

1. Ideal body weight (IBW) is calculated (Lorenz formula) as:
   i. Men: IBW in kg = [height in cm minus 100] – [(height – 150) ÷ 4]
   ii. Women IBW in kg = [height in cm minus 100] – [(height – 150) ÷ 2]
2. If a patient weighs more than 1.15x their IBW, use 1.15x IBW to calculate surface area (SA).
3. Examples:
   i. A man is 174 cm tall. His IBW is 174 – 100 – (24 ÷ 4) = **68 kg**. So if his actual weight is less than 78.2 kg (68 x 1.15), we use his actual weight to calculate SA, but if he weighs more than 78.2 kg, we use 78.2kg to calculate SA (which gives us **1.93 m^2**).
   ii. A woman is 174 cm tall, so her IBW is 74 – 12 = **62 kg**. So if she is over 71.3 kg, we use 71.3 kg to calculate SA (this gives us **1.85 m^2**)

Fluorouracil dose banding

- First calculate the patient's surface area accurately to **2** decimal places, then calculate the exact target doses for the 5 minute 5FU bolus and 46-hour infusion
  - *For example, a patient of 1.59m^2 receiving the OxMdG regimen without dose-adjustments would have target doses of 400 x 1.59 = 636 mg Fluorouracil bolus and 2400 x 1.59 = 3816 mg Fluorouracil infusion.*
- Bolus Fluorouracil may then be rounded to the nearest 25 mg, and infusion Fluorouracil may be rounded to the nearest 50 mg.
  - *So the patient in the above example would receive 625 mg bolus + 3800 mg infusion.*
- Fluorouracil may be dose banded up to within 10% where this reflects local practice.

Oxaliplatin dose banding

- As for Fluorouracil, first calculate the patient's surface area accurately to 2 decimal places, then calculate the exact target dose.
  - *For example, the patient of 1.59m^2 receiving the OxMdG regimen without dose-adjustment would have a target dose of 85 x 1.59 = 135.15 mg*
- The round the Oxaliplatin dose to the nearest 10 mg.
  - *So the patient in the above example would receive 140 mg Oxaliplatin.*

Irinotecan dose banding

- As above, first calculate the patient's surface area accurately to 2 decimal places, then calculate the exact target dose.
    - *For example, the patient of 1.59m^2 receiving the IrMdG regimen without dose-adjustment would have a target dose of 180 x 1.59 = 286.2 mg*
- Irinotecan may be dose banded up to within 5% where this reflects local practice.

Cetuximab dose banding

- As above, first calculate the patient's surface area accurately to 2 decimal places, then calculate the exact target dose.
    - *For example, the patient of 1.59m^2 receiving Cetuximab with the OxMdG regimen without dose-adjustment would have a target dose of 500 x 1.59 = 795 mg*
- Then round the Cetuximab dose to the nearest 5 mg.
    - *So the patient in the above example would receive 795 mg Cetuximab.*
- Note that overweight patients are dosed using 1.15 x ideal body weight (see Appendix II) for all chemotherapy drugs. Cetuximab doses should not however be capped to 1.15 x ideal body weight, please dose according to the patients actual body weight.

Appendix III – Delivery of infused treatment

The OxMdG and IrMdG regimens may be delivered in hospital but are intended as a daycase/outpatient treatment. Investigators need to consider the following issues:

Venous access:

1. Semi-permanent venous access is required, e.g.:
    i. a single-lumen Hickman line.
    ii. a peripheral long line (PICC, etc).
    iii. a subcutaneous implantable port (Portacath, Infu-KT, etc).
2. Choices:
    i. **use only single-lumen lines, not double** (double-lumen lines have a higher complication rate and are not required for OxMdG or IrMdG).
    ii. for Hickman lines, use right subclavian approach not left.
    iii. if PICC lines are used, the non-return valve type is recommended.
3. Management:
    i. local protocol for insertion and management of the venous line is required.
    ii. nominated staff for insertion and management of lines.
    iii. written information for GPs and community nurses.
4. Flushing:
    i. subcutaneous ports (e.g. PortaCath) do not need flushing between treatments.
    ii. Hickman and PICC lines require weekly flushing.
    iii. district nurse, carer, or district nurse should perform the weekly between-treatment flush.

