FOCUS 3

Developed on behalf of the NCRI Colorectal Clinical Studies Group

FOCUS 3

A study to determine the feasibility of molecular selection of therapy using *KRAS*, *BRAF* and topo-1 in patients with metastatic or locally advanced colorectal cancer

CR12
CLINICAL PROTOCOL
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(Based on MRC CTU template protocol version 3.15)

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GENERAL INFORMATION

This document describes the FOCUS 3 trial coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) 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 has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the FOCUS 3 Trial Manager at MRC CTU to confirm they have the most up to date version.

Sponsor
The Medical Research Council is the trial sponsor and has delegated responsibility for the overall management of the FOCUS 3 trial to the MRC Clinical Trials Unit.

Funding
The trial is funded by the Medical Research Council. Merck KGaA, Roche and Pfizer are all providing financial support to the trial in terms of either free or reduced price drugs or educational/research support grants.

Compliance
The trial will be conducted in compliance with the protocol, ICH GCP, Data Protection Act (DPA number: Z5886415), NHS research governance and other regulatory requirements, as appropriate

Authorisation
The FOCUS 3 trial has been scientifically approved by the Medical Research Council and is thus part of the NCRN/NCRI portfolio of colorectal cancer trials.

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Appendices

Abbreviations and Glossary

ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine Aminotransferase
AR	Adverse Reaction
ASCO	American Society for Clinical Oncology
AST	Aspartate Aminotransferase
BS	Best Supportive Care
C	Twice Daily
bd	Carcino-Embyonic Antigen
CEA	Congestive Heart Failure
CHF	Consent Form
CF	Cell free DNA
cfDNA	Chief Investigator
CI	Colorectal Cancer
CRC	Case Report Form
CRF	Clinical Pathology Accreditation
CPA	Clinical Trials Authorisation
CTA	Common Toxicity Criteria
CTC	Clinical Trials Unit
CTU	Data Clarification Form
DCF	de Gramont
dG	District General Hospital
DGH	Deoxyribonucleic Acid
DNA	Data Protection Act
DPA	Dihydropyrimidine Dehydrogenase
DPD	Ethylene Diamine Tetraacetic Acid
EDTA	Epidermal Growth Factor
EGF	Epidermal Growth Factor Receptor
EGFR	European Union Drug Regulatory Agency Clinical Trial
EUDRACT	Folinic Acid (a.k.a. leucovorin)
FA	Full Blood Count
FBC	Food and Drug Administration
FDA	Fluorescence In Situ Hybridization
FISH	Formalin-Fixed, Paraffin-Embedded
FFPE	Failure-Free Survival
FFS	5FU, Folinic Acid and Irinotecan
FOLFIRI	5FU, Folinic Acid and Oxaliplatin
FOLFOX	5FU, Folinic Acid, Oxaliplatin and Irinotecan
FOLFOXIR	Fluoropyrimidine
I Fp FU	Fluorouracil
5FU	5-Fluorouracil
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GFR	Glomerular Filtration Rate
HE	Health Economics
HR	Hazard Ratio
HRQL	Health-Related Quality of Life
IB	Investigator's Brochure
IBW	Ideal Body Weight
ICH	International Congress on Harmonisation
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
INR	International Normalised Ratio
IPA	Interpretative Phenomenological Analysis
Ir	Irinotecan
IrMdG	Irinotecan, 5FU and Folinic Acid
IrOxMdG	Irinotecan, Oxaliplatin, 5FU and Folinic Acid
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-Treat
IV	Intravenous

LFTs	Liver Function Tests
LREC	Local Research Ethics Committee
m^2	Metre Squared
MdG	Modified de Gramont (5FU and Folinic Acid)
MDT	Multidisciplinary Team
mg	Milligram
Mg	Magnesium
MI	Myocardial Infarction
ml	Millilitre
mCRC	Metastatic Colorectal Cancer
MdG	Modified de Gramont
MHRA	Medicines and Healthcare Regulatory Authority
MI	Myocardial Infarction
MRC	Medical Research Council
MRC	Medical Research Council Clinical Trials Unit
CTU	National Cancer Research Institute
NCRI	National Cancer Institute (USA)
NCI	National Health Service
NHS	National Institute for Clinical Excellence
NICE	National Research Ethics Committee
NREC	Once Daily
od	Office of National Statistics
ONS	Overall Response Rate
ORR	Overall Survival
OS	Oxaliplatin
Ox	Oxaliplatin, 5FU and Folinic Acid
OxMdG	Phosphoinositide-3 Kinase
PI3K	Principal Investigator
PI	Progression-Free Survival
PFS	Patient information Sheet
PIS	By Mouth
po	When Necessary
prn	Performance Status
PS	Phosphatase and Tensin Homolog
PTEN	Quality Assurance
QA	Four Times Daily
qds QL	Quality of Life
RECIS	Response Evaluation Criteria in Solid Tumours
T	Real-time Polymerase Chain Reaction
RTPCR	Surface Area
SA	Serious Adverse Event
SAE	Serious Adverse Reaction
SAR	Subcutaneous
s/c	Standard Operating Procedures
SOP	Summary of Product Characteristics
SPC	Site Specific Assessment
SSA	Suspected Unexpected Serious Adverse Reaction
SUSAR	Three Times Daily
tds	Tissue Microarray
TMA	Trial Master File
TMF	Trial Management Group
TMG	Topoisomerase 1
Topo-	Trial Steering Committee
1 TSC	Unexpected Adverse Reaction
UAR	Urea & Electrolytes
U&Es	Upper Limit of Normal
ULN	Vascular Endothelial Growth Factor
VEGF	White Blood Cells
WBC	Wales Cancer Trials Unit
WCTU	World Health Organisation
WHO	

1. TRIAL SCHEMA

The results of the molecular testing will produce 4 subgroups (types) of patients. Within each subgroup, each patient will be randomised to one of 3 arms; a control arm which is common to each of the 4 subgroups and two alternative, research arms. The 4 molecular type subgroups are as follows:

- Type 1: Low topo-1, Both *KRAS* and *BRAF* wildtype
- Type 2: Low topo-1, Either *KRAS* or *BRAF* mutant
- Type 3: High topo-1, Both *KRAS* and *BRAF* wildtype
- Type 4: High topo-1, Either *KRAS* or *BRAF* mutant

There are five treatment regimens in this trial, but each patient, depending on their molecular type, will be assigned to one of three regimens (the control regimen or one of two experimental regimens). Specific details on each of these treatment regimens can be found in Appendix I.

- Regimen A: IrMdG (Irinotecan and Modified de Gramont) (Control)
- Regimen B: MdG (Modified de Gramont)
- Regimen C: IrOxMdG (Irinotecan, oxaliplatin and Modified de Gramont)
- Regimen D: IrMdG plus cetuximab
- Regimen E: IrMdG plus bevacizumab

Two alternative trial schemas, each illustrating the trial are included below.

Figure 1.1 Trial Schema detailing treatment arms for each Molecular Type

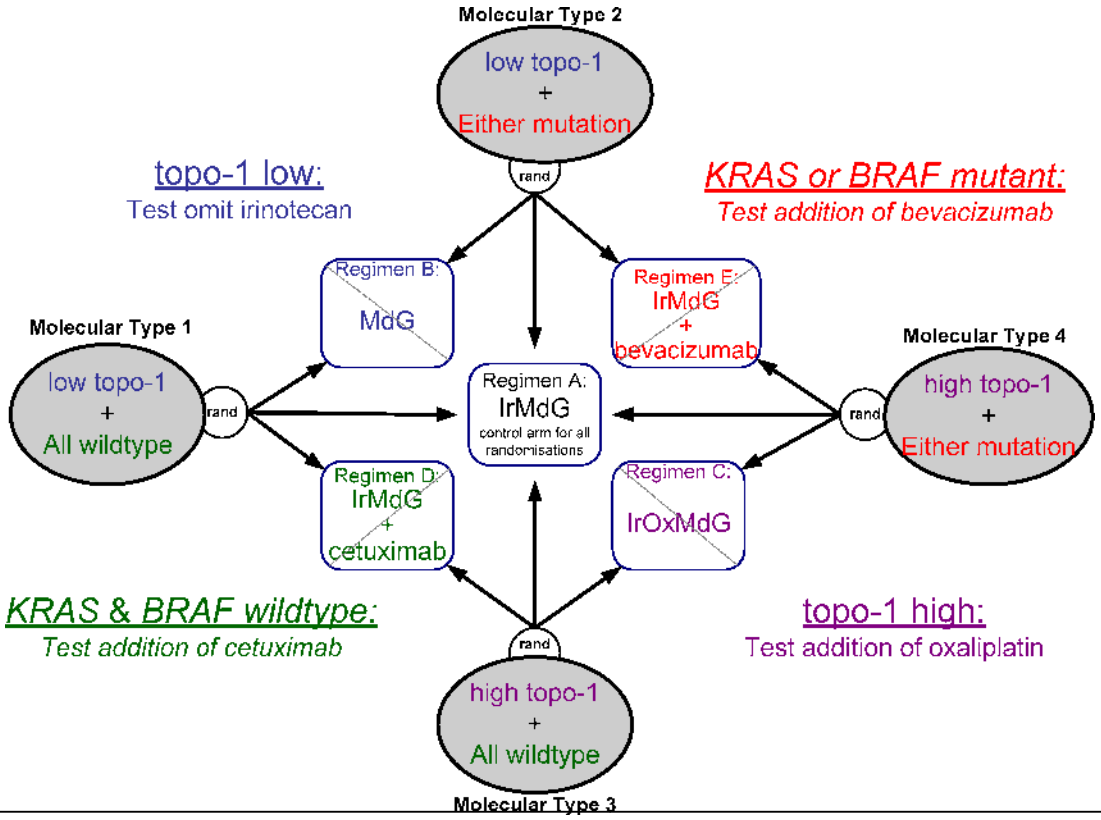
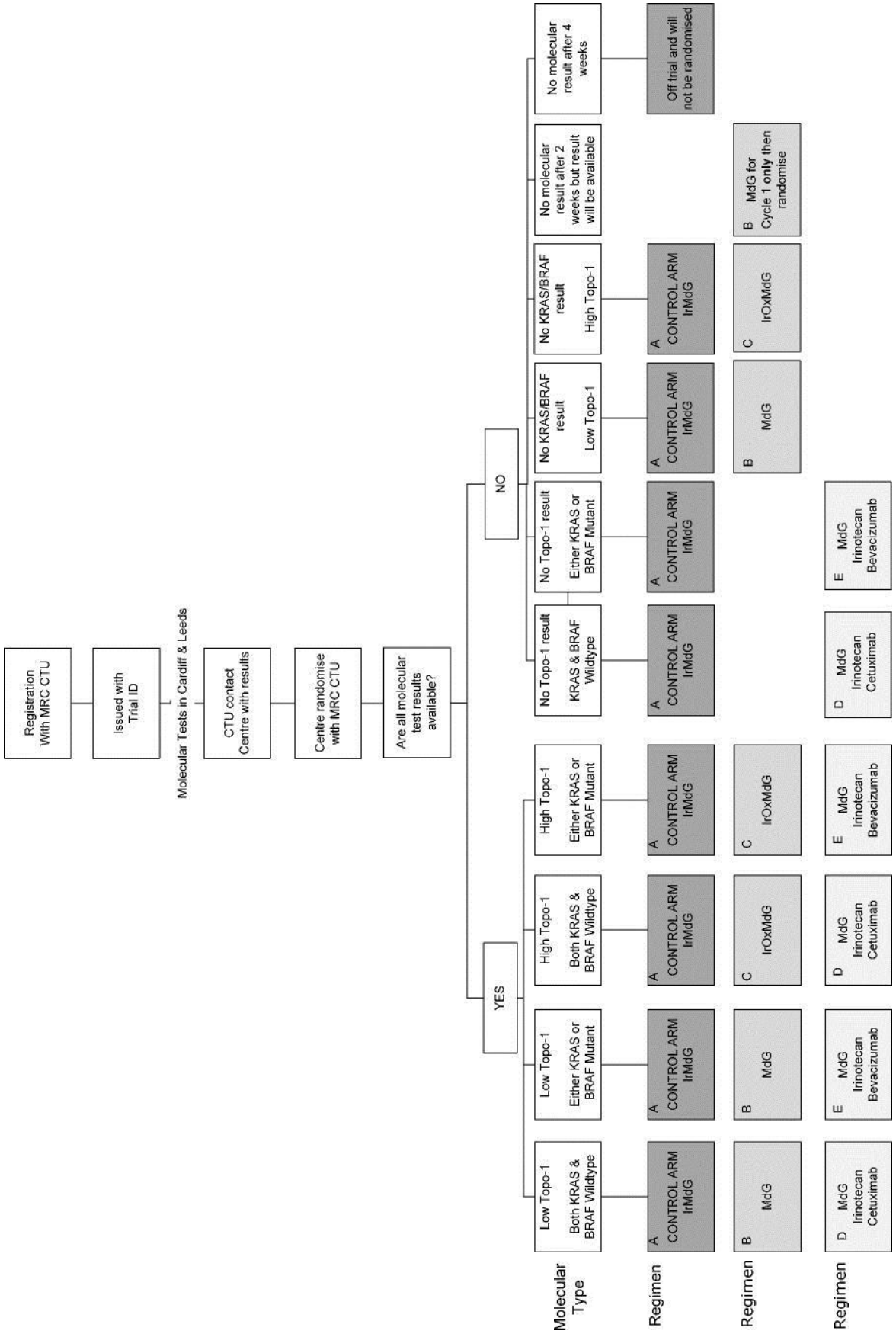


Figure 1.2 Trial Schema detailing all randomisation combinations including those applicable when no molecular results are available



2. SUMMARY

2.1 Abstract and summary of trial design

Recent data has demonstrated that any benefits of Epidermal Growth Factor Receptor (EGFR) targeted monoclonal antibodies are limited to patients with no mutations in the ras oncogene in their tumour, i.e. those patients who are *KRAS* wildtype (*KRAS*^{wt}). Also, it is becoming clear that patients whose tumours harbours a *BRAF* mutation have both a very poor prognosis and seem to gain little or no benefit from the addition of EGFR monoclonal antibodies. In addition, data from the FOCUS trial suggest that high topoisomerase-1 (topo-1) levels in the tumour predict benefit from use of irinotecan in combination with 5FU in first-line therapy. FOCUS 3 addresses the issue of individualisation of therapy for patients with metastatic colorectal cancer (mCRC) based on these biomarkers (molecular markers) in each patient's tumour. This feasibility trial tests a number of elements required for any future large scale and definitive trial of molecular selection in this disease setting. It is also structured to pose specific, clinically relevant questions about optimal use of currently available agents, and the design is such that the randomised feasibility data may be included in the subsequent full trial.

2.1.1 Type of design

FOCUS 3 is an open-label, multi-arm, randomised controlled feasibility trial. The results of the molecular testing will produce 4 subgroups of patients, and within each subgroup each patient will be randomised to one of 3 arms; a control arm (IrMdG) which is common to each of the 4 subgroups and two alternative, research arms (see Figure 1.1).

- Subgroup 1: Low topo-1, Both *KRAS* and *BRAF* wildtype ○
  IrMdG v MdG v IrMdG + cetuximab
- Subgroup 2: Low topo-1, Either *KRAS* or *BRAF* mutant ○
  IrMdG v MdG v IrMdG + bevacizumab
- Subgroup 3: High topo-1, Both *KRAS* and *BRAF* wildtype ○
  IrMdG v IrOxMdG v IrMdG + cetuximab
- Subgroup 4: High topo-1, Either *KRAS* or *BRAF* mutant ○
  IrMdG v IrOxMdG v IrMdG + bevacizumab

If both the *KRAS* and *BRAF* genotyping fails, patients will be entered into the topo-1 randomisation only and be randomised between the control arm A and either regimen B or C (depending on topo-1 level) only. It is now known that *BRAF* and *KRAS* mutations are mutually exclusive and thus, a mutation in either can be accepted as criteria for entry into subgroup 2 or 4 even if the read out on the other is not sufficient. If the *KRAS* result is wildtype and the *BRAF* result has failed or alternatively, the *BRAF* result is wildtype and the

KRAS result has failed, the patient will be included in the wildtype randomisation (Subgroups 1 or 3) based on the available evidence.

If the topo-1 tests fail to give a result, the patient will be entered into the *KRAS* randomisation only, and be randomised between the control arm A and either regimen D or E (depending on *KRAS* status). If neither result is technically possible or the block is unobtainable, the patient will not be randomised and is off trial. The reasons for this failure will be recorded for analysis purposes. Further details are given in section 6.3.2.

2.1.2 Disease/patients studied

240 patients with proven mCRC who are fit to receive any of the treatment regimens proposed and willing to consent to the release of a single tumour block for analysis of biomarkers will be entered into the trial. Patients potentially suitable for surgical resection of metastatic disease after response to 1st line or adjuvant chemotherapy will be excluded. For more details refer to section 5.

2.1.3 Trial interventions – research and control

The first trial intervention is the analysis of *KRAS* and *BRAF* mutation status, and topo-1 expression from archival formalin-fixed paraffin-embedded (FFPE) tumour blocks. This will be performed centrally in reference laboratories in Cardiff and Leeds subject to documented Quality Assurance procedures. The control chemotherapy regimen for all four biomarker defined subgroups is irinotecan plus infusional 5FU and folinic acid (IrMdG) as per the best arm of the MRC FOCUS trial (Regimen A). There are four research regimens: 5FU alone (MdG) (Regimen B); 5FU, irinotecan plus oxaliplatin (IrOxMdG) (Regimen C); IrMdG + cetuximab (Regimen D); IrMdG + bevacizumab (Regimen E). Specific details on each of these treatment regimens can be found in Appendix I. Capecitabine will not be allowed except for cases of venous access failure and individual cases must be discussed with MRC CTU prior to commencement of capecitabine treatment.

2.1.4 Outcome measures

Primary:

- Of those patients randomised, in how many patients was the interval between registration and the provision of results to the investigator to allow randomisation less than or equal to 10 working days
- Of those patients randomised, in how many patients was the interval between registration and the date of randomisation less than or equal to 10 working days

Secondary:

- Time from date of requesting hospital pathology laboratory to release a tumour sample to date of receipt of sample at central laboratory (Leeds or Cardiff)
- Of those patients registered but not subsequently randomised, for what reasons did randomisation not occur (insufficient sample material, technical failure, unacceptable delay, patient refusal, patient ineligibility)
- Time from registration consent to start of treatment
- In all randomised patients, time from the provision of KRAS, *BRAF* and topo-1 results to the investigator to allow randomisation to the date of randomisation.
- Reproducibility of *KRAS* and *BRAF* mutations and topo-1 results between laboratory centres and methodological problems identified
- Distribution frequencies of topo-1 expression and *KRAS* and *BRAF* mutation analysis and the distribution of patients between sub-groups to inform power calculations for the main study
- Costs of the molecular testing
- Toxicity, response rates and progression free survival (PFS) of the different regimens in the molecular subgroups
- Attitude of patients to study design, the consent process and refusal rates for trial entry

2.1.5 Translational:

- Frequency of EGFR gene amplification on FISH, PI3K mutation, PTEN loss on IHC, amphiregulin and epiregulin mRNA, protein assessment and evaluation of impact on the use or further investigation of these markers in the main study

2.1.6 Duration

Patients will continue on trial treatment for at least 24 weeks or until disease progression on treatment. After 24 weeks of treatment, patients may have a break of up to 6 weeks before restarting trial treatment. Once treatment has stopped, patients remain in the trial for the purpose of follow-up. Accrual is expected to take approximately 1 year.