Infusion pumps:

5. Suitable pumps for this study are:
    i. elastomeric balloon infusors (e.g. Baxter 'LV5')
    ii. battery-powered electrical pumps (e.g. Walkmed).
6. It is important that staff including out-of-hours on-call staff are familiar with the types of pump being used in the unit.
7. Note that with elastomeric pumps, flow-rates through PICC lines may be less consistent than through Hickman lines. Pumps should be allowed to complete before disconnecting, even if this takes a little longer than the intended 46 hours.

Liaison with community services:

8. Good communication with general practitioners and community nursing teams is particularly important. District nurses should be invited to attend the chemotherapy unit to learn the procedure for disconnecting chemotherapy pumps at the end of the 46-hour infusion. Written nursing protocols for care of the venous lines and pumps should be prepared for this purpose.

In-patient delivery via a peripheral vein:

9. Occasionally it is necessary to give OxMdG or IrMdG as an inpatient via a peripheral vein, e.g.:
    i. for the first cycle if there is a waiting-list for permanent venous access insertion
    ii. if venous access has had to be removed because of a complication
10. In this instance, the 46-hour infusion of 5FU should be divided into two 23-hour infusions, each given in 1 litre normal saline.
11. Repeated treatment administration in this way may lead to discolouration and pain over the arm veins and is not recommended. A heated pad is recommended during the Oxaliplatin infusion if OxMdG is being given.
12. Never use a peripheral vein cannula for ambulatory home chemotherapy, or to administer concentrated 5FU intended for central venous line use.

Appendix IV – Renal & hepatic function

		Cetuximab dose	Oxaliplatin dose	5FU dose
Renal function	GFR > 50 ml/min	Full	Full	Full
	GFR 30–50 ml/min	Full	Full	Full
	GFR < 30 ml/min	Full	Do not give	Reduce by 25%
Hepatic function	Bili ≤ 3x ULN and AST/ALT ≤ 2.5x ULN	Full	Full	Full
	AST/ALT > 2.5 x ULN	Full	Withhold until recovery	Withhold until recovery
	Bili > 3x ULN	Full	Reduce by 50%	Reduce by 50%

		Irinotecan dose
Renal function	GFR > 50 ml/min	Full
	GFR 30–50 ml/min	Full
	GFR < 30 ml/min	50%
Hepatic function	Bili ≤ 1.5x ULN **and** ALP ≤ 2.5x ULN	Full
	Bili 1.5-3x ULN **or** ALP > 5x ULN	50%
	Bili > 3x ULN	Omit

Notes:

1. Organ function at the time of enrolment must meet the eligibility criteria (see section 8), i.e. GFR ≥ 50 ml/min, bilirubin ≤ 1.25 x ULN, alkaline phosphatase ≤ 5 x ULN and transaminase ≤ 2.5 x ULN (use either AST or ALT – it is not necessary to measure both).

2. If renal or hepatic function changes at any point after randomisation, use the table above. **Deteriorating organ function may be a sign of disease progression, so always discuss with the treating investigator.**

3. GFR: see notes in Appendix VIII for the use of Cockcroft formula to estimate GFR. For patients with a Cockcroft estimate <50 ml/min, a measured EDTA clearance (or 24 hour urinary creatinine clearance) should be obtained on at least one occasion, and this value takes precedence over the Cockcroft estimate.

Appendix V – RECIST response definitions

- RECIST (Response Evaluation Criteria In Solid Tumours) has now superseded the old WHO response criteria for solid tumours.
- The key differences are:
  - instead of measuring lesions in 2 dimensions it is now only necessary to measure the longest diameter.
  - disease is classified as measurable or not measurable but the term evaluable is no longer used.

Measurable disease:

- Disease is measurable if there is at least one measurable target lesion. Target lesions should be selected on the basis of size and suitability for repeat measurement, up to a maximum of 5 measurable lesions per organ, and up to a maximum of 10 lesions in total. These should be representative of all involved organs.
- Target lesion must be accurately measurable in at least 1 dimension, with the longest diameter ≥20 mm (or ≥10 mm with spiral CT scan). If the lesion is smaller than this then it is classed as non-measurable.
- Measurements must be taken as close as possible to the beginning of treatment and never more than 6 weeks before the start of treatment. Target lesions should be assessed by CT, MRI or CXR, not by clinical assessment alone. The same imaging modality should be used throughout for any given patient.
- When intra-venous contrast agents are given with CT, it is important to measure hepatic lesions in the same vascular phase on subsequent examinations.
- If MRI is used than the same sequence (e.g. T1 or T2 weighted images) in the same anatomical plane should be used.
- Add the longest diameters of the target lesions and report this as the **baseline sum longest diameter.** This will be used as a reference by which the tumour response will be measured.

Response definitions:

- **Complete response (CR)**: disappearance of all lesions (i.e. all evidence of disease, not just the target lesions) determined by 2 observations not less than 2 weeks apart (in *New EPOC* the 12-week assessment should be used as the confirmatory assessment; there is no need for additional confirmatory scans).
- **Partial response (PR)**: ≥30% decrease in the sum of longest diameters of target lesions compared to baseline, with response or stable disease observed in non-target lesions, and no new lesions.

- **Stable disease (SD)**: neither sufficient shrinkage to qualify for response or sufficient increase to qualify for progressive disease in target lesions, with response or stable disease observed in non-target lesions, and no new lesions
- **Progressive disease (PD)**: ≥20% increase in the sum of longest diameters of target lesions compared to smallest sum longest diameter recorded, or unequivocal progression of non-target lesions, or appearance of new lesions.

Reminder:

- Response is judged against baseline, but progression is judged against the smallest recorded score.

Example:

Month	0	3	6	9	12
Measurement (mm)	100	90	50	55	≥60
Classification	Baseline	SD	PR	PR	PD

References:

Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumours. J Natl Cancer Inst 2000, 92, 205-216.

Gehan EA and Tefft MC. Will there be resistance to the RECIST (Response Evaluation Criteria in Solid Tumours)? J Natl Cancer Inst 2000, 92, 179-181.

Appendix VI – Guidelines for the evaluation of resectability and histology

The consulting surgeon and the radiologist will determine resectability according to local practice. Spiral CT with injection of contrast medium, or MRI is mandatory. Patients with potentially resectable liver metastases can be included in the study.

Eligibility of patients with synchronous liver metastases and rectal cancer

1. Patients with synchronous liver metastases (LM) can undergo resection of the primary tumour first particularly if they have a risk of intestinal obstruction; these patients are eligible to be randomised in the protocol one month after the procedure. If resections of the primary tumour and LM are to be performed during the same procedure sufficient evidence that the primary tumour is completely resectable and that resection of primary cancer can be delayed for 3 to 4 months should be obtained (for example by CT scan or diagnostic laparoscopy) prior to randomisation. In patients with cancer of the rectum and synchronous liver metastases radiation therapy must not interfere with chemotherapy administered according to protocol.
2. If rectal and liver surgery are to be carried out at the same time no pre- or post-operative radiotherapy should be administered.
3. If surgical excision of rectal cancer is performed first, it must be decided before randomisation if radiotherapy will be administered or not. In any case, it should not delay treatment of liver metastases. Thus short pre-operative radiotherapy (Swedish scheme) is preferable.

Resectable liver metastases are defined as metastases which can be totally resected by surgery

1. With one or several anatomical resections provided the amount of remnant liver parenchyma after surgery is not less than 30% of total functional parenchyma.
2. With one or several wedge resections alone or in combination with anatomical resections.
3. The clearance between the tumour and the cut surface of the liver should be one centimeter or more whenever possible. However resection with a shorter clearance does not preclude inclusion in the study provided all tumour has been removed.
4. Patients with metachronous metastases must have undergone complete resection of the primary tumour without gross or microscopic evidence of residual disease (R0).