2.1.7 Ancillary studies/substudies

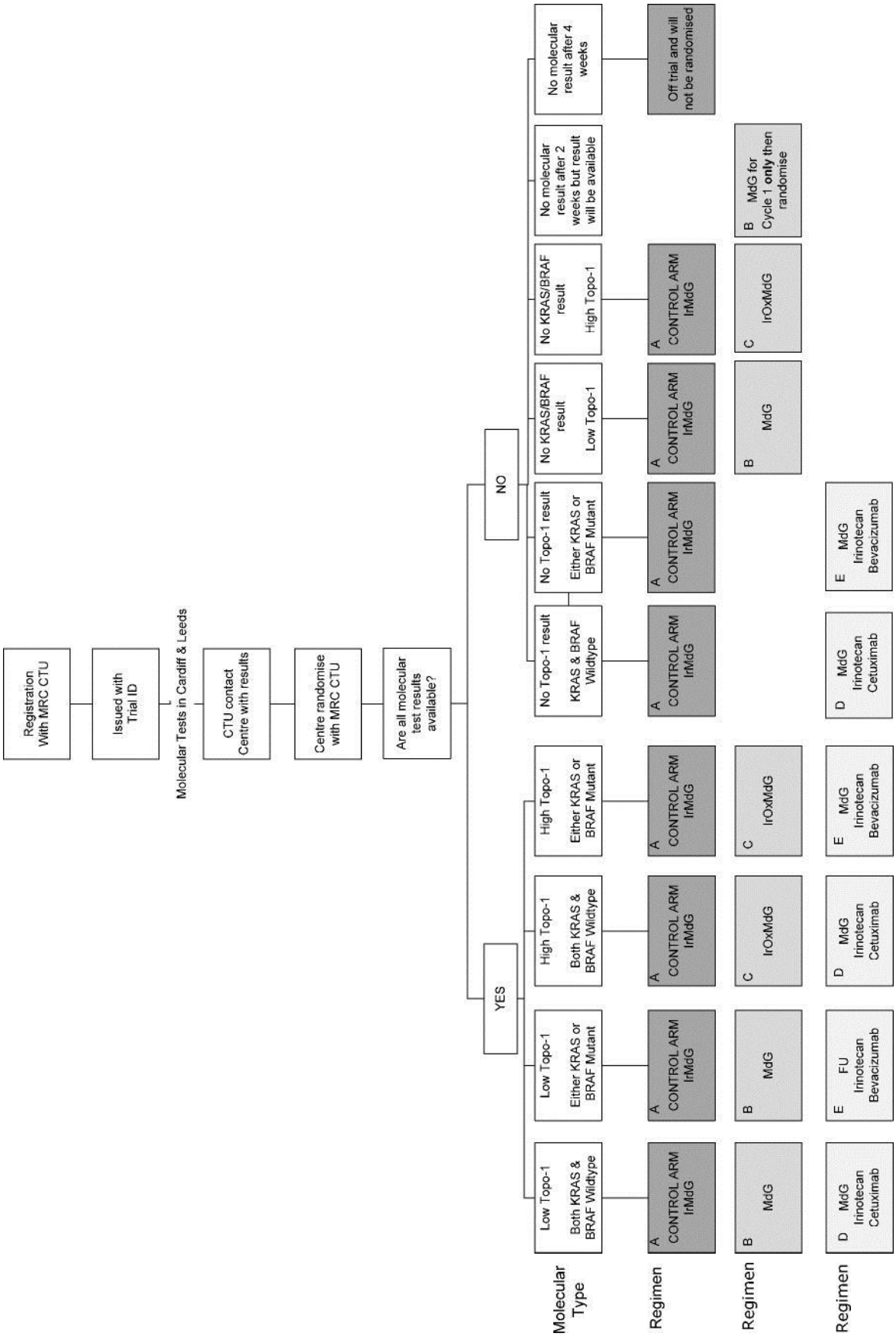
The frequency of EGFR gene amplification on Fluorescence In Situ Hybridisation (FISH), PI3K gene mutation, Phosphatase and Tensin Homolog (PTEN) loss on immunohistochemistry (IHC), estimation of mRNA for EGFR ligands (amphiregulin and epiregulin) and other protein assessments will be performed. An evaluation of the impact on the use or further investigation of these markers in the main study will be undertaken.

Cell free DNA (cfDNA) is a readily available, economic source of tumour-derived DNA, amenable to reliable detection of tumour specific *KRAS* mutations in mCRC patients. A sub-study will compare the relative sensitivity and reliability of using plasma derived cfDNA for mutation detection.

2.1.8 Organisation

This trial is funded and sponsored by the Medical Research Council (MRC) and will be coordinated by staff in the Cancer Group of the MRC Clinical Trials Unit (MRC CTU). Merck KgaA and Roche have agreed to support this trial by providing free cetuximab and bevacizumab respectively for patients randomised to these arms of the trial. Pfizer is also providing support for educational meetings through an unrestricted educational grant.

Figure 2.1: Trial entry, randomisation and treatment



3. BACKGROUND

3.1 Introduction

Over 16,000 people die of colorectal cancer per annum in the UK[1] most of whom die with metastatic disease. However, both the prevention of metastases (through adjuvant chemotherapy) and the treatment of metastatic colorectal cancer (mCRC) are improving. The five-year survival rates for both men and women with colon and rectal cancer have doubled between the early 1970s and the late 1990s[1]. Median survival for patients with metastases has improved from about 6 months with best supportive care (BSC) alone to 16-20 months in recent randomised controlled trials (RCTs) including bevacizumab (a Vascular Endothelial Growth Factor (VEGF)-targeted monoclonal antibody), irinotecan and oxaliplatin as well as 5FU[2,3]. In addition the Epidermal Growth Factor Receptor (EGFR) targeted monoclonal antibody, cetuximab has been shown to increase response rates and progression free survival (PFS) in combination with chemotherapy in first-line therapy[4] and increase survival as a single agent in salvage therapy[5]. However, many patients gain little benefit from systemic therapy, while all patients experience toxicity. In addition, the economic costs of treatment for both adjuvant and metastatic colorectal cancer have escalated such that the use of all agents at various stages of the disease has been calculated to cost £80,000 per person treated[6]. In September 2009 NICE approved cetuximab for patients with inoperable liver-only metastases, who have had their primary tumour resected and are *KRAS* wildtype. This is the only indication for which cetuximab is approved for use within the NHS. Bevacizumab is not currently approved for use within the NHS. The goal of much clinical cancer research is to define ways of selecting the right patients for the right treatments and this trial aims to do this using three biomarkers (molecular markers): topo-1 expression and *KRAS* and *BRAF* mutation status. This type of approach is most developed in the settings of leukaemia and breast cancer, where the validation of relatively simple predictive biomarkers (such as oestrogen receptor and Her-2 receptor status) has led to evolution of trial design into distinct subsets of patients with stepwise improvements in outcome.

In the following sections the rationale and outcomes for the current design of the definitive FOCUS 3 trial are presented. It should be noted that the design of the definitive trial may change as more data become available or as NICE guidance in the UK is updated. The feasibility study has been powered for the primary outcome measures. The numbers in each arm are too small during the feasibility stage to provide information on the efficacy of the regimens.

3.1.1 Topoisomerase-1 as a Predictor of Response to Irinotecan and Oxaliplatin Therapy

The MRC FOCUS (CR08) trial[2] identified that the level of immunohistochemical (IHC) expression of topo-1 enzyme predicts for benefit from treatment with combination chemotherapy in first-line mCRC treatment. 1288 patients were assessable for topo-1 expression. Patients with low topo-1 (n=602) had little evidence of improvement in PFS with the addition of either irinotecan (HR 0.98 [95%CI=0.78-1.22]) or oxaliplatin to 5-fluorouracil (5FU) (HR=0.85 [0.68-1.07]); in 677 patients with higher topo-1, major benefit was seen with the addition of either drug (HR=0.5-0.7); test for interaction p=0.005. Patients with highest topo-1 (n=219) derived major overall survival (OS) benefit from receiving combination chemotherapy first-line instead of deferred to second-line (HR=0.60 [0.44-0.82]; absolute benefit in median overall survival of 5.3 months) but those with lower topo-1 did not; test for interaction p=0.0056. The implication of this observation is that around half of patients being treated for mCRC gain no significant benefit from the addition of the toxic and costly agents irinotecan or oxaliplatin to first-line therapy i.e. the approximately 50% of patients with low topo-1.

Since this first report, two further sets of tumour samples from randomised clinical trials have been analysed for the effect of topo-1 immunohistochemistry on benefit from the addition of a second drug to a fluoropyrimidine backbone. The FOCUS 2 trial examined the effect of adding oxaliplatin to either infusional 5FU or capecitabine and has shown a similar effect as in the FOCUS trial. In predictive analysis including 361 patients, moderate/high topo-1 was associated with a benefit for adding oxaliplatin (PFS: HR 0.71 [0.55–0.91]; OS: HR 0.84 [0.65–1.10]), whilst patients with low topo-1 gained no benefit (PFS: HR 0.97 [0.65–1.46]; OS: HR 1.03 [0.66–1.60]). These results, although not independently significant, are fully consistent with the results of the FOCUS trial. The interaction was more pronounced with OxFU/FU (ratios of HRs: PFS = 1.63 [0.83–3.18]; OS = 1.42 [0.69–2.94]) than with OxCap/Cap (ratios of HRs: PFS = 1.20 [0.60–2.4]; OS = 0.98 [0.47–2.06])[7]. For comparison, the ratios of HRs for OxFU/FU in FOCUS were PFS = 1.35 [0.99–1.83], OS = 1.35 [1.05-1.74]. In contrast the CAIRO trial by the Dutch Colorectal Cancer Group did not observe an interaction between topo-1 expression and treatment with capecitabine plus irinotecan with respect to PFS or OS (interaction p = 0.710 for PFS; interaction p = 0.65 for OS in 545 patients comparing low v moderate/high topo-1)[8]. Taken together, these datasets are consistent in showing a predictive effect for topo-1 in those patients treated with infusional 5FU as the fluoropyrimidine, in that patients with low topo-1 IHC gain no benefit from addition of a second agent (either oxaliplatin or irinotecan) whereas those with moderate or high topo-1 expression consistently benefit from the addition of the second agent.

These findings have not been shown in patients treated with capecitabine as the backbone, which may be a causal or chance association. In FOCUS 3 the backbone is infusional 5FU so

the concept remains valid. This observation needs to be prospectively validated as it represents a mechanism to identify which patients are likely to benefit from first-line combination chemotherapy. FOCUS 3 patients with low topo-1 expression will be randomised between 5FU + irinotecan (IrMdG) and 5FU (MdG) alone (with folinic acid in the modified de Gramont schedule) to prospectively validate this hypothesis by the omission of irinotecan in these patients in whom FOCUS and FOCUS 2 data predict no benefit (Regimen A v B, See Figure 1.1).

In addition, in those patients with moderate to high levels of topo-1, there may be benefit in giving both oxaliplatin and irinotecan with 5FU in first-line therapy[10]. In the recently reported Gono trial, 244 patients were randomised to 5FU and irinotecan (FOLFIRI regimen, Arm A) or 5FU, oxaliplatin and irinotecan (FOLFOXIRI regimen, Arm B)[11]. At a median follow-up time of 15.2 months, median PFS was 6.9 vs 9.8 months (HR=0.63, p=0.0006) and median OS was 16.7 vs 22.6 months (HR=0.70, p=0.032) all favouring the triple combination, FOLFOXIRI. In contrast, a Greek randomised trial using a different regimen with lower drug concentrations, showed only 43% response rate, with a median overall survival of 21.5 months on the triple combination but no significant benefit over FOLFIRI[12].

In FOCUS 3, patients with high topo-1 expression will therefore be randomised between (i) 5FU + irinotecan (IrMdG) and (ii) the triple combination of 5FU, irinotecan plus oxaliplatin (IrOxMdG) to assess whether the addition of oxaliplatin in this chemosensitive subgroup may be more effective (Regimen A vs. Regimen C) (See Figure 11.4). Doses for the IrOxMdG regimen vary depending on patient age and performance status. Please refer to Appendix I for more information on the IrOxMdG dosing schedules.

3.1.2 *KRAS* Mutational Status as a Predictor of Response to EGFR Therapy

Many potential candidate predictors of response to EGFR targeted therapy in colorectal cancer have been evaluated[21]. Cetuximab was chimerized from the mouse monoclonal antibody M225, which blocks the ligand binding site of the EGFR, and a human immunoglobulin IgG constant region gene segment[22]. It has a binding affinity one log higher than endogenous ligand, preventing their binding, inducing receptor internalisation and inhibiting downstream signal transduction[23]. Preclinical studies showed activity in chemotherapy resistant colorectal cancer xenografts and synergy with both radiation and irinotecan chemotherapy[24]. The license for cetuximab continues to require EGFR expression in the absence of clear evidence of its relevance. The evidence is now strong that the key predictor for non-response is the presence of activating *KRAS* mutations which act downstream of the EGFR and therefore, has biological plausibility. This is now reflected in the European license for cetuximab which allows usage of cetuximab in combination with 5FU-based chemotherapy in the treatment of patients with EGFR expressing, *KRAS* wildtype (normal) mCRC. The evidence base for this emerged from 6 single centre series[25-30], in which *KRAS* mutation was detected in 123 of 329 patients

(37%), of whom 5 responded (4%) compared with 75/206 patients (36%) responders in patients with *KRAS* wildtype (*KRAS*^{wt}).

The clinical benefit of EGFR targeted therapy with cetuximab has now been reported in randomised trials in first-[4], second-[13] and third-[5] line treatment for mCRC.

In the Crystal trial, 1198 patients were randomised to irinotecan, 5FU and cetuximab in first-line therapy. In an updated analysis in which 1063 (89%) of patients were assessed for *KRAS* mutation status, the results in the *KRAS*^{wt} population (n=666) showed an increase in response rate of 17.6% (39.7% to 57.3%, p<0.0001) with improved PFS, (HR=0.696, p=0.0012), (data presented at ECCO/ESMO 2009). The effect of the addition of cetuximab to FOLFIRI on overall survival in the *KRAS* wildtype cohort was also confirmed (OS: FOLFIRI 20 months, FOLFIRI + cetuximab 23.5 mo, HR 0.8 (0.67-0.95, p 0.0094)[14].

In contrast the addition of cetuximab to oxaliplatin and fluoropyrimidine therapy in the COIN trial has failed to show a benefit for either PFS or for OS[15]. In a preplanned test for interaction there is a suggestion that the lack of effect is due to an interaction with capecitabine; patients who received cetuximab plus fluorouracil/oxaliplatin showed a trend to benefit. While this interpretation of the COIN trial result needs further exploration, it is supported by comparison with other trials of cetuximab in similar patients with mCRC (CAIRO2[16], OPUS[17], CRYSTAL[18]). In FOCUS 3 neither oxaliplatin nor capecitabine is to be used in combination with cetuximab. Therefore there is no rationale to change the current randomisation options for those patients with *KRAS* wildtype tumours.

The results obtained from the use of EGFR-targeted therapy as monotherapy in the third-line setting are consistent, with two trials showing improvements in OS with the addition of EGFR-targeted therapy to BSC[19,20].

Table 3.1 Summary of results from Crystal trial

	ITT		***KRAS* wt**		***KRAS* mt**	
	Cetuximab+ FOLFIRI	FOLFIRI	Cetuximab +FOLFIRI	FOLFIRI	Cetuximab +FOLFIRI	FOLFIRI
N	599	599	316	350	214	183
ORR* (%)	47	39	57	40	31	36
p-value	0.0038		<0.001		0.35	
PFS (mo)	8.9	8.0	9.9	8.4	7.4	7.7
HR	0.85		0.7 (0.56-0.87)		1.17 (0.89-1.54)	
p-value	0.048		0.0012		0.26	
OS (mo)			23.5	20.0	16.2	16.7
HR			0.8 (0.67-0.95)		1.03 (0.83-1.28)	
p-value			0.009		0.75	

* Overall Response Rate

Therefore, there is strong evidence from third-line monotherapy data and from first-line combination chemotherapy trials that any benefit of EGFR-targeted antibody therapy on PFS and OS is limited to patients with no mutations in codons 12 or 13 of *KRAS*. Codon 61 is the third most common recognised mutation so will also be tested in FOCUS 3. However, the magnitude of the benefit is still modest and there is still the need to further refine the selection algorithm for patients with *KRAS*^{wt} by the investigation of other biomarkers as discussed in section 3.1.3 and 3.2.1 below.

3.1.3 *BRAF* mutation as a predictive factor

In advanced colorectal cancer, 6-10% of patients' tumours harbour a *BRAF* mutation. This is always found in association with wildtype KRAS, i.e. the two mutations are non-overlapping. In COIN 8% of patients had a *BRAF* mutation and these patients had a median PFS of only 10 months, reduced to 7.2 months with the addition of cetuximab. This finding is consistent with other data in which *BRAF* mutation is associated with poor prognosis and lack of benefit from the addition of EGFR inhibitors. In this trial therefore we will assess *BRAF* mutation status at the same time as *KRAS* and will allocate patients with *BRAF* mutations into the same randomisations as those with *KRAS* mutations.

In this trial, *KRAS* codons 12, 13 and 61 along with *BRAF* codon V600E will be assessed and patients with no mutations (*KRAS* and *BRAF* wildtype) will be randomised to IrMdG with or without cetuximab (Regimen A v Regimen D) (See
Figure 11.6).