LM considered not resectable:

1. Tumours invading right and left branches of hepatic artery or portal vein.
2. Tumours extended to the 3 main hepatic veins.
3. Tumours that cannot be totally resected due to their size, location or number of deposit.
4. Association to liver metastases of extra hepatic cancer extension such as lung metastases. However the presence on chest CT scan of equivocal lesions measuring less than one centimeter is not considered a criteria for non inclusion. Note: tumour ablation techniques (cryosurgery, radiofrequency, laser hyperthermia) are not considered to be equivalent to resection.

When unexpected tumour extension is discovered at surgery, it should be managed by the most appropriate way and mentioned in CRF. In particular, if the number of metastases is higher than expected or if extrahepatic involvement is discovered it should be resected whenever possible.

Note: due to the risk of abdominal wall seeding, biopsy of the metastases prior to randomisation is not mandatory if the diagnosis is considered obvious according to the practice in each participating institution (i.e. if hepatic lesions are recent and have radiological characteristics of metastases, if tumour markers are elevated, etc.). In all cases metastases should be proven by biopsy during surgery even if unresectable. **When non-malignant disease cannot be ruled out, histology must be obtained prior to randomisation.**

Appendix VII – WHO performance status

Clinical performance status

0 Able to carry out all normal activity without restriction.

1 Restricted in physically strenuous activity but ambulatory and able to carry out light work.

2 Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.

3 Capable only of limited self-care; confined to bed or chair more than 50% of waking hours.

4 Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Appendix VIII – Cockcroft & Gault formula

- The estimated GFR is given by:

Males: $$\frac{1.25 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/l})}$$

Females: $$\frac{1.05 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/l})}$$

- This formula usually under-estimates GFR by 10-30% compared with EDTA or measured 24-hour creatinine clearance, so is used in this trial as a screening test.
- A Cockcroft/Gault estimate of ≥ 50 ml/min is accepted as evidence of adequate renal function.
- Patients with a Cockcroft/Gault estimate of < 50 ml/min prior to randomisation should have formal GFR measurement with EDTA or 24 urinary creatinine, which must be within the normal range. The corrected EDTA clearance should be ≥50ml/min.
- After the start of treatment, if the Cockcroft/Gault estimate falls by >25% from baseline or to below 50 ml/min, the formal EDTA measurement should be re-checked.

Appendix IX – EORTC QLQ questionnaires

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Additional Questions

During the past week:

	Not at all	A little	Quite a bit	Very much	Not applicable
31. Have you had a dry and/or sore mouth?	1	2	3	4	
32. Have you had problems eating or drinking because of a sore mouth?	1	2	3	4	
33. Have you had difficulty handling small objects (e.g. doing up buttons or zips)?	1	2	3	4	
34. How much has your treatment interfered with your normal daily activities?	1	2	3	4	N/A
Since you started chemotherapy:					
35. How worthwhile do you think your treatment has been?	1	2	3	4	N/A

Over the past 6 weeks:

36. How many times have you been visited by your GP? ☐

37. How many times have you visited your GP? ☐

38. How many times have you been visited by a district nurse? ☐

39. How many times have you been visited by a MacMillan nurse? ☐

The aim of this questionnaire is to measure how much any skin problem you may have experienced has affected your life OVER THE PAST WEEK.

	Not at all	A little	A lot	Very much	Not applicable
40. Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	1	2	3	4	
41. Over the last week, **how embarrassed** or **self conscious** have you been because of your skin?	1	2	3	4	
42. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	1	2	3	4	N/A
43. Over the last week, how much has your skin influenced the **clothes** you wear?	1	2	3	4	N/A
44. Over the last week, how much has your skin affected any **social** or **leisure** activities?	1	2	3	4	N/A
45. Over the last week, how much has your skin made it difficult for you to do any **sport**?	1	2	3	4	N/A
46. Over the last week, has your skin prevented you from **working** or **studying**?	Yes	No			N/A
If "No", over the last week how much has your skin been a problem at **work** or **studying**?	1	2	3		
47. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	1	2	3	4	N/A
48. Over the last week, how much has your skin caused any **sexual difficulties**?	1	2	3	4	N/A
49. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	1	2	3	4	N/A

EORTC QLQ – LMC21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :	Not at all	A little	Quite a bit	Very Much
50. Have you had trouble with eating?	1	2	3	4
51. Have you felt full up too quickly after beginning to eat?	1	2	3	4
52. Have you worried about losing weight?	1	2	3	4
53. Have you had problems with your sense of taste?	1	2	3	4
54. Have you had a dry mouth?	1	2	3	4
55. Have you had a sore mouth or tongue?	1	2	3	4
56. Have you been less active than you would like to be?	1	2	3	4
57. Have you had tingling hands or feet?	1	2	3	4
58. Have you had pain in your stomach area?	1	2	3	4
59. Have you had discomfort in your stomach area?	1	2	3	4
60. Have you been bothered by your skin or eyes being yellow(jaundiced)?	1	2	3	4
61. Have you had pain in your back?	1	2	3	4
62. Have you felt "slowed down"?	1	2	3	4
63. Have you felt lacking in energy?	1	2	3	4
64. Have you had trouble having social contact with friends?	1	2	3	4
65. Have you had trouble talking about your feelings to your family or friends?	1	2	3	4
66. Have you felt stressed?	1	2	3	4
67. Have you felt less able to enjoy yourself?	1	2	3	4
68. Were you worried about your health in the future?	1	2	3	4
69. Were you worried about your family in the future?	1	2	3	4
During the past four weeks:				
70. Have you been bothered by the effect of the disease or treatment on your sex life?	1	2	3	4

Appendix X – EQ-5D questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

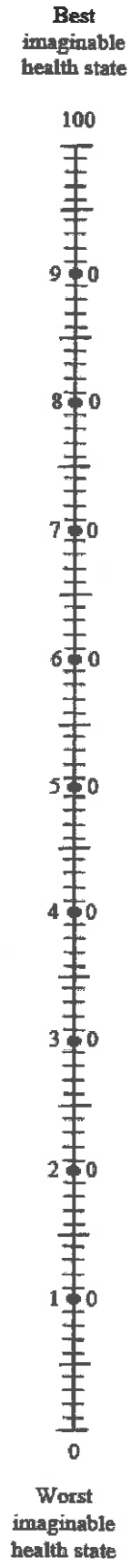
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix XI – NCI common terminology criteria for adverse events (v3.0)

Toxicity	0	1	2	3	4	5
NAUSEA	None	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated < 24hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥ 24hrs	Life-threatening consequences	Death
VOMITING	None	1 episode in 24 hours	2-5 episodes in 24 hours; IV fluids indicated < 24hrs	≥ 6 episodes in 24 hours; IV fluids, or TPN indicated ≥ 24hrs	Life-threatening consequences	Death
ANOREXIA	None	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition; IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
ALOPECIA	Normal	Thinning or patchy	Complete	-	-	-
RASH: ACNE/ ACNEIFORM	None	Intervention not indicated	Intervention indicated	Associated with pain, disfiguremnet, ulceration, or desquamation	-	Death
RASH: HAND-FOOT SKIN REACTION	None	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, oedema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain, interfering with function	-	-
NAIL CHANGES	None	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	-	-
PAIN	None	Mild pain not interfering with function	Moderate pain: pain or analgesics interfering with function, but not interfering with ADL	Severe pain: pain or analgesics severely interfering with ADL	Disabling	-
MUCOSITIS/ STOMATITIS (clinical exam)	None	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
MUCOSITIS/ STOMATITIS (functional/ symptomatic)	None	Minimal discomfort, intervention not indicated	Symptomatic, medical intervention indicated but not interfering with ADL	Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
DIARRHOEA (patients without colostomy)	None	Increase of <4 stools/day over baseline	Increase of 4-6 stools/day over baseline; IV fluids indicated < 24hrs	Increase of ≥ 7 stools/day; incontinence; IV fluids ≥ 24hrs; hospitalisation	Life-threatening consequences (e.g., haemodynamic collapse)	Death
DIARRHOEA (patients with a colostomy)	None	Mild increase in ostomy output compared with baseline	Moderate increase in ostomy output compared with baseline, not interfering with ADL	Severe increase in ostomy output compared to baseline, interfering with ADL	Life-threatening consequences (e.g., haemodynamic collapse)	Death
LETHARGY	None	Mild fatigue over baseline	Moderate or causing difficulty performing some activities	Severe fatigue interfering with ADL	Disabling	-
HAEMO-GLOBIN	Within normal limits	10.0g/dl - normal	8.0 - 9.9g/dl	6.5 - 7.9g/dl	<6.5g/dl	Death
PLATELETS	Within normal limits	$75x10^9/l$ - normal	$50 - 74x10^9/l$	$25 – 49x10^9/l$	$<25x10^9/l$	Death
NEUTROPHILS	Within normal limits	$1.5x10^9/l$ – normal	$1.0 - 1.4x10^9/l$	$0.5 - 0.9x10^9/l$	$<0.5x10^9/l$	Death
ALT	Within	>ULN – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5 – 20.0 x ULN	> 20 x ULN	-