3.1.4 Targeted therapy for *KRAS/BRAF* Mutant Tumours

There is no specific rationale for a biologically targeted therapy in patients whose tumours have a mutation in their *KRAS* or *BRAF* oncogene at present. We propose the use of bevacizumab in this subgroup. A phase III trial[3] compared IFL (a bolus regimen of 5FU, leucovorin (folinic acid) and irinotecan) plus placebo to IFL + 5 mg/kg of bevacizumab every two weeks in patients previously untreated for mCRC. Patients randomised to IFL + bevacizumab had improved median OS (20.3 v 15.6 months; p=0.00003) and median PFS (10.6 vs. 6.2 months; p<0.00001) compared with IFL alone. IFL combined with bevacizumab had comparable toxicity to IFL alone, with an increase in the incidence of grade 3 hypertension (10.9% vs. 2.3%) being the exception. An analysis of the effect of various biomarkers on the outcomes in that trial has been published[34]. For patients with *KRAS* mutations, the effect of bevacizumab in addition to IFL was to increase median overall survival from 13.6 to 19.9 months (n=78, HR 0.69, 95% CI 0.37-1.31). In the very few patients with *BRAF* mutations reported in this study the hazard ratio for the addition of bevacizumab was 0.11. It is also accepted that bevacizumab is effective in *KRAS* and *BRAF* wildtype patients.

To confirm a benefit of bevacizumab in *KRAS or BRAF* mutant tumours in this trial, patients with either a *KRAS* or *BRAF* mutation will be randomised to IrMdG v IrMdG + bevacizumab (Regimen A v E in randomisation 2 and randomisation 4). (See Figure 11.8).

3.1.5 Randomisation Combinations with Unavailable Tumour Results

Where it has not been possible to obtain a conclusive topo-1 result, patients will be randomised between Regimens A and D or E only. If both the *KRAS* and *BRAF* genotyping fails, patients will be entered into the topo-1 randomisation only and be randomised between the control arm A and either regimen B or C (depending on topo-1 level) only. It is now known that *BRAF* and *KRAS* mutations are mutually exclusive and thus, a mutation in either can be accepted as criteria for entry into subgroup 2 or 4 even if the read out on the other is not sufficient. If the *KRAS* result is wildtype and the *BRAF* result has failed or alternatively, the *BRAF* result is wildtype and the *KRAS* result has failed, the patient will be included in the wildtype randomisation (Subgroups 1 or 3) based on the available evidence.

If the molecular results have been delayed by more than 10 working days and are expected to be available within a further 10 working days as the block has been received at the designated laboratory, the patient can receive MdG for cycle 1 only as per regimen B (Appendix I). Once the results are available, the patient should be randomised immediately and begin their allocated chemotherapy regimen at their next cycle. Please note that the MdG dose may be lower if the patient is subsequently randomised to a different regimen.

If neither result is technically possible or the block is unobtainable, the patient will not be randomised and is considered off trial. Further treatment is at the treating physician's discretion. See Table 3.2 below.

Table 3.2: Randomisation combinations with unavailable tumour result(s)

Tumour result	Randomisation
Both topo-1 and both *KRAS* & *BRAF* available	**A** vs. **B or C** vs. **D or E**
Only topo-1 result available	**A** vs. **B or C**
Only *KRAS* & *BRAF* result available	**A** vs. **D or E**
Neither topo-1 or *KRAS* or *BRAF* result available	Patient is off trial

3.2 Rationale and objectives

3.2.1 Objectives to be Addressed in the Feasibility Study

Topo-1 and *KRAS/BRAF* mutations as potential predictors of response both require prospective validation.

The barriers to proceeding directly to the definitive phase III trial lie in the feasibility of achieving the desired turnaround of the molecular testing and related issues as described below, each of which will be addressed in this feasibility trial:

- In what proportion of consenting patients can a formalin-fixed paraffin-embedded (FFPE) block-containing-tumour be retrieved from the local pathology department, sent to a central laboratory, be analysed for topo-1 IHC and, *KRAS* and *BRAF* mutational status and a reliable result returned to the MRC CTU for treatment allocation within ten working days of their initial consent?

Currently pathology departments will release FFPE blocks from consenting patients for central review and research purposes, but the turnaround time can be exceedingly slow and varies across the UK. The logistical uncertainty in planning a major trial where fast tracking of this process is a requirement needs to be tested for feasibility in the real world of the NHS. Once the samples are received in the central laboratory, the blocks will be registered, sections cut and a core taken for DNA extraction, DNA extracted, *KRAS* and *BRAF* mutational analysis performed, slides stained for IHC and results interpreted and transferred to the MRC CTU. We estimate that it will take 7 days to perform the laboratory work, allowing one week for sample procurement from the participating hospital.

Part of the trial set-up procedure is obtaining documented agreement from each contributing pathology department at each centre, including identifying key personnel and contact details to encourage rapid turnaround of the blocks (see section 4.1).

- How reproducible are the results when replicated in different laboratories?

Quality Assurance (QA) of the molecular tests and their performance to Good Laboratory Practice (GLP) is a requirement for this trial. The analyses for this trial are therefore being carried out in laboratories that have Clinical Pathology Accreditation (CPA) and/or are GLP assured. During this feasibility stage the two reference laboratories (Cardiff and Leeds) will follow approved protocols. Prior to taking part in the trial, both laboratories will exchange blocks for comparison of results and QA confirmation.

- What are the real costs of molecular testing?

Undertaking this feasibility study will enable us to provide robust costings for the definitive trial, with comparisons between two different laboratories and differing methods.

- What are the opinions of patients?

Patients may find this study challenging because of the complexity of the study design, the delay in treatment allocation and the possibility of omission of components of standard therapy and these concerns may affect the consent rate for both this feasibility trial and the definitive RCT. The suite of Patient Information Sheets (PIS) (Appendix XI) uses a staged approach and has been developed with input from patients and nursing staff. Patient responses and their understanding of the issues raised in the PIS will be captured on a response questionnaire delivered immediately following their reading of the stage 2 PIS (See Appendix XIII). Data will, therefore, be collected both on patients consenting to trial entry and (if agreeable to data collection) patient refusing trial entry. Part of the feasibility testing of the trial will be in assessing participants' ability to fully comprehend the trial as explained to them. If the data suggests that there are difficulties highlighted by a low recruitment rate (less than 50% of eligible patients consenting), a schedule of cognitive interviewing to explore where the PIS and consent procedure needs to be improved will be initiated.

Attitudes of participants to the waiting period necessary for tumour testing, before allocation of treatment, will be evaluated by one-to-one semi-structured interviews in a subgroup of patients four weeks after starting therapy (n=20). Verbatim transcripts of the audiotaped interviews will be analysed using Interpretative Phenomenological Analysis (IPA) to explore emergent themes.

- Additional studies which may further refine the selection of patients for specific therapies will be undertaken during the feasibility phase, particularly to further identify the EGFR responsive subset within the *KRAS*^{wt} population. Clinical evidence suggests there may only be a subset of 10-20% of patients who achieve major benefits from EGFR targeted therapy. This trial provides further opportunity to evaluate those who are *KRAS*^{wt} for more precise patient selection. One or more may be included in the allocation algorithm in the definitive study if data from this or other studies indicates a

clear predictive value. The following will be undertaken as they directly impact on the integrity of the EGFR pathway functions.

- IHC on TMAs for PTEN and Phospho-EGFR, MAPkinase and AKT will be undertaken. PTEN is a regulatory protein, loss of which results in un-opposed AKT phosphorylation with resultant cell survival signalling and potential lack of response to EGFR targeted therapy[36.] It is rarely mutated but more frequently silenced by methylation of the promoter. Loss of PTEN staining on IHC will report both these mechanisms. Phosphorylation-specific IHC is functional in both Cardiff and Leeds and will be performed on TMAs from the study.

- Data are accumulating that show patients with high tumour levels of mRNA for amphiregulin and epiregulin ligands for the EGF receptor are more likely to benefit from EGFR inhibition[30].

- EGFR copy number has been proposed as a predictor of response to cetuximab, with amplified/polysomic tumours more likely to benefit; however it is uncertain whether this would be an independent predictor or whether it would interact with *KRAS*/*BRAF* status as a predictive marker[37,38,39].

- PI3kinase mutational analysis. Recent data has reported that up to 34% of mutations in CRC result in constitutive activation of AKT with resultant cell survival effects and resistance to multiple agents including EGFR targeted therapy[40].

- Proteomic analyses. Full-length proteins from archival tumour blocks, obtaining over 100µg protein from a 10mm x 10mm, 10µm-thick tumour slice can reliably be extracted. Lysate concentration gradients are arrayed on nitrocellulose-coated glass slides (requiring 0.1µg per array). Each multi-patient array is then used to quantitate an individual protein. Using this technique we will quantitate topo-1 and up to 200 additional candidate predictive protein biomarkers. The lysates are also suitable for quantitative mass spectrometry (requiring 25µg for full proteome analysis).

- Cell free DNA (cfDNA) is a readily available, economic source of tumour-derived DNA, amenable to reliable detection of tumour specific KRAS mutations in mCRC patients. A sub-study will compare the relative

sensitivity and reliability of using plasma derived cfDNA for mutation detection. Two methods are to be employed and compared, namely rtPCR using ARMs technology and pyrosequencing.

3.2.2 Rationale for the Choice of Control Arm

Irinotecan (rather than oxaliplatin) is selected as the control arm because i) it resulted in the longest median survival (16.5 months) in the FOCUS trial[2]; ii) it allows patients receiving oxaliplatin-based adjuvant therapy to be included[41]; iii) its efficacy is not curtailed by cumulative toxicity (such as the cumulative neurotoxicity observed with oxaliplatin).

Cetuximab is not included in the control arm because it is not currently available off study in the UK.

Bevacizumab is not included in the control arm because it is not approved by NICE[9] and, therefore, is not available for use in the NHS. This may limit international acceptability of the trial as it is routine in many developed countries to use bevacizumab in all first-line treatments unless specifically contraindicated based on the Hurwitz trial[3]. In addition, the addition of bevacizumab to FOLFOX / XELOX only resulted in a 1.4 month increase in PFS from 8 months to 9.4 months in the Roche sponsored trial (HR=0.83, 97.5% CI 0.72-0.95, p=0.0023)[42] and the formal phase III comparison of infusional 5FU + irinotecan + bevacizumab has not been performed. Not using bevacizumab in every arm does not undermine the rationale for the molecular selection of drugs; indeed, it makes that rationale more compelling.

3.3 Risks and Benefits of Undertaking This Trial

The risks of undertaking a study of molecular selection of therapy are as follows:

1. A short delay to the start of therapy to allow the blocks to be obtained and the analyses performed. The primary outcome measure of this feasibility study is to see if, in the UK, we can accomplish this in the two week window which is considered clinically acceptable.
2. The omission of a part of usual therapy on the basis of an unvalidated marker. This applies to those patients allocated 5FU alone in Regimen B. However, the strategy of starting therapy with 5FU alone was tested in the FOCUS, CAIRO, FFCD and LIFE studies all of which confirmed that there is no overall survival deficit to starting with 5FU monotherapy.
3. Access to bevacizumab and cetuximab is currently limited in the UK by NICE guidance. Patients not allocated to receive one or other of these antibodies may have their awareness raised and hopes for 'targeted therapy' eventually unrealised. This is a constant issue in the current NHS and is frequently in the press. It is beyond the scope of a research trial to resolve such issues. The hope is that by identifying the right patient groups, the cost effectiveness of the therapy will improve and therefore these expensive agents may be made accessible through revision of NICE guidance to every patient in whom they will be beneficial.
4. The risks associated with the individual therapies will be discussed under each in turn (see Appendix I).

The benefits of the trial lie in the attempt to select the best available treatment for each patient, thereby avoiding the unnecessary toxicity of ineffective treatments. In this trial, full access to the NICE-approved agents 5FU, oxaliplatin and irinotecan continues so all patients will be eligible for any of those treatments after this study.

3.4 Investigational product

All drugs in the trial are licensed individually and are being used within their licensed indications except for the use of irinotecan and oxaliplatin in the combination regimen IrOxMdG and cetuximab. IrOxMdG has been used in combination in other clinical trials[11,12]. Further information on all products can be gained from their Summary of Product Characteristics (SPCs). Complete treatment schedules for each regimen are in Appendix I.

4. SELECTION OF CENTRES/CLINICIANS

4.1 Selection of Centres

To participate in the FOCUS 3 trial, investigators/institutions must fulfil a set of basic criteria which has been agreed by the FOCUS 3 Trial Management Group (TMG) and agree this by signature of the FOCUS 3 Investigator Statement. Centres are selected for participation in FOCUS 3 based on their return of pathology samples for the COIN trial. Criteria are:

- The institution regularly undertakes the treatment of patients with mCRC.
- Each participating Cancer Centre will need to provide confirmation from the lead colorectal pathologist and/or Head of Histopathology Service that a FFPE tumour block will be released following patient registration and sent to the designated laboratory for topo-1 and, *KRAS* and *BRAF* testing so that the result can be available, and the patient randomised within 10 working days following registration. To that end, an identified secretarial or technical contact person and their fax and telephone numbers and the name of the designated pathologist with their written agreement of participation will be required from the Cancer Centre before being accredited to participate in the trial.
- Similarly, each District General Hospital (DGH) and Cancer Centre from which patients will be recruited will be required to provide the same confirmation before being accredited to participate in the trial.
- Patients must be under the care of a consultant medical or clinical oncologist.
- Treatment must be administered in a dedicated oncology facility where, in addition to specialist nursing and junior medical staff, the consultant medical or clinical oncologist is routinely on-site and available to discuss/assess patients prior to treatment.
- Defined arrangements must be in place for the management of acute complications. These may include admission to the designated facility at the Cancer Centre or Unit under the direct supervision of the consultant oncologist, haemato-oncology colleague or general medical service, but should not include admission under the surgical service.
- Defined arrangements are required for nursing support and data collection.
- Members of staff are familiar with the appropriate use of the investigational products, as described in the protocol (and in the current Summary of Product Characteristics (SPC)).
- At least 3 patients have been treated with irinotecan using IrMdG
- At least 3 patients with mCRC have been treated with the monoclonal antibodies bevacizumab and cetuximab at the institution.
- The institution has an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
- All staff assisting with the trial are adequately informed about the protocol, the investigational products and their trial related duties.

- The trial will be conducted in accordance with the current protocol and changes will only be made when necessary to protect the safety, rights or welfare of patients.
- Written policies for acute management of expected toxicities (including neutropenic sepsis and anaphylaxis) must be in place and familiar to relevant staff including on-call staff and those answering telephone queries.
- The trial will be conducted in compliance with GCP and applicable regulatory requirements.
- The institution will permit monitoring and auditing by the MRC Clinical Trials Unit (CTU) and inspection by the appropriate regulatory authorities. Direct access will be made available to all trial related sites, data/documents and reports.
- The institution will maintain a trial master file (TMF), which will contain essential documents for the conduct of the trial.
- All trial data will be submitted in a timely manner and as described in the protocol. Individual institutions may be suspended if data returns are poor or if trial conduct is violated in other ways. A copy of the FOCUS 3 data compliance policy is available on request.
- The trial pharmacist will sign a document to confirm that local hospital systems are in place to cover drug ordering, drug receipt, drug storage and dispensing, and will enable accurate traceability of all drugs used in the trial.
- All Serious Adverse Events (SAEs) will be reported immediately to the MRC CTU (within one working day of the investigator becoming aware of the event). The initial SAE report shall be promptly followed by detailed written reports.
- No data on trial patients will be disclosed without the approval of the Trial Steering Committee (TSC).
- All trial related documents will be retained for at least 5 years after the completion of the trial.

The FOCUS 3 investigator statement is signed by the Principal Investigator for that institution on behalf of all staff at that site who will be working on the FOCUS 3 trial.

In addition and in compliance with ICH GCP all institutions participating in the trial will complete a delegation log and forward this to the MRC CTU. Each person working on the FOCUS 3 trial must complete a section of this log and indicate their responsibilities. The MRC CTU must be immediately notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the TMF at the institution and also at the MRC CTU.

4.2 Centre approval process

The following documentation must be received by the MRC CTU in order for a centre to become an approved FOCUS 3 centre:

- Confirmation of ethics approval
- A copy of the most recent version of the patient information sheets (PIS) and consent form on local headed paper
- Completed delegation log (signature list and delegation of responsibilities). The MRC CTU must be notified immediately of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the Trial Master File at the site and also at the MRC CTU
- Full contact details for all site personnel
- Confirmation from the MHRA that institutions/investigators have been added to the FOCUS 3 Clinical Trials Authorisation (CTA). The CTA for the FOCUS 3 trial requires that the Medicines and Healthcare Products Regulatory Agency (MHRA) be supplied with the names and addresses of all participating investigators/institutions. Staff at the MRC CTU will perform this task
- Completed investigator statement (signed by the institution PI)
- Signed agreement from Lead colorectal pathologist and/or Head of Histopathology Service with contact details of designated secretarial or technical person at the DGH
- R&D approval of the study
- Signed document by pharmacist to confirm that local hospital systems are in place to cover drug ordering, drug receipt, drug storage and dispensing, accurate traceability of all drugs used in the trial is possible
- Signed agreement between MRC and hospital NHS trust

Once all of this documentation has been received, confirmation of institution approval will be sent to the Principal Investigator at each institution by the trial team at the MRC CTU. Each centre will be assigned to a reference laboratory in Cardiff or Leeds where their patient's pathology samples will be sent for topo-1, *KRAS* and *BRAF* analysis.

5. SELECTION OF PATIENTS

Patients should be potentially eligible as assessed by the investigator prior to registration. A full evaluation of inclusion and exclusion criteria must be confirmed prior to randomisation.