	normal limits					
AST	Within normal limits	>ULN – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5 – 20.0 x ULN	> 20 x ULN	-
BILIRUBIN	Within normal limits	>ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3 – 10.0 x ULN	> 10 x ULN	-
SENSORY NEUROPATHY	Normal	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
MOTOR NEUROPATHY	Normal	Asymptomatic; weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk indicated	Life-threatening; disabling (e.g., paralysis)	Death
ALLERGIC REACTION/ HYPER-SENSITIVITY (INCLUDING DRUG FEVER)	Normal	Transient flushing or rash; drug fever < 38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥104°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
MAGNESIUM, SERUM LOW (HYPOMAGNES -EMIA)	Within normal limits	<LLN - 1.2 mg/dL <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL <0.4 - 0.3 mmol/L	<0.7 mg/dL <0.3 mmol/L	Death

- ***These are selected categories. For full list see*** *http://ctep.cancer.gov/reporting/ctc.html*

Appendix XII – Economic evaluation

1. Overview

The economic evaluation will take the form of a cost-effectiveness analysis. The differential cost of the alternative treatments will be related to their differential benefits in terms of quality-adjusted life years (QALYs), and standard cost-effectiveness acceptability curves will be used to show the probability of one option being more cost-effective than the others.

2. Estimating costs

All significant NHS resource consumption that is expected to differ between treatment options will be estimated within the study. This will include hospital and non-hospital costs. In addition, we will record patient borne travel costs to attend hospital appointments. These are dealt with in turn below.

2.1 Hospital resource use

Within the trial, hospital resource use data will be collected on all patients entering the trial. These will be collected using case record forms completed at clinical review at 12 weekly intervals. Some visits to and stays in hospital may relate to non-study hospitals. To ensure that data on this form of resource use are captured, a questionnaire will be administered to patients as part of the QoL assessments at baseline and 12-weekly.

These resources will be valued in monetary terms using unit costs representative of UK practice at the time of analysis. For drugs, this will be based on British National Formulary prices. For hospital procedure and hotel costs, unit costs will if available, be based on NHS Reference Costs. If not available, these will be based on nearest appropriate equivalent.

2.2 NHS non-hospital resource use

Patients' use of community-based NHS (and complementary health) services will be collected from patients in the form of a short questionnaire administered at 12 weekly intervals. The resources will include visits to and from a GP or district nurse. Costing of community-based resources will be based on published unit costs. Other services will be costed using data available at the point of analysis.

2.3 Patient travel costs

Patients' travel costs will be estimated using a cost per hospital visit and multiplying that cost by the number of occasions each patient visits hospital. In order to cost a given visit to hospital for each patient, specific questions will be asked of each patient at baseline. This will collect information on the typical mode(s) of transport, distance and time of journeys to hospital, and whether the patient had a companion. Based on these data, patients' travel costs will be based on published unit costs for travel.

Questions will also be asked at baseline to collect information to cost the time patients and any companions allocate to the visit. Time will be valued using an average national wage rate with

sensitivity analysis used to explore the implications of valuing the time of patients who are not in employment differently from those that are in employment.

3. Measuring effects

The clinical trial is estimating a range of clinical and Health Related Quality of Life (HRQL) effects in trial patients. The purpose of the economic evaluation will be to set these in context of the resource costs incurred in achieving them. The cost-effectiveness analysis will relate differential cost to an aggregated measure of effect in the form of a quality-adjusted life-year (QALY).

4. Analysis

All resource use data will be valued in monetary terms as described above such that each patient has a cost over the period of follow-up. A full stochastic analysis will be undertaken to allow for sample variation in resource use and effect data. Methods are altering quickly in this area and, by the time of the analysis, 'best practice' may have altered markedly from today. If such an analysis were to be undertaken now, the general methods would be as follows.

Allowance will have to be made – both for the costs and effects – for censored data due to differential follow-up and the fact that it is unlikely that all patients would have died at the point of analysis. For effects, these methods are clear and established using standard methods of survival analysis. For costs, methods are now available for handling censored data[5].

Although cost data are likely to be heavily skewed, it is important that means are reported as this is the relevant statistic for decision makers. Parametric methods or non-parametric bootstrapping will be used as appropriate.

For the cost-effectiveness analysis, two analyses will be undertaken (one taking a health care system perspective on costs, the other a societal perspective). QALYs will be the measure of effectiveness.

A QALY profile will be estimated for each patient based on their survival duration weighted by their responses to the EQ-5D HRQL questionnaire, which generates a single index value for health at each point of follow-up[6]. The profiles will assume a straight-line relationship between the index value at time t and the value at time t+1. The number of QALYs they experience during the period of follow-up in the trial will be the area under the QALY profile.

In the primary analysis only data collected in the trial will be used in the analysis; in other words, the estimate of QALYs for each group is likely to reflect the fact that some patients are still alive after the year's follow-up (i.e. the survival curve is truncated and survival techniques will be used to estimate QALYs).

As a secondary analysis, extrapolation techniques will be used to estimate the final portion of the curve so as to provide a full estimate of differential life expectancy. A range of extrapolation techniques exists, with currently no consensus as to the best. The methodological literature will be monitored.

Cost-effectiveness acceptability curves will be used to facilitate a measure of uncertainty around cost-effectiveness estimates[1]. These curves show the probability of one form of management

being more cost-effective than the others assuming alternative levels of the maximum amount decision-makers are willing to pay for an extra QALY.

Sensitivity analysis will be used to consider the importance of sources of uncertainty other than sample variation (e.g. unit costs, discount rates, cost perspective). Multiple regression techniques will be employed to provide as precise a measure of cost-effectiveness as possible and to undertake sub-group analysis using baseline patient characteristics that will be defined in advance in the analysis plan.

Appendix XIII – Hypomagnesemia

Hypomagnesemia with Cetuximab

Hypomagnesemia has many well documented causes: predominantly excessive losses through diarrhoea, stoma output or fistula but other causes include renal tubular damage, malnutrition and alcoholism in association with malnutrition, and various drugs. Cisplatinum therapy is a well documented iatrogenic cause of renal wasting of magnesium and requires standardized replacement. Other drugs include diuretics, digoxin and prolonged aminoglycoside usage.

There have recently been several reports of hypomagnesemia and/or hypocalcaemia in relation to Cetuximab therapy, including two abstracts from ASCO GI 2005 (Schrag et. al. 2005 and Carson et. al. 2005). Carson et. al. identified that 65% of patients on single agent Cetuximab developed hypomagnesemia at a median of 8 weeks of therapy: patients were treated with oral or iv therapy. Despite Oxaliplatin being a platinum derivative, it is not commonly believed to cause symptomatic hypomagnesemia; however, there may be an enhancing/synergistic effect in combining Oxaliplatin with Cetuximab. The FDA have advised that 'periodic' monitoring for hypomagnesemia and accompanying hypocalcaemia and hypokalemia should be undertaken during and for eight weeks after Cetuximab therapy (www.fda.gov/medwatch/safety/200505.htm#Erbitux).