5.1 Patient inclusion criteria

1. Male/Female patients at least 18 years or over.
2. Confirmed colorectal adenocarcinoma:
   - **Either** previous or current histologically confirmed primary adenocarcinoma of colon or rectum, together with clinical or radiological evidence of locally advanced disease or metastatic disease or both
   - **Or** histologically confirmed metastatic adenocarcinoma, together with clinical and/or radiological evidence of colorectal primary tumour
3. Inoperable metastatic or locoregional disease
4. Unidimensionally measurable disease (RECIST criteria, Appendix VIII). Baseline CT scan must be performed within 5 weeks prior to treatment
5. Adjuvant chemotherapy with 5FU +/- FA, capecitabine or oxaliplatin combinations may have been given, if chemotherapy completed at least 6 months prior to trial entry. QUASAR 2 patients who have continued bevacizumab for 6 months following completion of chemotherapy are eligible immediately following completion of bevacizumab (Avastin).
6. Rectal chemoradiotherapy with 5FU +/- FA or capecitabine may have been given, if completed at least 1 month prior to trial entry
7. Fit to receive any of the treatment regimens proposed as defined by:
   - WHO performance status (PS) 0, 1 or 2 (See Appendix VII) and considered by responsible consultant to be fit to undergo combination chemotherapy.
   - Baseline laboratory tests (within 1 week prior to randomisation normally):
     - Neutrophils ≥1.5 x10^9/l and platelet count ≥100 x10^9/l
     - Alkaline phosphatase ≤5 x upper limit of normal (ULN), Serum bilirubin ≤1.25 x ULN, and serum transaminase (either AST or ALT) ≤2.5 x ULN
     - Estimated creatinine clearance (Cockcroft and Gault; Appendix IV) ≥30ml/min or measured GFR (EDTA clearance) ≥30 ml/min
8. For women of childbearing potential, negative pregnancy test and adequate contraceptive precautions
9. Effective contraception for male patients if the risk of conception exists
10. Written informed consent including consent to the immediate release of tumour blocks for analysis of molecular markers: see section 6 and figure 6.2 below about the process of obtaining consent for the study

5.2 Patient exclusion criteria

1. Patients expected to be suitable for surgical resection of metastatic disease after response to chemotherapy as decided by MDT. (These patients should be considered for the New-EPOC trial)
2. Previous systemic chemotherapy for metastatic disease (patients who had neoadjuvant therapy prior to hepatic resection followed by resection and adjuvant therapy are eligible as per section 5.1 (5)).
3. Pregnant or lactating women
4. Inability to attend or comply with treatment or follow-up scheduling
5. Patients who are unfit for the chemotherapy regimens in this protocol, e.g.:
    - Severe uncontrolled concurrent medical illness (including poorly controlled angina, uncontrolled hypertension or very recent Myocardial Infarction (MI), (i.e. in previous 3 months) likely to interfere with protocol treatments.
    - History of severe peptic ulcer disease
    - 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.
    - Nephrotic Syndrome
    - Known coagulopathy
    - Patients requiring ongoing therapy with ciclosporin-A (due to interaction with irinotecan)
6. Patients requiring ongoing treatment with a contraindicated concomitant medication (see section 8.10.2)
7. Patients with another previous or current malignant disease which, in the judgement of the treating investigator, is likely to interfere with FOCUS 3 treatment or assessment of response
8. Patients with known hypersensitivity reactions to any of the components of the study treatments
9. Patients with brain metastases
10. Patients with bone metastases only
11. Patients with a personal or family history suggestive of DPD deficiency or with known DPD deficiency
12. History of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant precluding informed consent
13. History of surgery <4weeks prior to commencement of cycle 1

6. REGISTRATION & RANDOMISATION

6.1 Patient Screening and Information Giving Process

The process for giving information to patients about this study has a staged approach to reduce the possibility of information overload. A four-step process has been designed to overcome this. Patients will be given a folder with a section for each patient information sheet to be stored.

1. **Patient Information Sheet (PIS) 1**. This contains information about the nature of the research being considered and the need for further analyses of tumour tissue, with consent for release of a tumour block for molecular analyses. This will usually be given at the first consultation with the oncologist when the diagnosis of metastatic disease has been discussed as information overload is a real issue. Space is provided for the patient to document any questions that they think of at a later stage, and to serve as a reminder to them to discuss the oncologist at their next appointment. Therefore, this first PIS is as simple and minimal as possible to sufficiently inform the patient to provide informed consent for release of the tumour block. Once written consent for block release has been signed, the patient is registered by telephone with the MRC CTU using the information on the patient registration form.
2. **PIS 2**. This will cover the general issues of a three-arm randomised controlled trial, general issues regarding possibly/likely unwanted side-effects and toxicity from treatment. This is designed for the next consultation with the patient, prior to the results of the molecular tests being known, while the patient has still not committed to study entry.
3. **PIS 3**, **Versions a-d.** This describes in detail the three-arm randomisation that is specific to the patient in light of their now-known biomarker results. Therefore, there are four versions of this PIS (PIS 3 a-d), one for each tumour molecular type. These will provide more specific details of the potential advantages and disadvantages of the three arms between which the patient will be randomised. At this point, and given the previous staged information process, the patient should be ready to give informed consent at the clinic when the results of the marker tests are available. Once this consent has been given the patient will then be randomised as described below.
4. **PIS 4**, **Versions a-e.** These give full treatment details of the regimen to which the patient is allocated and is designed to be given out after randomisation. If a patient wishes to see all the treatment regimens that are used in the trial then the full suite of these information sheets may be given out earlier at the specific patient request.

Patients wishing to receive all information about the trial before providing consent for the release of a tumour tissue block may wish to receive information about the first two steps at first contact. Patients are entitled however to receive all of the information sheets at their

first appointment if they so wish. (See Figure 6.2 for a flow-chart illustrating the process). The Patient Information Sheets are in Appendix XI.

The investigator must keep a patient screening log and an enrolment log of all patients being considered for the FOCUS 3 trial. Reasons for non-inclusion should be listed in the log which will be provided to centres at accreditation.

6.2 At Registration

- Confirm the potential patient's eligibility with:
  - History and examination
  - Assessment of WHO performance status
  - Assessment of eligibility criteria
- Give PIS 1 and seek patient's consent for release of tumour block
- Once consent obtained, complete registration CRF and register the patient with MRC CTU. This is the point at which the 10 working day timeline for turnaround of samples begins.
- Contact pathologist to arrange for the fast-track release of the patient's tumour sample blocks to the laboratory which was assigned at accreditation (Cardiff or Leeds), and compete the *KRAS, BRAF* and topo-1 Sample Request and Report Form
- Book a chemotherapy slot for 2 weeks time and arrange for central line insertion.

During registration with the MRC CTU, a trial number will be issued. This trial number will be used to identify tumour blocks sent to the designated reference laboratory. The patient's date of birth should also be used to cross-reference the sample. No treatment allocation will be performed at this point. The trial number will be a unique identifier and the primary way in which the patient will be identified and should be used in all correspondence throughout the trial.

REGISTRATIONS

Tel: 020 7670 4777 Mon - Fri, 09:00 – 17:00

It is requested that the following CRF is completed before calling the registration line:

- Registration form

6.2.1 Block Request and Dispatch Procedure

Once consent for tissue block release has been obtained and the patient has been registered with the MRC CTU, the research nurse should immediately contact the pathology laboratory

designated FOCUS 3 contact (see Section 4.2), faxing a copy of the patient consent form and a completed *KRAS*, *BRAF* and topo-1 Sample Request Form. They should also notify the MRC CTU that this has been done. The Sample Request Form requests that the pathologist identifies and releases a tumour bearing FFPE block to their assigned reference laboratory immediately by First Class post. Please note that the 10 working day timeline for sample return begins from the registration call to the MRC CTU.

The pathologist must also confirm dispatch of the FFPE block by faxing a copy of the Request Form to the MRC CTU. These forms will be sent to sites on accreditation.

6.2.2 Tumour Block Tracking

Tumour blocks will be tracked from time of patient registration to time of patient randomisation. The sample tracking process is as follows:

- When a patient is registered, staff at MRC CTU will inform the reference laboratory so that they are aware that a sample should be expected. The research nurse will also confirm with the MRC CTU that a request has been placed for the release of the block.
- Upon dispatch of the patient's block to the reference laboratory the hospital pathologist will fax a Confirmation Form to the MRC CTU.
- When the block arrives at the reference laboratory staff at the laboratory will inform the CTU of receipt.
    - If the block has not arrived at the reference laboratory within one week after registration, MRC CTU staff will contact the hospital pathology laboratory to reconfirm that the block was sent.
    - If the sample has been delayed such that a result is unlikely to be available within 10 working days, but expected within a further 10 working days, consenting patients will be treated for one cycle with MdG and then randomised once the results become available. (See 3.1.5).
- Once a result is available within the 10 working day turnaround time, staff at the reference laboratory will inform the MRC CTU who will notify the patient's clinician/lead research nurse and pathologist.
- Centres will be informed if there are any minor changes to these procedures.

6.3 Prior to randomisation

- Confirm patient's fitness for treatment
- Full blood count and biochemistry. Calculate creatinine clearance using Cockcroft and Gault formula (see Appendix IV). If the Cockcroft and Gault estimate is < 30 ml/min, a measured GFR is required (e.g. by EDTA clearance). See Appendix V. (NB. Magnesium levels should also be recorded at baseline)

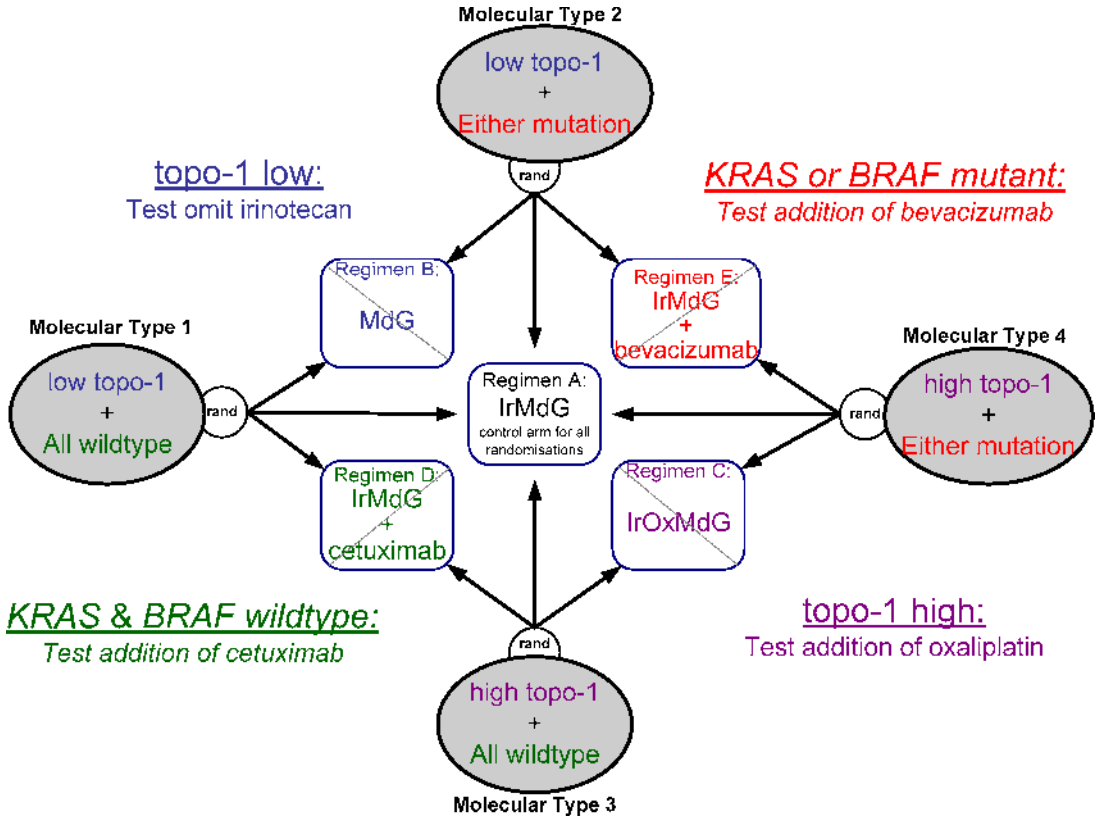
- Ensure patient has measurable disease (RECIST criteria, Appendix VIII) and that a baseline CT scan has been (or will be) performed **within 5 weeks prior to the planned start date for chemotherapy**
- Check all other inclusion and exclusion criteria in protocol section 5.
- Give PIS 2 and book a clinic appointment for when molecular results will be available. This can be done at the first clinic if the clinician feels patient information overload is not an issue.
- Provide patient with the optional response questionnaire (See Appendix XIII). Patients will consent to this on the registration consent form.

6.3.1 Molecular Tests

The reference laboratories will perform topo-1 IHC and will assess *KRAS* codons 12, 13 and 61 and *BRAF* codon V600E. Patients will be classified as:

1. Topo-1 low **or** topo-1 high and;
2. Either *KRAS* or *BRAF* mutant **or** Both *KRAS* and *BRAF* wildtype (normal) On the basis of these two tests, the individual patients will be allocated to the relevant randomisation according to the trial schema (See Figure 6.1).

Figure 6.1 Trial Schema



Further details of the analyses are in Section 11.

6.3.2 Failure of Molecular Tests

If the topo-1 tests fail to give a result, the patient will be entered into the *KRAS* randomisation only, and be randomised between the control arm A and either regimen D or E (depending on *KRAS* status). (See Table 3.2). If both the *KRAS* and *BRAF* genotyping fails, patients will be entered into the topo-1 randomisation only and be randomised between the control arm A and either regimen B or C (depending on topo-1 level) only. It is now known that *BRAF* and *KRAS* mutations are mutually exclusive and thus, a mutation in either can be accepted as criteria for entry into subgroup 2 or 4 even if the read out on the other is not sufficient. If the *KRAS* result is wildtype and the *BRAF* result has failed or alternatively, the *BRAF* result is wildtype and the *KRAS* result has failed, the patient will be included in the wildtype randomisation (Subgroups 1 or 3) based on the available evidence.

If neither result is technically possible or the block is unobtainable, the patient will not be randomised and is off trial. The reasons for this failure will be recorded for analysis purposes. Further treatment is at the treating physician's discretion.

6.3.3 Delay of Molecular Tests

If the molecular results have been delayed by more than 10 working days and the results are expected to be available within a further 10 working days as the block has been received at the designated laboratory, the patient can receive MdG for cycle 1 only as per regimen B. Please refer to Appendix I for treatment information. Once the results are available, the patient should be randomised immediately. **Please note that the MdG dose may be lower if the patient is subsequently randomised to a different regimen.**

6.4 Randomisation

- Confirm patient is fully eligible in light of all baseline investigations
- Obtain molecular results from MRC CTU and identify which randomisation the patient is eligible for
- Give PIS 3 with specific details of the randomisation for which the patient is eligible and discuss the details of the relevant randomisation with the patient
- Given that the patient has already had two weeks in which to consider the general issues related to the research study and this third PIS confirms the details of the two experimental arms for which the patient is suitable, many patients may be ready to sign the consent form at this third consultation. However, if required the patient should have further time after the full information is available and the final invitation to participate is given before signing the consent form
- Ensure that the patient understands that they are free to give or withhold permission for the additional molecular studies without affecting their participation in the study

- Obtain patient's written consent for the trial

Also at this point, provided the patient has not withheld consent for the pharmacogenomic study (Q7 Randomisation consent form), take blood sample (Refer to 6.5).

It is requested that the following CRFs are completed before calling the randomisation line:

- Randomisation form
- Pre-treatment form

RANDOMISATIONS

Tel: 020 7670 4777 Mon - Fri, 09:00 – 17:00

Further details on the randomisation method can be found in section 11.1.

6.5 Blood Sample Collection

Blood sample collection is an optional sub-study that patients will consent to on Q7 of the randomisation consent form. The blood sample **must be taken before the patient receives any FOCUS 3 treatment** and sent immediately to the address below. In order to ensure the blood sample does not arrive at the laboratory over a weekend, the blood sample should be taken **Monday – Thursday**. There will be a couple of opportunities before the patient's treatment commences to take this sample. It may be preferable for the patient if this sample is taken at the same time as a sample is taken for pre-treatment blood measurements.

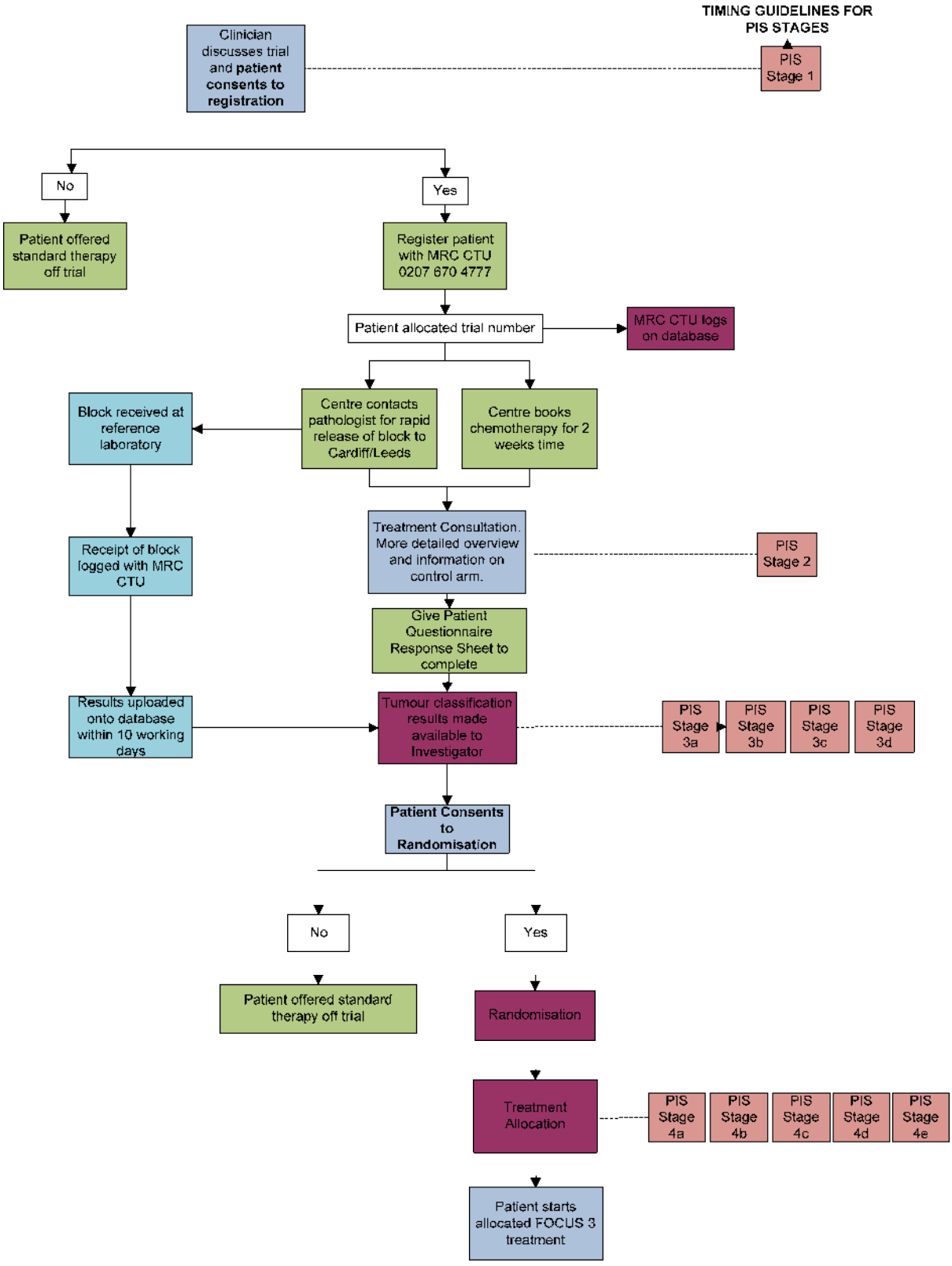
- Take 20ml blood in an EDTA tube(s).
- Label with the following:
  - **Date and time of sample collection** (24 hour notation HH:MM)
  - **Patient's trial number but not name**
  - **Patient's date of birth**
- Seal the tube(s) in the postage prepaid safe box provided by the MRC CTU and post to:

Dr Rachel Butler,
FOCUS 3 Molecular Genetics Laboratory,
Institute of Medical Genetics,
University Hospital of Wales
Heath Park,
Cardiff, CF14 4XW

6.6 Registered Patient who does not consent to Randomisation

Patients may register to the trial, and then decide not to consent to the randomisation. We are interested in finding out the reasons for non-consent to the trial and would therefore also like these patients to document their understanding of the PIS and trial on the response questionnaire (Appendix XIII).

Figure 6.2 Patient Consent Process



7. SAMPLE HANDLING - PATHOLOGY

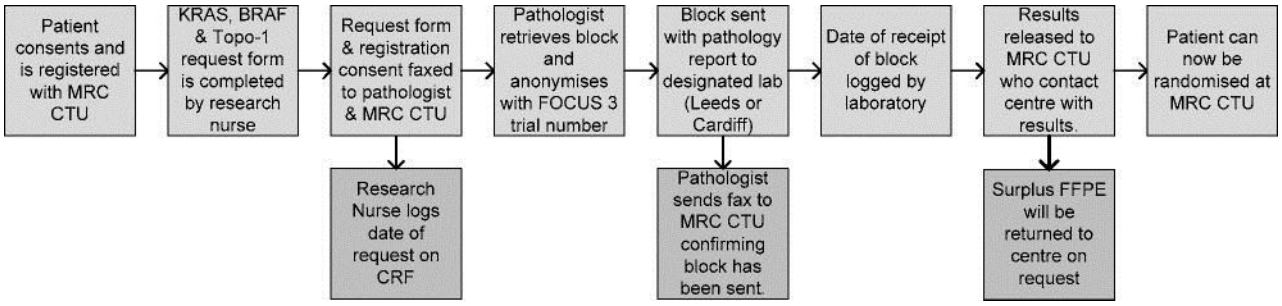
7.1 Pathology Sample for *KRAS*, *BRAF,* and Topo-1 Testing

All patients who consent to registration in FOCUS 3 require prospective testing of the *KRAS*, *BRAF* and topo-1 status of their primary tumour to determine their eligibility for randomisation and treatment within the trial. Each patient will have given consent for release of tumour material and you will be provided with a copy of this consent form. **Receipt of these samples in an appropriate timeline is a rate-limiting step in starting the patient's treatment within the trial so it is very important these blocks are sent to the designated reference laboratory as soon as possible.**

We request that a block containing the maximum quantity of viable tumour is sent and ask that you supply a copy of the histology report with the specimen.

The aim of the FOCUS 3 feasibility study is to establish whether we can have topo-1, *KRAS* and *BRAF* results available to allow randomisation within 10 working days of the patient being registered and a request for the release of a tumour block being made. We will therefore be documenting the dates of each step of the process. It is requested that you complete the second section of the request form and include the completed form with the tumour sample block. This must also be faxed to MRC CTU in order for the date that the sample was sent to the designated laboratory (Cardiff or Leeds) can be tracked. It is also requested that a copy of this form is kept for your records. A flow chart detailing the process is found in Figure 7.1.

Figure 7.1: Tumour Sample Block Request Process



Please note it is estimated that it will take a maximum of seven days to turnaround the results from the date of block receipt. The MRC CTU will contact the lead research nurse at each site as soon as the results are available.

The blocks and the associated pathology reports that are sent must be anonymised, and should only include the FOCUS 3 trial number and date of birth. If the patient has consented to future research, any other further analyses will also be performed anonymously.

We will return all blocks at the end of the trial but will undertake to return the blocks at short notice if these are required to further assist patient management.

A detailed laboratory protocol has been prepared between Cardiff and Leeds laboratories. This can be supplied to your pathology department on request.

8. TREATMENT OF PATIENTS

8.1 Treatment Allocation

On the basis of the biomarker tests, patients will be classified into one of four subgroups and then randomised to either a control arm A common to each of the four subgroups or one of two experimental treatment regimens (see Figure 1.2).

- Regimen A: IrMdG (Irinotecan and Modified de Gramont)
- Regimen B: MdG (Modified de Gramont)
- Regimen C: IrOxMdG (Irinotecan, oxaliplatin and Modified de Gramont). Doses in this regimen are dependent on patient age and WHO performance status.
- Regimen D: IrMdG plus cetuximab
- Regimen E: IrMdG plus bevacizumab

Further details on each of these regimens are in Appendix I.

8.2 Introduction

- Following randomisation, patients should start treatment as soon as possible (see section 8.3 for details of acceptable time windows)
- **Appendix I contains full details of the treatment regimens and dose modifications.**
- It is the responsibility of the treating consultant to ensure that the protocol treatment regimens are followed. In particular:
    - Renal, hepatic and bone marrow function and magnesium must be monitored carefully, and dose-adjustments made as indicated (see appendices I and VI) ○ Dose modifications should only be made after consulting the written protocols (if in doubt, please discuss with the MRC CTU)
- Dose-banding of drugs to ±5% is acceptable. Each centre should inform the MRC CTU of its intention to dose band before recruitment commences and apply dose banding to all patients
- **Obese patients (approx. BMI >30) should be dosed according to Appendix II**

8.2.1 Bevacizumab-specific pre-treatment tests

- Blood pressure should be measured before each cycle. If BP is raised at baseline, patient should commence anti-hypertensive medication until controlled, prior to receiving bevacizumab treatment. A delay of up to 3 weeks is acceptable.
- A 24 hour urine collection should be performed before starting cycle 1. For each following cycle, monitoring of proteinuria will be assessed by dipstick urinalysis up to 3 days prior to each bevacizumab dose.
- Details on dose modifications related to these toxicities are in Appendix I.

8.3 Start of Chemotherapy

- If the molecular results have been delayed by more than 10 working days and the results are expected to be available within a further 10 working days as the block has been received at the designated laboratory, the patient can receive MdG for cycle 1 only as per regimen B. Please refer to Appendix I for treatment information. Once the results are available, the patient should be randomised immediately. **Please note that the 5FU dose may be lower if the patient is subsequently randomised to a different regimen.** (See Section 6.3.2).
- Treatment should start as soon as possible after randomisation
- 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 5 weeks of the CT scan used to assess their disease
- If the line cannot be fitted sufficiently quickly, the first cycle of treatment may be given as an inpatient

8.4 Treatment Duration and Breaks

8.4.1 Treatment Duration

Patients will continue on trial on their allocated regimen (with dose reductions as required) until at least 24 weeks of treatment have been received or until progressive disease, if sooner. After 24 weeks of treatment, patients may have a break of up to a maximum of 6 weeks before restarting trial treatment. It will not be possible to provide cetuximab or bevacizumab antibodies for restarting treatment following a prolonged (>6 week) treatment break. See 8.4.2 for further details on treatment breaks.

8.4.2 Treatment Breaks

During the first 24 weeks of trial therapy patients should continue on treatment with no more than a 3-week interval off treatment (i.e. 5 weeks between day 1 of two cycles) for any reason. If a treatment break of longer than three weeks occurs before 24 weeks, the patient is considered off trial treatment.

After 24 weeks of treatment, patients may have a break of up to a maximum of 6 weeks before restarting trial treatment. It will not be possible to provide cetuximab or bevacizumab antibodies for restarting treatment following a prolonged (>6 week) treatment break.

Progression free survival will be the key outcome measure of the full FOCUS 3 study so clinicians are encouraged to use a consistent approach to treatment duration whichever treatment plan the patient is receiving. Treatment may be continued until progressive disease is identified on radiological grounds (RECIST) (Appendix VIII), or the development of cumulative toxicity, or because of patient choice to stop chemotherapy, or discontinued for an

'off treatment' break after 24 weeks. Patients will be evaluated with a CT scan every 12 weeks to assess radiological evidence of progression. If a patient has progressed at a 12 week scan, following a 6 week break in chemotherapy, please contact the FOCUS 3 Trial Manager to discuss further treatment options for that patient.

8.4.3 Stopping treatment

Cetuximab and bevacizumab will be continued if chemotherapy is stopped because of chemotherapy-associated toxicity or patient choice, but should be discontinued on evidence of disease progression or unacceptable antibody-related toxicity.

If patients have stopped treatment due to toxicity, clinician or patient choice and progress off-treatment they may be considered for second-line therapy or reuse of the chemotherapy component of trial therapy off trial. Refer to Section 10.1 for further information.

8.5 Further chemotherapy after FOCUS 3 protocol therapy

When there is disease progression after FOCUS 3, options of further chemotherapy, entry into a clinical trial or purely symptomatic treatment may be considered.

8.6 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. resection of metastatic disease, palliative radiotherapy, bypass surgery).
- If appropriate, FOCUS 3 trial treatment may be continued after the other treatment, assuming the reason for the other therapy was not due to progression of disease while on FOCUS 3 treatment.
- If protocol treatment is stopped due to a medical or surgical intervention such as liver surgery in patients who are responding (or with stable disease), these patients may continue on protocol treatment after their intervention. If any surgery is deemed to be curative leaving patients in a complete response state with no detectable tumour on radiological imaging, investigators can offer a maximum of 12 weeks of treatment, if clinically acceptable to the patients. These patients should be discussed with the MRC CTU. However, please note that patients with operable liver metastases at the start of chemotherapy are not eligible for this trial.

8.7 Drug Supplies

- 5-fluorouracil, folinic acid, irinotecan and oxaliplatin will be used from commercially available stock.
- Bevacizumab will be provided free of charge by Roche. Further details on the storage and preparation of bevacizumab are available in the bevacizumab SPC. Details on the procedures for ordering bevacizumab are provided in the Pharmacy Pack on accreditation.
- Cetuximab will be provided free of charge by Merck KGaA. Further details on the storage and preparation of cetuximab are available in the cetuximab SPC. Details on the procedures for ordering cetuximab are provided in the Pharmacy Pack on accreditation.
- All support medication such as antiemetics, loperamide, ciprofloxacin will be commercially available stock.
- Accountability logs for bevacizumab and cetuximab will be provided.
- The guidelines in this protocol are in line with manufacturers' recommendations at the time of writing, but SPCs are updated from time to time. Up-to-date SPCs are posted on the Medicine Guide website (http://emc.medicines.org.uk/).
- All drugs are licensed products and are being used within their licensed indications except for the use of irinotecan and oxaliplatin in the combination IrOxMdG and cetuximab. Details of reconstitution can be found in the SPCs for each drug, (http://emc.medicines.org.uk/).

8.8 Accountability and unused drugs

- The trial pharmacist will sign a document to confirm that local hospital systems are in place to cover drug ordering, drug receipt, drug storage and dispensing, and will enable accurate traceability of all trial drugs.
- Full drug accountability records must be maintained for bevacizumab and cetuximab which will be provided in the Pharmacy Pack at accreditation. All drug receipts, dispensings, and destructions should be recorded on the logs provided.
- No special accountability arrangements are required for the commercial stock used in the trial, however there should be pharmacy records, such as aseptic unit worksheets, detailing; patient name/identifier, date and quantity dispensed, batch number of drug, as per local policy.
- Used or partially used vials of drug should be disposed of at site according to local policy.
- Details of how to destroy expired or unused bevacizumab or cetuximab at the end of the trial will be given in the Pharmacy Information Pack.

- The number of capecitabine tablets taken will be recorded by the patient on the diary card that they complete. The number of tablets not taken can be completed on the treatment CRF from this data.

8.9 Treatment data collection

Every administration of the trial treatment must be recorded in the appropriate part of the CRF. In addition, reasons for any dose delays, reductions or omissions or for permanent discontinuation of trial treatment must be documented in the appropriate part of the CRF.

8.10 Non-trial treatment

8.10.1 Medications permitted

All patients receiving irinotecan should take home supplies of loperamide and ciprofloxacin. Patients should also receive instruction on their use.

- Loperamide: 4mg at first loose stool, then 2mg every 2 hours until 12 hours after the last stool, up to a maximum of 48 hours.
- Ciprofloxacin: If diarrhoea lasts > 24 hours, ciprofloxacin 500mg bd should be added. Supply 5 days treatment.

GCSF (Granulocyte colony-stimulating factor) is permitted for patients with neutropenia as a secondary prophylaxis following the appropriate dose reduction.

8.10.2 Concomitant Medications

- The following medications may interact with FOCUS 3 medications.
    - Allopurinol: may potentially reduce the effectiveness of 5-fluorouracil.
    - Cimetidine: may increase plasma concentrations of 5-fluorouracil.
    - Metronidazole: may increase the toxicity of 5-fluorouracil.
    - Inducers of CYP3A4 (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin): leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide. Concurrent administration should be avoided.
    - Inhibitors of CYP3A4 (e.g. ketoconazole): may lead to an increase in exposure to irinotecan and should be used with caution.
- Brivudine or sorivudine may produce a dangerous interaction with 5-fluorouracil and are contraindicated. These medications are not licensed in the UK but may be prescribed for viral infections in other countries.
- St. John's Wort (*Hypericum perforatum*) decreases SN-38 plasma levels. St. John's Wort should not be administered with irinotecan.
- There are no specific drug interactions documented with cetuximab or bevacizumab. 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).

8.10.3 Surgery on trial

For patients requiring surgery whilst receiving bevacizumab treatment, surgeons should be aware that there is an increased risk of impaired wound healing and careful consideration should be given to the benefits and risks of any potential operation.

9. ASSESSMENTS AND FOLLOW-UP

9.1 Trial Timelines

	Registration	Pre-randomisation	Pre cycle 1	6 weeks & 12 weeks	Each cycle when on chemo	Every 12 weeks	If any SAE occurs
Clinical evaluation	X●	X"			X*	X	X
FBC, U&Es, Mg, LFTs		X"			X* #		
CEA, CRP, LDH, ALKP, Albumin			X□	X			
Blood Pressure	X				X◊		
24 hour urine collection			X◊				
Proteinuria					X◊		
Blood for DNA		X‡					
Tumour block sent to lab	X						
GFR†		X"					
NCI CTC scores		X			X		X
WHO PS	X●	X"				X	
CT Scan		X¶				X	
RECIST response + clinical benefit status						X	
CRFs to be returned to MRC CTU (Form No.)	Registration form (1)	Randomisation form (2) Pre-treatment form (3)		Additional Blood Tests (11)	Treatment Form (4) at each cycle	Progress Report Form (5)	SAE Report Form (6)

- ● within 1 week prior to registration
- " within 1 week prior to randomisation
- * within 3 days prior to starting chemotherapy
- ¶ within 5 weeks prior to starting chemotherapy
- ◊ only required for patients receiving bevacizumab
- † not required if Cockcroft estimate Creatinine Clearance ≥30 ml/min
- ‡ not required if patient has withheld consent for molecular research
- # Mg to be measured for all patients showing possible symptoms of hypomagnesaemia
- □ Pre-treatment – on any blood sample within 1 month of starting treatment

CEA, CRP, LDH, albumin and ALKP should be collected at baseline, 6 weeks and 12 weeks and recorded on the Additional Blood Test CRF.

9.2 Data Return Timelines

- **Registration CRFs** should be completed prior to registration and posted immediately.
- **Randomisation and Pre-treatment CRFs** should be completed before the patient is randomised and sent immediately afterwards.
- **Treatment CRFs for cycles 1 – 3** should be completed fortnightly following each cycle (Weeks 2, 4 and 6) and sent to the MRC immediately so the doses can be checked.
- All subsequent **Treatment CRFs** should be sent 6 weekly.
- **Progress CRFs** are due 12 weekly and must be sent within one month of being due.
- **SAEs CRFs** must be sent within one working day of site becoming aware of the event.

9.3 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 NHS 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 institutions.

9.4 Loss to follow-up

Every effort should be made to follow-up patients who have been randomised. Patients should, if possible, remain under the care of an oncologist for the duration of the trial. If the care of a patient is returned to the General Practitioner, it is still the responsibility of the investigator to ensure that the follow-up data required by the protocol is collected and reported.

10. PATIENT WITHDRAWAL OR TRANSFER

10.1 Patient Withdrawal

In consenting to the trial, patients are consenting to trial treatment, trial follow-up and data collection. However, a patient has the right to withdraw consent for participation in any aspect of this trial at any time. 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. Clear distinction must be made as to whether the patient is withdrawing from trial treatments/procedures whilst allowing further follow-up, or whether the patient refuses **any** further trial treatments/procedures **and** follow-up participation. In all instances the staff at the institution must inform the MRC CTU immediately in writing.

10.1.1 Withdrawal from (stopping) trial treatment

Patients may be withdrawn from treatment for any of the following reasons:-

- Disease progression whilst on therapy.
- Patient withdraws consent for further treatment.
- Unacceptable toxicity.
- Intercurrent illness which prevents further treatment.
- Any change in the patient's condition which justifies the discontinuation of treatment in the clinician's opinion.

Patients should however remain in the trial, following the same visit schedule, for the purposes of follow-up and data analysis.

10.1.2 Withdrawal of consent to all further participation in the trial

If a patient explicitly states their wish not to contribute further data to the study, the MRC CTU should be informed in writing of the patient's decision. Data up to this time can be included in the trial if it is anonymised. Further follow-up is possible only through the usual NHS mechanisms (e.g. ONS), providing the patient consented to this when joining the trial. Patients who withdraw from the trial for other reasons have previously consented to follow-up in the trial.

Patients should be given every encouragement to adhere to protocol treatment and follow-up, in order to reduce biases. However, a patient has the right to withdraw consent for participation in any aspect of this trial at any time. They may refuse to take certain treatments, attend scheduled follow-up visits, or move from the area.