Symptoms/Signs

Hypomagnesemia causes a range of symptoms from non-specific malaise to cardiac arrhythmias and death. However, symptoms of hypomagnesemia are non-specific and do not always correlate with level of hypomagnesemia. Hypomagnesemia may be associated with resistant hypocalcaemia as well as hypokalaemia and hyponatraemia. The magnesium deficit should be corrected in all cases.

Fatigue, malaise, tremor, ataxia, carpopedal spasm, hyperreflexia, confusion, hallucinations, convulsions and arrhythmias may occur. ECG changes include prolonged QT interval and broad flattened T waves. Patients with marked hypomagnesemia require ECG and intravenous administration of magnesium (see BNF for guide to administration). This may require admission to hospital and should be considered as a SAE/SUSAR to be reported to UoSCTU within 24 hours.

Treatment

The British National Formulary states that "symptomatic hypomagnesemia is associated with a deficit of 0.5–1 mmol/kg. Up to 160 mmol Mg^{2+} over up to 5 days may be required to replace the deficit (allowing for urinary losses). Magnesium is given initially by intravenous infusion of magnesium sulphate. Plasma magnesium concentration should be measured to determine the rate and duration of infusion and the dose should be reduced in renal impairment" (BNF 2005).

There appears to be no standard guidelines, with respect to magnesium administration in the well hypomagnesemic patient. Oral supplementation has limitations due to the laxative effect of magnesium salts but lower dose supplementation may be reasonable, "magnesium may be given

by mouth in a dose of 24 mmol Mg^{2+} daily in divided doses; a suitable preparation is magnesium glycerophosphate tablets [not licensed, available from IDIS and Special Products]" (BNF 2005).

Monitoring

It is recommended that magnesium levels are measured:

_ at baseline

_ prior to each chemotherapy cycle

_ for all symptomatic patients

_ for any patient with hypocalcaemia

After completion of Cetuximab therapy, magnesium should be measured at 6-8 weeks after the last dose of Cetuximab and at intervals until hypomagnesemia has resolved. This information will be collected on the CRFs and recorded as per NCI CTC toxicity grading criteria (see Appendix XI).

References

Schrag. D, Flombaum.C, Chung.K, Saltz. L; Cetuximab therapy may occasionally cause profound hypomagnesemia and hypocalcemia. Abstract no. 264; ASCO GI 2005

Carson. E, Novak. A, Stella. P; Hypomagnesemia in patients with stage IV colorectal cancer treated with Cetuximab as a single agent; Abstract no. 3655; ASCO GI 2005.

BNF (British National Formulary) March 2005 (Ed)

Appendix XIV - New EPOC k-RAS Request Form

UNIVERSITY OF Southampton

Site number: _____ Patient initials: _____ Patient year of birth: _____

Has this patient consented for their tumour sample to be used for further research? Yes ☐ No ☐

Type of tissue	Sample available? (tick)	Disease site	If not available, state reason	Sample sent (e.g. block, biopsy, etc)	Cassette identification	Quantity sent
Tumour						
Lymph node						
Metastases						
Blood*						

*** = please note that blood should ONLY be collected and sent for k-RAS testing if specially requested by the Cardiff laboratory (required in rare cases where unusual variant in tumour is identified)**

Please specify by what method these tissues have been fixed:

☐ Neutral buffered formalin ☐ Acidified formalin
☐ Formol saline ☐ Bouin's fixative
☐ Other, please **specify** _____

I confirm that the sample(s) enclosed is / are tumourous (checked by local histopathologist; not applicable if sending blood only).

Pathologist's name (BLOCK CAPITALS): _____

Signature: _____ Date: _____

Please send this form and associated samples (anonymised by trial ID) marked as "**Urgent Clinical Sample**" to:

Molecular Genetics Laboratory
Institute of Medical Genetics
Cardiff & Vale NHS Trust
Heath Park
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Laboratory Use only

k-RAS Result: ☐ Mutant

☐ Wildtype

Date result sent to trial contact: _____

Print name: _____ Signed: _____