10.1.3 Patient transfers

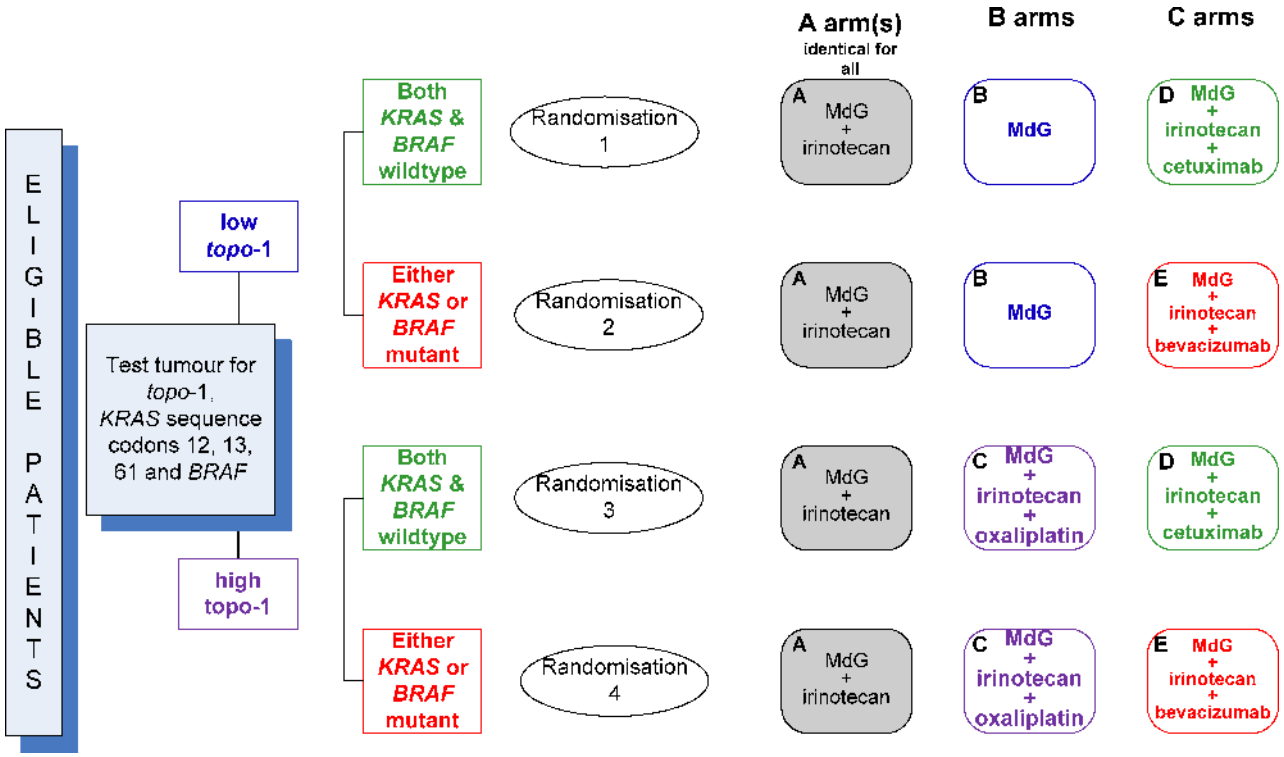
For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient. A copy of the patient CRFs will need to be provided to the new site. The patient will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. If the investigator moves, appropriate arrangements should be made to arrange for trial follow-up to continue at the institution.

11. STATISTICAL CONSIDERATIONS

11.1 Method of Randomisation

The trial design includes 4 individual randomisations based on the biomarkers in the patients' tumours. Patients will be registered at the MRC CTU on the day they provide written informed consent for the release of a tumour tissue block. Upon successful and timely analysis of the two biomarkers, patients will be allocated to one of 4 subgroups for randomisation (See Figure 11.1). All randomisations will be stratified by standard clinical prognostic factors.

Figure 11.1: Randomisation Sub-groups



11.2 Outcome Measures for Feasibility Study

The outcome measures for the feasibility study are process outcomes, and as such are multiple. While the sample size calculation is based around the first primary end-point listed below, both of the co-primary end-points will contribute important information to guide an assessment of the feasibility of this type of study design.

11.2.1 Primary

- Of those patients randomised, in how many patients was the interval between registration and the provision of results to the investigator to allow randomisation less than or equal to 10 working days
- Of those patients randomised, in how many patients was the interval between registration and the date of randomisation less than or equal to 10 working days

11.2.2 Secondary

- Time from date of requesting hospital pathology laboratory to release a tumour sample to date of receipt of sample at central laboratory (Leeds or Cardiff)
- Of those patients registered but not subsequently randomised, for what reasons did randomisation not occur (insufficient sample material, technical failure, unacceptable delay, patient refusal, patient ineligibility)
- Time from registration consent to start of treatment
- In all randomised patients, time from the provision of *KRAS*, *BRAF* and topo-1 results to the investigator to allow randomisation to the date of randomisation.
- Reproducibility of *KRAS* and *BRAF* mutations and topo-1 results between laboratory centres and methodological problems identified
- Distribution frequencies of topo-1 expression and *KRAS* and *BRAF* mutation analysis and the distribution of patients between sub-groups to inform power calculations for the main study
- Costs of the molecular testing
- Toxicity, response rates and progression free survival (PFS) of the different regimens in the molecular subgroups
- Attitudes of patients to study design, the consent process and refusal rates for trial entry

11.2.3 Translational:

- Frequency of EGFR gene amplification on FISH, PI3K mutation, PTEN loss on IHC, amphiregulin and epiregulin mRNA, protein assessment and evaluation of impact on the use or further investigation of these markers in the main study

11.3 Outcome Measures for Definitive Study

- In patients with low topo-1 tumours, to confirm that FU alone is non inferior to IrFU. **(B vs. A)** (See Figure 11.1).
- In patients with high topo-1 tumours, the addition of oxaliplatin to IrFU is superior to IrFU alone. **(C vs. A)**
- In patients with both *KRAS*^{wt} and *BRAF*^{wt} tumours the addition of cetuximab to chemotherapy is superior to chemotherapy alone. **(D vs. A)**
- In patients with either *KRAS* mutant or *BRAF* mutant tumours the addition of bevacizumab to chemotherapy is superior to chemotherapy alone. **(E vs. A)**

11.4 Sample Size

11.4.1 Feasibility study

A total of 240 patients will be recruited into the feasibility study and a 95% confidence interval for the proportion of samples processed within 10 working days will be calculated. With 240 patient samples, if 226 or more are processed within 10 working days we can reliably say that the turnaround rate is unlikely to be less than 90% (i.e. the lower 95% confidence limit would exclude rates below 90%). If 206 or fewer blocks are processed within 10 working days we could reliably say that we would not achieve a turnaround rate of 90% (i.e. the upper 95% confidence limit would exclude 90%). If we had good evidence of a return rate of less than 90% during the trial then remedial action would be required.

240 patients will also allow us to gain useful multicentre information on all of the above points of feasibility, as well as on the safety of the treatment regimens. 60 patients will be included in each randomisation, with 20 patients in each arm. Patients will be treated on defined clinical protocols with CT scans for assessment of response at 12 weekly intervals. It is anticipated that the patients that participate in the feasibility study will also be included in the analysis of the definitive trial.

11.4.2 Primary Hypotheses of the Definitive Trial

There are four hypotheses that will be addressed in the definitive trial, although these may change with emerging data. These four hypotheses have also dictated the design of the feasibility study. The outcomes described in this section will not be answered during the feasibility stage but the randomised feasibility data may be included in the subsequent full trial. The design, control and investigational arms and molecular selection criteria may all change in the definitive trial in the light of emerging data. This section shows the principles behind the current design and works through the statistical implications of the definitive study if it is to proceed on the current design.

The definitive trial objectives are as follows:

Hypothesis 1: To confirm that in low topo-1 expressing tumours, the non-inclusion of irinotecan to FU (MdG) alone does not lead to worse clinical outcomes i.e. that FU is non inferior to IrFU (MdG + irinotecan). Test cohorts: (B vs A in randomisation 1 and randomisation 2).

Figure 11.2: Hypothesis 1 - Low topo-1 expressing tumour randomisation

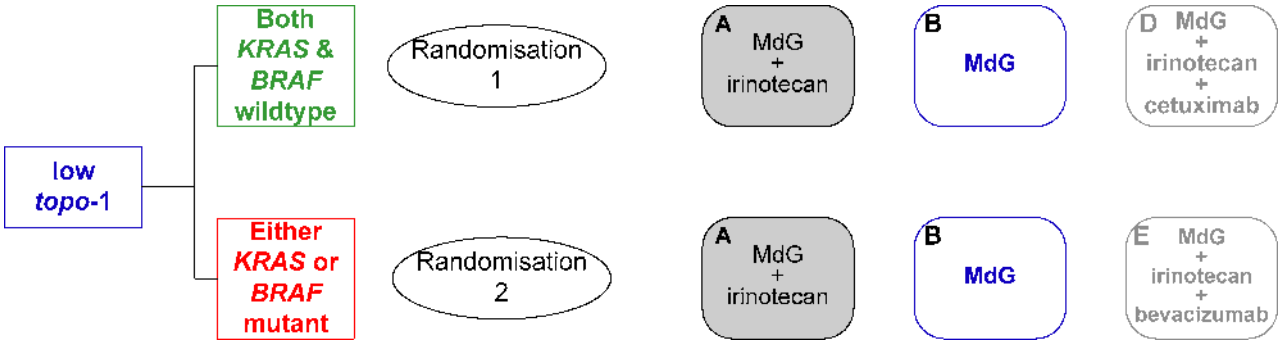
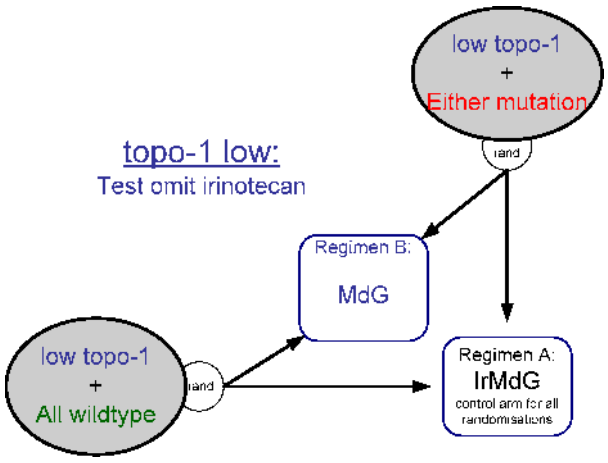


Figure 11.3: Hypothesis 1 – Alternative diagram



- 5FU monotherapy as first-line treatment is controversial, but both FOCUS and CAIRO trials[2,35] have reported non-inferiority of 5FU monotherapy compared with combination first-line chemotherapy, assuming other agents (irinotecan and oxaliplatin) are available subsequently, as will be the case in this trial.
- The omission of irinotecan allows the 5FU dose to be escalated, and avoids the toxicity and cost of irinotecan in first-line usage.

Hypothesis 2: In patients with high topo-1 expressing tumours, the addition of oxaliplatin to IrFU will provide a PFS benefit. Test cohorts: (C vs A in randomisation 3 and randomisation 4)

Figure 11.4: Hypothesis 2 - High topo-1 expressing tumour randomisation

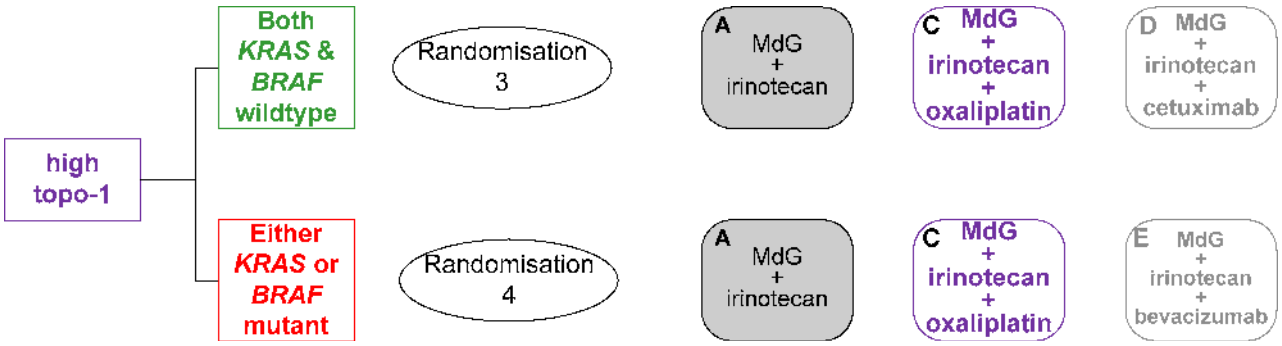
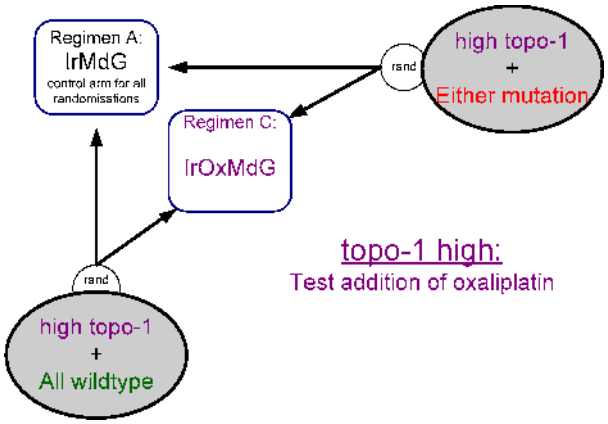


Figure 11.5: Hypothesis 2 – Alternative diagram

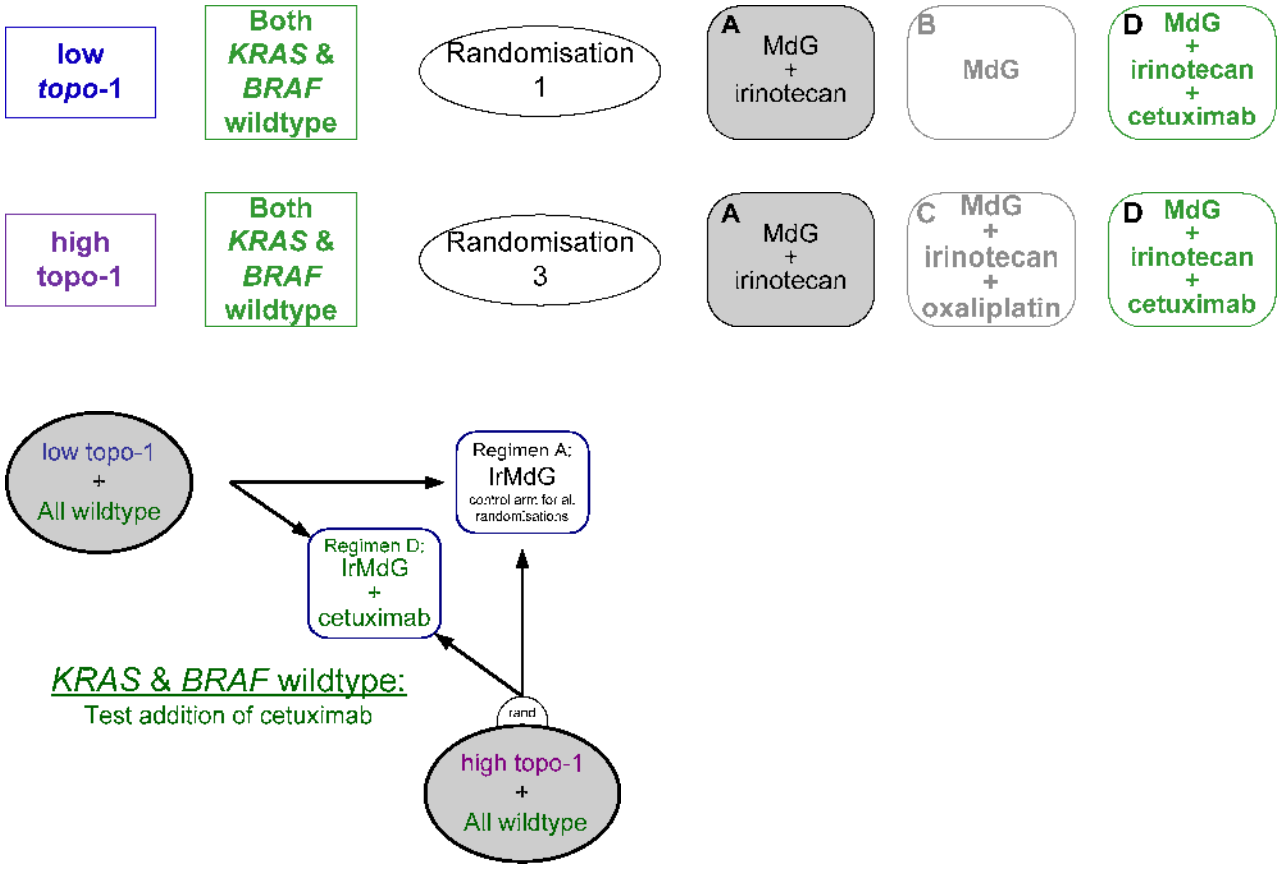


- FOCUS data demonstrated benefit of FU + irinotecan and of FU + oxaliplatin separately over FU alone in this cohort[6]. There is no evidence to indicate that using all three drugs together will be more beneficial, but that is our hypothesis.
- The triple therapy (IrOxMdG)[11] has not been widely used in the UK but has been reported from studies in Europe and toxicity data will be collected in detail in the feasibility study.

Hypothesis 3: In *KRAS*^{wt} and *BRAF*^{wt} tumours, the addition of cetuximab to chemotherapy is superior to chemotherapy alone. Test cohorts: (D vs A in randomisation 1 and randomisation 3)

Figure 11.6: Hypothesis 3 - *KRAS* and *BRAF* wildtype expressing tumour randomisation

Figure 11.7: Hypothesis 3 – Alternative diagram



- The Crystal trial has already demonstrated the efficacy of adding cetuximab to 5FU and irinotecan in a group of patients whose tumours were retrospectively analysed for *KRAS* mutational status. The hazard ratio for PFS in the wildtype population was shown to be 0.851, and the median PFS was improved by 1.5 months (8.4 to 9.9 months). This trial will prospectively validate that finding.
- It is not proposed to test the 4 drug combination of IrFU + oxaliplatin + cetuximab, as this is likely to result in excessive toxicity.

Hypothesis 4: In patients with *KRAS* or *BRAF* mutant tumours, who are unlikely to respond to EGFR inhibition, a different targeted approach with the addition of bevacizumab to chemotherapy is superior to chemotherapy alone. Test cohorts: (E vs A in randomisation 2 and randomisation 4).

Figure 11.8: Hypothesis 4 - *KRAS* or *BRAF* mutant expressing tumour randomisation

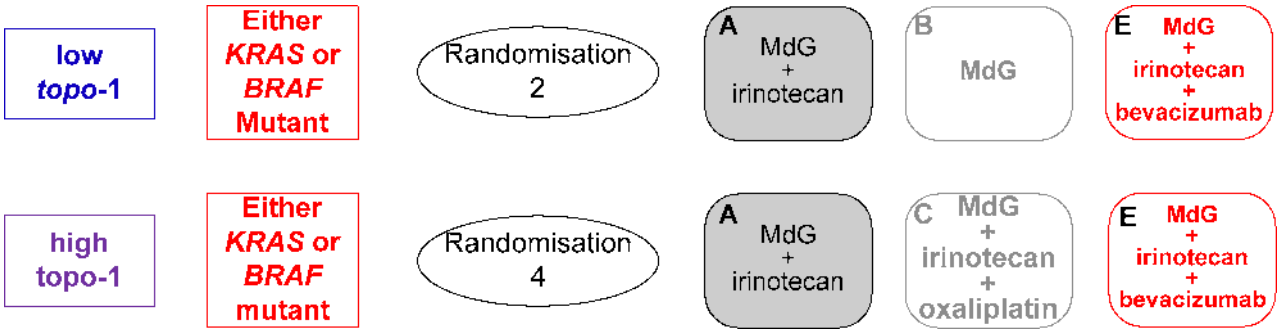
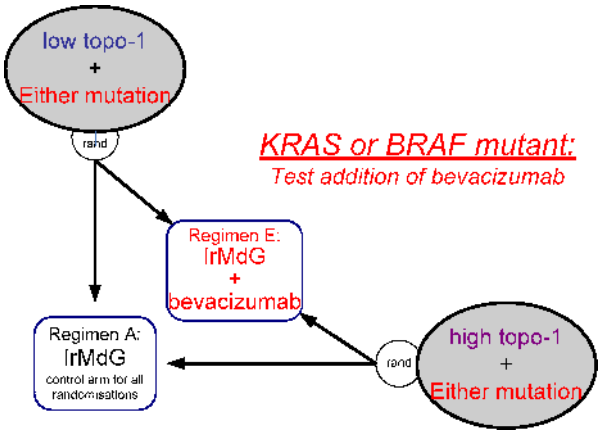


Figure 11.9: Hypothesis 4 – Alternative diagram



- There is no specific rationale for a biologically targeted therapy in this group at present. We propose the use of bevacizumab in this subgroup, by exclusion, as discussed above (section 3.1.3).
- There is no published phase III trial of irinotecan plus infusional 5FU +/- bevacizumab and only 34 patients from the Hurwitz study were known to be *KRAS* mutant, so outcomes in this group will be novel[43].

11.4.3 Definitive trial

Sample Size Calculation for Hypothesis 1 (Non-inferiority Question)

- Using a 1-sided log-rank test, a significance level of 0.05 and power of 90%, a total of 1000 patients are required to reliably exclude a difference worse than 6% in 1-year PFS from 17% to 23% (Hazard Ratio (HR) =1.21). Approximately 1000 patients, means randomisation of approximately 250 patients into each of the 4 arms contributing to this comparison.
- A non-inferiority bound of 1.21 for the HR is equivalent to excluding an absolute difference in median PFS of 1.4 months (or approximately 6 weeks).

Sample Size Calculation for Hypotheses 2-4 (Superiority Questions)

- With 1000 patients available for each comparison (250 in each arm), we will have 90% power to detect an 8.3% advantage in PFS at 1 year (HR=0.79). This is based on a 2-sided log-rank test and significance level = 0.02.
- A HR of 0.79 is equivalent to an absolute improvement in median PFS of 2.1 months (or approx. 9 weeks).

Overall sample size for the definitive trial based on these calculations is 3000 patients. However, this calculation does not take into account the proportions of patients who are both *KRAS* and *BRAF* wildtype : *KRAS* or *BRAF* mutant or high topo-1 : low topo-1 and therefore will be recalculated with these assumptions included following completion of accrual to the feasibility trial.

These sample size estimates will be revised prior to the commencement of the definitive study.

11.5 Interim Monitoring and Analyses

As this is a feasibility trial, no interim analyses are planned.

11.6 Analysis Plan

Both co-primary outcome measures will be reported as proportions of total randomised patients with 95% confidence intervals. Further information on the primary analyses of secondary outcome measures is detailed in the Statistical Analysis Plan that is available on request from the MRC CTU.

12. TRIAL MONITORING

12.1 Risk assessment

The MRC CTU has performed a risk assessment to assess the impact of trial participation on the rights and safety of patients, the reliability of trial results and the impact of trial results on the research site leading the trial. This has guided the development of procedures in the trial with respect to informed consent, confidentiality and trial monitoring which are recorded in separate document.

12.2 Monitoring at MRC CTU

The MRC CTU will conduct day-to-day central monitoring of the trial. The MRC CTU staff will:

- Check that participating centres have confirmed that they have an up-to-date trial master file
- Check centres adhere to the current version of the protocol
- Review source documents centrally (e.g. pathology reports, consent forms) and on-site during monitoring visits to confirm patients' existence
- Perform data entry (database) checks for validity and consistency
- Query missing or questionable data with the centre, and return for correction or clarification via a data query form
- Check that CRFs are completed by authorised persons listed on the FOCUS 3 accreditation form
- Check adverse events are reported in accordance with the protocol and CRF
- Review data return rates from centres at regular intervals
- Review recruitment rate during the recruitment period of the trial

12.3 Clinical site monitoring for cause

Each institution may be visited during the course of the FOCUS 3 trial. The MRC CTU will give the responsible investigator adequate notice of the monitoring visit to allow adequate time, space and staff for these visits. The standard operating procedures (SOP) for monitoring are available from the MRC CTU. After the monitoring visit the monitor will complete a site visit report. This report will be circulated to the TMG for comment. Once the TMG have reviewed the report and agreed on any recommendations the monitor will finalise the report and send a copy to the Principal Investigator (PI) at the site. A copy will also be sent to the CI for the trial and another copy will be kept in the MRC CTU FOCUS 3 master file.

12.3.1 Direct Access to Data

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data/documents as required. Patients' consent for this is obtained as part of the consent process.

12.3.2 Quality Assurance and Quality Control of Data

The data collected will be entered into the study database from the original CRF received from the site. The site will retain a copy of the CRF. If investigator input is required to clarify or correct any missing, ambiguous or inconsistent data, the Data Manager will generate a data query form. The Data Manager will send this form to the Research Nurse at the site for completion. When the completed data query form is returned to data management, the data on the clinical database will be corrected accordingly.

13. SAFETY REPORTING

ICH GCP requires that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol. Section 13.1 lists definitions, section 13.2 gives details of the institution/investigator responsibilities and section 13.3 provides information on MRC CTU responsibilities.

13.1 Definitions

The definitions of the EU Directive 2001/20/EC Article 2 based on ICH GCP apply in this trial protocol. These definitions are given in Table 13.1.

Table 13.1: SAE Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial 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 to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (or Investigator Brochure) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: . results in death . is life-threatening* . requires hospitalisation or prolongation of existing hospitalisation** . results in persistent or significant disability or incapacity . consists of a congenital abnormality or birth defect

13.1.1 Clarifications and Exceptions

*The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

13.1.2 Trial Specific Exceptions to Expedited SAE Notification and Reporting:

Disease progression or death as a result of disease progression are not considered to be SAEs and should be reported on the Progress Form and Death Report Form respectively.

Due to the seriousness of the disease in this study, the following situations that fulfil the definition of an SAE are excluded from expedited notification on an SAE form and should be reported on the treatment and progress forms (Forms 5 and 6).

- Elective hospitalisation to simplify treatment or procedures
- Elective hospitalisation and surgery for treatment of disease or its complications e.g. bowel obstruction.
- Elective hospitalisation for pre-existing conditions that, in the investigator's opinion, have not been exacerbated by trial treatment.

13.1.3 Pregnancy

Pregnancy occurring during a patient's participation in the FOCUS 3 trial should be reported on an SAE form and sent to the MRC CTU within the timelines set out above. The outcome of the pregnancy should be carefully followed with updated information sent to the MRC CTU.

13.2 Institution/Investigator Responsibilities

All non-serious AEs/ARs, whether expected or not, should be recorded in the toxicity (symptoms) section of the Progress Form and/or Treatment Forms, and sent to the MRC CTU within one month of the form being due. SAEs/SARs should be notified to the MRC CTU as described below.

The severity (i.e. intensity) of all AEs/ARs (serious and non-serious) in this trial should be graded using the NCI CTCAE v3.0. A version summarised for this trial is available in Appendix IX (the full list is available at http://ctep.cancer.gov/reporting/index.html).

A flowchart is given at the end of this section to help explain the notification procedures (

Figure 13.1). Any questions concerning this process should be directed to the MRC CTU in the first instance.

13.2.1 Investigator Assessment

(a) Seriousness

When an AE/AR occurs the investigator responsible for the care of the patient must first assess whether the event is serious using the definition given in Table 13.1. If the event is serious and not exempt from expedited reporting, then an SAE form must be completed and faxed to the MRC CTU.

(b) Causality

The Investigator must assess the causality of all serious events/reactions in relation to the trial therapy using the definitions in Table 13.2. There are 5 categories: unrelated, unlikely, possible, probable and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as a SAE. If the causality is assessed as either possible, probable or definitely related, then the event is classified as a SAR.

Table 13.2: Definitions of causality

Relationship	Description	Event Type
Unrelated	There is no evidence of any causal relationship	SAE
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	SAE
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

(c) Expectedness

If the event is a SAR the Investigator must assess the expectedness of the event. The definition of an unexpected adverse reaction (UAR) is given in Table 13.1. Please see Appendix X for a list of expected toxicities associated with the drugs being used in this trial. If a SAR is assessed as being unexpected it becomes a SUSAR.

(d) Notification

The MRC CTU should be notified within one working day of the investigator becoming aware of an event that requires expedited reporting. Investigators should notify the MRC CTU of all SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration. SARs and SUSARs must be notified to the MRC CTU indefinitely (i.e. no matter when they occur after randomisation).

Notification Procedure:

1. The SAE form must be completed by the Investigator (consultant named on the signature list and delegation of responsibilities log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator the form should be completed and signed by a member of the site trial team. The responsible investigator should subsequently check the SAE form, make changes as appropriate, sign and then re-fax to the MRC CTU as soon as possible. The initial report shall be followed by detailed, written reports as appropriate.

2. Send the SAE form by fax to the MRC CTU. Fax Number: 0207 670 4818

3. Follow-up: Patients must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. Follow-up information should be noted on a further SAE form by ticking the box marked 'follow-up' and faxing to the MRC CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient must be identified by trial number, date of birth and initials only. The patient's name should not be used on any correspondence.

4. Staff at the institution must notify their local research ethics committee (LREC) of the event (as per the institutions standard local procedure).

SAE NOTIFICATION

Within one working day of becoming aware of an SAE,
please fax a completed SAE form to the MRC Clinical Trials
Unit on:
Fax: 020 7670 4818

13.3 MRC CTU Responsibilities

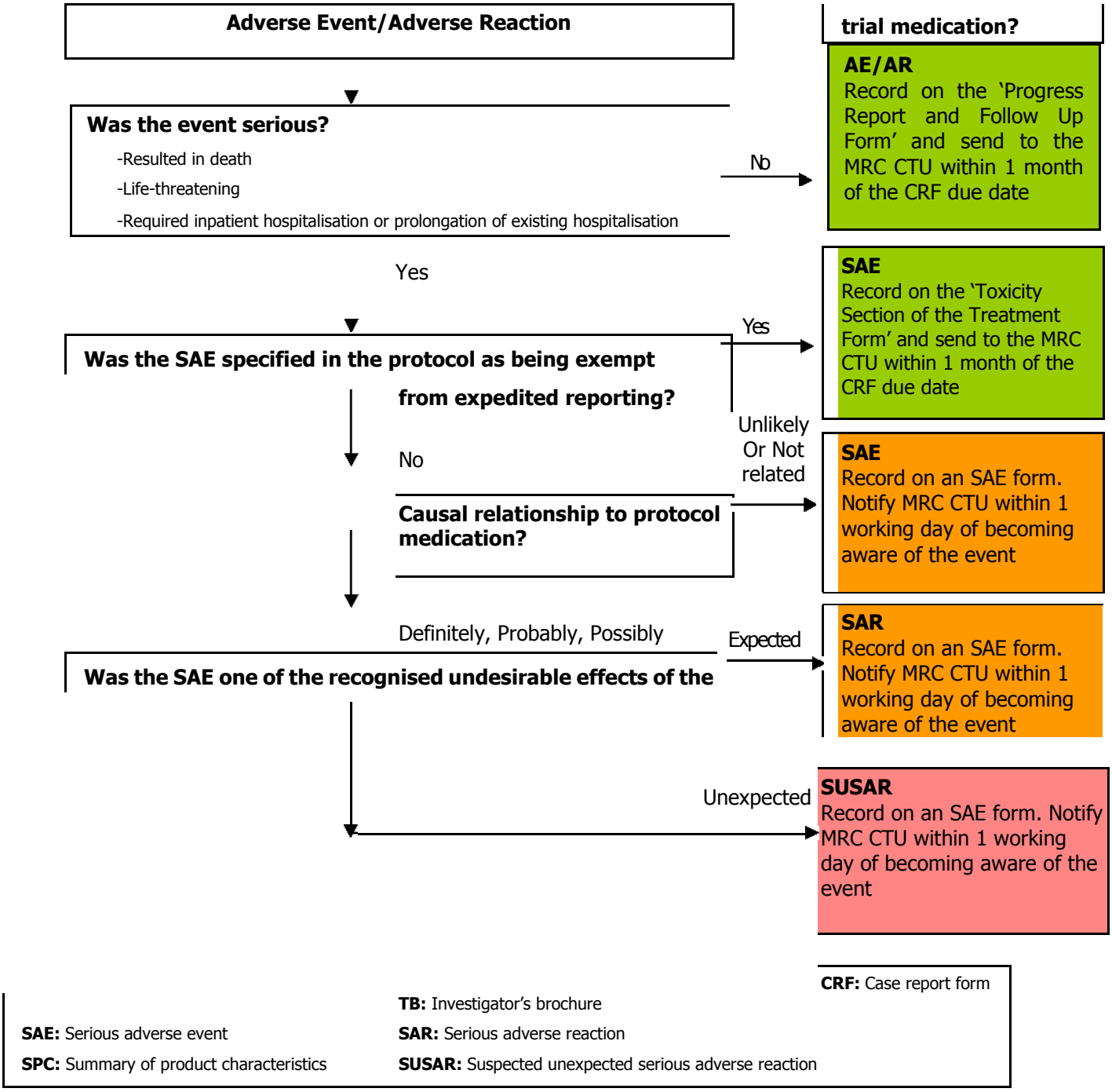
Medically qualified staff at the MRC CTU and/or the Chief Investigator (or a medically qualified delegate) will review all SAE reports received. The causality assessment given by the local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided in any subsequent reports.

The MRC CTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authority (MHRA) and NRES.

The MRC CTU will also keep all investigators informed of any safety issues that arise during the course of the trial.

Merck KGaA and Roche will also be notified of all reportable (serious and unexpected and drug related/unknown relationship) events. MRC CTU will also provide both companies with a copy of the annual safety report (line-listing of SARs and SUSARs).

Figure 13.1: Safety Reporting Flowchart



14. ETHICAL CONSIDERATIONS & APPROVAL

14.1 Ethical considerations

Participation in a randomised controlled trial means that the patient and clinician are not able to choose all aspects of patient treatment but do choose to be randomised. 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. Patients will receive different treatments and the potential toxicities associated with each treatment are different; this will all be explained to patients before they consent to randomisation into the trial. The risk of experiencing any toxicity is set against the potential benefits of increased effectiveness and reduced toxicity provided by individually targeted therapy.

Each patient's consent to participate in the trial should be obtained after a full explanation of the treatment options, including the conventional and generally accepted methods of treatment. The investigator must ensure that patient's anonymity will be maintained and that their identities are protected from unauthorised parties. On CRFs patients will not be identified by their names, but by an identification code, date of birth and hospital number.

Patients randomised to Regimen B will receive 5FU only, rather than the standard treatment combination of irinotecan and 5FU. Results from the FOCUS study[2] have shown that that the staged approach of initial single-agent treatment upgraded to combination when required is not worse than first-line combination. By removing irinotecan from the combination, the patient will not experience the associated toxicities. Patients randomised to regimen D are at risk of additional skin toxicity. This is set against the potential benefits of increased effectiveness of combined chemotherapy with cetuximab in patients who are *KRAS* and *BRAF* wildtype. Patients in regimen E are at risk of bevacizumab specific toxicity (hypertension, proteinuria). This has also been balanced against the potential benefit of bevacizumab.

The study will abide by the principles of the Declaration of Helsinki.

14.2 Ethical approval

The protocol has a Favourable Opinion from Wales Research Ethics Committee. A copy of local R&D approval and of the PIS and Consent Forms on local headed paper should be forwarded to MRC CTU before patients are entered. The patient's informed 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.

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 clinician 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 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 further treatment.

A statement of MRC policy on ethical considerations in clinical trials of cancer therapy, including the question of informed consent, is available from the MRC Head Office web site (http://www.mrc.ac.uk).

For details of any changes since the original version of the protocol that have been NRESapproved, see section 22.

15. REGULATORY ISSUES

This is a trial of Investigational Medicinal Products (IMPs) and has therefore been registered with the MHRA and granted a Clinical Trial Authorisation (CTA). The CTA reference is 00316/0236/001-0001.

16. TRIAL CLOSURE

For the purposes of regulatory requirements, the end of the trial is defined as 12 weeks after the date of the last treatment visit for the last patient undergoing protocol treatment. This will be followed by a non-interventional phase of long-term follow-up, which will continue for a minimum of three years after entry of the last patient.

17. INDEMNITY

The sponsor of the trial is the Medical Research Council (MRC).

The Medical Research Council ("the MRC") is not insured but it has indemnity arrangements in place such that public funding is provided to meet claims.
The likely scenarios in which the MRC might face claims for damages are set out below. The MRC also sets out below instances where it might make *ex gratia* payments without any admission of liability.

1. The MRC accepts that it might face claims for damages in cases where:

a) it sponsors the research: (that is it has responsibility for securing the arrangements for initiating, managing and financing the study including any research carried out by its Units); **and**

b) the MRC, or any of its employees, or any person formally acting with the MRC's authority, have been negligent or have failed to adhere to the relevant guidelines/guidance, legislation or procedure on good practice in relation to medical research; **and**

c) That negligence or failure to adhere to legislation, etc has caused or has materially contributed to the personal injury suffered by the individual making the claim.

2. In relation to instances where the MRC is the sponsor of research the MRC may consider making an ex gratia payment when a significant adverse reaction in the form of a personal injury has occurred which is likely to have been caused by, or materially contributed to, by participation in a research study. In deciding whether to make such a payment, the MRC will not require the research participant to demonstrate that the personal injury has been caused by a breach of any duty of care that may have been owed by the MRC.

18. ANCILLARY STUDIES

18.1 Qualitative Research

18.1.1 What are the opinions of patients waiting to start treatment?

Attitudes of patients to the waiting period necessary for tumour testing, before allocation of treatment, will be evaluated by one-to-one semi structured interview in a subgroup after starting therapy. This methodology will collect richer data than could be achieved by questionnaire, albeit in far fewer patients. The consent form for the interview is in Appendix XII.

18.1.2 Arranging interviews

Recruitment to this part of the study will be limited to 20-30 patients. Centres will therefore be managed geographically in order to be reasonably local to the qualitative interviewer. Once a patient has been consented to the interview, the patient will be contacted by the qualitative researcher to arrange the most suitable time and place for the interview. This may be at clinic or at the patient's home, according to patient preference.

18.1.3 The interviews

An experienced interviewer will be appointed and supervised by Annmarie Nelson, Study Qualitative Research Advisor. The interviewer will receive additional training, if necessary. The interview team will develop a master interview schedule with questions and prompts, however, the interview is likely to evolve over time with the interview content developing in line with the interviewees' answers. The interviewers will digitally record the interview but will also make field notes (with the patient's permission) to record incidents occurring during the interview, non verbal communication, or reactions at the time of the interview. The interview is likely to last between 30 minutes and 1 hour. Ideally patients will be interviewed alone but, if they prefer, a carer may be present.

18.1.4 Data transfer and transcription

Interviewers will upload the digital media files onto a computer and files will be labelled with a study number. No identifiable data will be stored. Digital files will be emailed via a password protected attachment to Annmarie Nelson at the Wales Cancer Trials Unit (WCTU). The media files will be stored on a secure server. The transcriber at the WCTU will transcribe the interviews verbatim and the anonymised transcripts will be stored securely at the WCTU. The digital tapes from the interviews will be wiped as soon as they have been transcribed, and the anonymised transcripts will be used for analysis.

18.1.5 Data Analysis: Interpretative Phenomenological Analysis (IPA)

The analytic framework for this qualitative sub-study will be based on Interpretative Phenomenological Analysis (IPA). This approach, developed within psychology and rooted in phenomenology and symbolic interactionism, is increasingly used to address healthcare and quality of life research topics. The aim of IPA is to explore how patients make sense of their experiences, i.e. to understand the meaning that events or states have for patients based on their subjective accounts. It is also interpretative in the sense that the researcher's conceptions, and experience, as brought to the analysis, are also recognised. The data for this study will be collected from semi-structured interviews. The interview technique is an iterative process with each interview building on the recognition of themes of interest from the previous. For this reason, the same interviewer will be used for each centre.

IPA is based on an idiographic approach beginning with a single case as a basis to develop more general categories developed in a detailed case-by-case analysis. The transcripts will be systematically analysed in several stages:

- Preliminary reading. The first transcript is read line-by-line and annotated with initial comments.
- Early analysis. Initial comments are grouped into themes.
- Higher level abstraction. Connections between themes are developed until an organised master list and thematic account of the case is achieved.
- Subsequent transcripts. New themes are tested against the previous transcripts as non-recurring themes are tested against following transcripts. Connections across cases are noted to identify a set of superordinate themes for the group.

Results will be analysed for consistent themes. A coding framework for emergent themes will be developed and then validated and compared.

18.1.6 Reporting results

Results will be reported to the TMG as soon as a full analysis has been undertaken. This is likely to be before the end of the feasibility study.

18.2 Translational Research

A number of analyses will be performed using stored formalin fixed paraffin embedded material (FFPE) to further refine the predictive criteria for response to EGFR targeted therapy in *KRAS*^{wt} and *BRAF*^{wt} patients.

18.2.1 Tissue Microarray (TMA):

TMA has a proven role in efficient and effective assessment of IHC in trial series and has been used by this group effectively for FISH assessment. This collaborative group has extensive knowledge of TMA production and utilisation from the FOCUS and COIN trials. It is planned that duplicate TMAs will be created with three to six tumour cores (dependent on samples available) per trial patient. Each TMA will contain 120 cores plus controls, thus the total number of TMAs to be produced for the feasibility study will be 24 (maximum).

Planned investigations from TMA:

- **EGFR FISH:** There is debate in the scientific community with respect to the effect of EGFR gene copy number on response to EGFR targeted therapy. Much of this controversy arises through an attempt to pool polysomy (increase in chromosome number) and true EGFR gene amplification (increase in gene number) into a combined group. It is hypothesised that EGFR gene amplification results in sensitivity to EGFR targeted therapy, whilst polysomy with its inherent multiplication of multiple genes does not. The true rate of EGFR gene amplification is uncertain with series suggesting between 0% and 10%[25,46,52]. It will be important to assess this phenomenon in relation to other potential predictive markers in this study.

- **Phospho-EGFR:** Phosphorylations of the tyrosine kinase domain of EGFR indicates receptor activation and therefore function within the tumour cell. EGFR targeted therapy is evidently able to switch of this phenomenon and cause cell death. In vitro evidence suggests that tumours which demonstrate constitutive activation of EGFR are sensitive to EGFR targeted therapy, whilst, tumours that in their basal state do not utilise (have non-activated) EGFR will not respond to this therapy. A further cohort of tumours activates EGFR in response to chemotherapeutic agents such as 5-fluorouracil or irinotecan[47], a factor, which may correlate with topoisomerase expression or other yet unexplored pathways/proteins (i.e. thymidylate synthetase). It is hypothesised that within this study a cohort of *KRAS*^{wt} and *BRAF*^{wt} tumours will express pEGFR and be sensitive to EGFR targeted therapy in combination with chemotherapy, another cohort will not express pEGFR some of which will respond and some not. Identifying those tumours, which are potentially induced to utilising the EGFR in response to chemotherapy, will greatly assist in our ability to molecularly select patients for combination therapies.

- **Phospho-ERK:** A relatively robust phospho-antigen which can be assessed by IHC and is likely to correlate with *KRAS* mutation in the majority but not all cases[48]. Constitutive activation in *KRAS* wild type tumours is likely to give clues to tumours which will not respond to EGFR targeted therapy and may correlate with alternative mutations such as *BRAF*.

- **PTEN:** Is a regulatory protein, loss of which results in un-opposed AKT phosphorylation with resultant cell survival signalling and potential insensitivity to EGFR targeted therapy[31]. A reduction in PTEN protein is most frequently due to gene silencing through methylation as opposed to gene mutation in CRC[49,50].

- **Phospho-AKT:** IHC assessment has been fraught with difficulties, not least because of the limited half-life of this phospho-antigen, which is greatly affected by time from specimen removal to fixation. Despite this, evidence is still accruing for its role as a predictive marker for insensitivity to EGFR targeted therapy[51] and it will be important in this study to analyse the upstream pathways of AKT which may result in this constitutive activation (these include PTEN and PI3K).

Gene mutation assessment from FFPE extracted DNA:

PI3K mutation: Is evident in 10-34% of mCRC[40]; resulting in constitutive activation of AKT with resultant cell survival effects and resistance to multiple agents including EGFR targeted therapy. The combination of PTEN loss and PI3K mutation may explain a cohort of high pAKT expressing tumours with resistance to EGFR targeted therapy.

Ligand mRNA levels: Recent data has identified that about 30% of patients with metastatic colorectal cancer have elevated levels of the EGFR ligands amphiregulin and epiregulin[30]. These are usually present in low concentration, but in these patients (all of whom have KRAS wildtype in the tumour) appear to indicate a pathological mechanism of activation of the EGFR receptor which may be associated with high rates of response to EGFR inhibition.

The assessment of the above as potential predictive markers is essential to identify a pattern of mutation, activation and gene silencing which optimise our sensitivity and specificity of patient selection for molecularly targeted therapy. Many studies have looked at individual or dual markers in small case series; the data from this feasibility study will enable us to develop a more specific algorithm in patients from a RCT.

18.2.2 Blood Sample analysis

cfDNA Analysis: Cell free DNA (cfDNA) is a readily available, economic source of tumour-derived DNA, amenable to reliable detection of tumour specific *KRAS* mutations in mCRC patients. A sub-study will compare the relative sensitivity and reliability of using plasma derived cfDNA for mutation detection. Two methods are to be employed and compared, namely rtPCR using ARMs technology and pyrosequencing. These two methods of *KRAS* mutation analysis will be undertaken and compared between the clinical and experimental pharmacology group (CEP, Manchester) and the All Wales Molecular Genetics Laboratory (AWMGL, Cardiff).

The extraction of cfDNA and analysis of *KRAS* mutations will be measured according to strict standard operating procedures (SOPs) in batches of plasma samples shipped from the designated hospital sites to the Paterson Institute or to AMMGL. Both the specificity and concordance of mutations will be evaluated against data derived from FFPE material. The impact of blood sample collection from multiple hospital sites and the variability in results from two different laboratories working to identical SOPs will be tested.

Blood samples for germline DNA extraction will also be collected for identification or validation of pharmacogenomic (SNP) predictors of response or toxicity to the treatments.

19. FINANCE

FOCUS 3 will be coordinated at the MRC Clinical Trials Unit in London. The trial is funded by the MRC. Merck KGaA, Roche and Pfizer are all providing financial support to the trial in terms of either free or reduced price drugs or educational/research support grants.

20. TRIAL COMMITTEES

20.1 Trial Management Group (TMG)

A Trial Management Group (TMG) has been formed comprising the Chief Investigator, other co-investigators and members of the MRC CTU. The TMG will be responsible for the day-to-day running and management of the trial and will meet hold monthly teleconferences and hold face-to-face meetings as required. TMG members include active trial representatives and members with specific interests (e.g. pharmacist; nurse; user representative), and are detailed in Appendix XV.

20.2 Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC. The TSC will meet twice a year.

20.3 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee will meet at regular intervals to review the data and 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, the general clinical community and the regulatory authorities. If a decision is made to continue, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDMC will make recommendations to the TSC as to the continuation of the trial.

21. PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual clinicians must not publish data concerning their patients that are directly relevant to questions addressed in the study until the TMG has published its report. A publication plan will be developed which will follow approved MRC CTU publication guidelines.

All publications shall include a list of participating sites/investigators, and if there are named authors, these should include the trial's Chief Investigator, Statistician and Project Lead at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, as a minimum. The ISRCTN83171665 that has been allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

22. PROTOCOL AMENDMENTS

Please check with the MRC CTU FOCUS 3 Trial Manager that you are using the most recent version of the FOCUS 3 protocol. For a full explanation and complete list of these changes, please contact the MRC CTU.

Third Amendment

The FOCUS 3 protocol was amended in November 2010. The following changes were made:

- Trial contact details updated.
- Addition to Abbreviations and Glossary.
- Addition to exclusion criteria.
- Qualitative research interviews may now take place at any time after starting therapy.

Appendices

- Clarification on the use of GCSF in each regimen.
- Haematological toxicities for IrOxMdG regimen includes dose reduction for irinotecan, oxaliplatin and 5FU (bolus and infusion).
- Addition of capecitabine doses to the capecitabine banding table.
- PIS Stage 3 – Statement added to each Randomisation type to confirm that the patient's doctor may amend the PIS if a treatment regimen is not applicable for that patient (e.g. one of the molecular tests has failed).

Second Amendment

The FOCUS 3 protocol was amended in October 2009. The following changes were made:

- Change to the title of the trial to include *BRAF*.
- All references to '*K-ras*' have been changed to the standard format of '*KRAS*'.
- Addition of information on *BRAF* mutation status testing which will now be assessed at the same time as the *KRAS* mutation testing.
- All trial diagrams have been updated to include *BRAF* where necessary.
- New data has been added to Section 3 – Background.
- Clarification of what happens when one or both of the molecular test results are unavailable.
- Updated Blood Sample collection procedure.

Appendices

- Version Number of all Patient Information Sheets, Consent forms and GP letter changed to V2.0, October 2009.
- All references to '*K-ras*' have been changed to the standard format of '*KRAS*'.
- Title of study updated on all Patient Information Sheets and Consent Forms.
- All trial diagrams now include reference to *BRAF*.
- PIS Stage 2

- Information updated to include information on *BRAF*
- Office of National Statistics (ONS) changed to NHS Information Centre
- Section 15 added – 'What if there is a problem?'

- PIS Stage 4 (Capecitabine)
  - Instructions to hospital emphasise that the MRC CTU must be contacted before a patient is switched from 5FU to capecitabine
- Randomisation Consent Form
  - Change of wording to Q4 of consent form
- GP Letter
  - Updated to include *BRAF* information and rationale.
  - Trial diagram updated
- Trial contact details updated.

First Amendment

The FOCUS 3 protocol was amended in September 2009. The following changes were made:

- Addition to Abbreviations and Glossary
- Updated introduction to include new information on the use of cetuximab within the NHS.
- Addition of details on the cfDNA sub-study and blood sample collection.
- Amendment to the inclusion criteria – a baseline CT must be performed within 5 weeks of starting treatment.
- Change from Data Monitoring Committee to Independent Data Monitoring Committee.
- Addition of summary table if IrOxMdG treatment Schedules.
- Change to the administration instructions for cetuximab in Appendix I (D)
- Change to the prophylactic premedication for the cetuximab regimen in Appendix I (D).
- Additional details on the management of cetuximab hypersensitivity reactions added.
- Additional reasons for discontinuation of cetuximab have been added.
- Addition of capecitabine dosing table summary to Appendix III.
- RECIST criteria updated to version 1.1.

There were no changes to the FOCUS 3 Patient Information Sheets or consent forms.

22.1 Current Versions of Trial Documents

FOCUS 3 Protocol	Version 4.0, November 2010
FOCUS 3 Patient Information Sheets	Version 3.0, November 2010
FOCUS 3 Registration Consent Form	Version 3.0, November 2010
FOCUS 3 Randomisation Consent Form	Version 3.0, November 2010
FOCUS 3 Interview Consent Form	Version 2.0, October 2009
FOCUS 3 GP Letter	Version 2.0, October 2009
FOCUS 3 Response Questionnaire	Version 1.0, March 2009

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APPENDIX I - The chemotherapy regimens

Investigators may find it helpful to copy the relevant schedule from this appendix and keep it with the patient's notes.

Appendix I (A)

Ir MdG (irinotecan + modified de Gramont) - Control Arm and Regimen A

Treatment schedule

Day 1 of treatment sche dule (14 day cycle)

0:00 **iv bolus granisetron 3 mg (or equivalent)**

iv bolus dexamethasone 8 mg

0:00 - 0:30 irinotecan 180 mg/m^2 iv infusion in 250 ml normal saline over 30 minutes

0:30 - 2:30 d,/-folinic aci d 350 mg OR /-folinic aci d 175 mg (flat dose) iv infusion in 250 ml 5% dextrose over 2 hours

2:30 - 2:35 5-fluorouracil 400 mg/m^2 iv bolus injection over 5 minutes

2:35 - 48:35 5-fluorouracil 2400 mg/m^2 iv infusion over 46 hours via ambulatory pump

48:35 **disconnect pump an d flush line as per local protocol**

- **Please note that the bolus 5FU must be given as a 5 minute injection, an d not as a short 15 or 30 minute infusion.**
- **A prophylactic dose of atropine s/c may be given before irinotecan accor ding to local stan dard practice.**

Oral antiemetics (startingday 2)

- **Dexamethasone 2 mg b d x 1 day.**
- **Domperi done or metocloprami de prn.**

Other supportingmedication

- **Ensure patient has supplies of loperami de and ciprofloxacin, and knows how to use them.**

Note on the use of dexamethasone

- **The dose of dexamethasone may be adjusted at the discretion of the investigator in patients with side effects attributable to steroids.**

Scheduled Tests

- **FBC and clinical assessment (NCI CTC grades) should be performed on the day of starting each cycle (or within 3 working days before) and the results available before starting.**
- **Biochemistry; U&Es, LFTs, magnesium and calcium are done at the same time as FBC.**

Toxicity and dose modifications for Ir MdG

Acute cholinergic syndrome

- **Irinotecan may provoke an acute cholinergic syndrome with diarrhoea, sweating, salivation, bra dycar dia, 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

- **Check FBC on (or up to 3 working days before) day 1 of each cycle. Delay 1 week if neutrophils $<1.5 \times 10^9$/l or platelets $<100 \times 10^9$/l. Only treat when neutrophils 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.**
- **No undue incidence of neutropenia has been observed with this regimen, but if neutropenia is dose limiting in an individual patient, GCSF may be used according to local hospital policy.**

Renal function (see also Appendix V)

- **Check serum creatinine at each cycle. If this rises >25%, re-check EDTA clearance or 24-hour urinary creatinine.**
- **If GFR drops to below 30 ml/min, reduce 5FU (bolus and infusion) by 20% and irinotecan by 50% until recovery.**

Hepatobiliary function (see also Appendix V)

- **Irinotecan and its metabolites are cleared by biliary excretion and patients with cholestasis have delayed clearance.**
- **LFTs should be checked before each treatment cycle.**
- **If serum bilirubin 1.5 - 3 x ULN reduce irinotecan by 50%.**
- **If serum bilirubin >3 x ULN omit irinotecan and reduce 5FU (bolus and infusion) by 50%.**
- **An isolated rise in transaminase (either AST or ALT) >2.5 x ULN during treatment is likely to be treatment-related, irinotecan and 5FU (bolus and infusion) should be interrupted until recovery.**

Stomatitis

- **Routine mouthcare (e.g. Corso dyl, nystatin) is recommended.**
- **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) by a further 20%.**
- **Also refer to section on DPD deficiency below.**

Diarrhoea

- **Irinotecan may produce delayed diarrhoea which, if untreated, may become severe. Early intervention with high-dose loperami de is highly effective. An upfront prescription of this should be provided. Patients must be carefully instructed and given the written information sheet, telephone contact numbers and supplies of loperami de and ciprofloxacin. Care should be taken that out-of-hours staff answering patient queries are familiar with the protocol.**
- **Patients should start loperami de 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 b d should be added. If it lasts >48 hours, or if the patient reports symptoms of dehydration, admit acutely for rehy dration and further management (e.g. octreoti de).**
- **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 further toxicity occurs reduce irinotecan and 5FU (bolus and infusion) by a further 20%.**

Hand-foot syndrome (HFS)

- **Treat symptomatically.**
- **If HFS is still a problem, reduce the 5FU doses (bolus and infusion) by 20% for subsequent cycles (no need to reduce irinotecan).**

DPD deficiency

- **DPD is the initial and rate-limiting enzyme for 5FU 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 5FU (in either iv or oral form). Reduced drug clearance results in markedly prolonged exposure to 5FU so that administration of standard doses of 5FU results in altered 5FU pharmacokinetics and severe toxicity including mucositis, granulocytopenia,**

neuropathy an d death. The onset of toxicity usually occurs twice as fast in patients with low DPD activity as compare d with patients with a normal DPD activity. Approximately 3-5% of the population has low DPD activity an d 0.1% have absent activity. We recommen d that (i) patients with a personal or family history suggestive of DPD deficiency shoul d not be enrolle d onto FOCUS 3, an d (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.

Card iotoxicity

- **5FU may provoke angina attacks or even MI in patients with ischaemic heart disease. Continue d treatment with upgra de d antianginal me dication an d re duce d 5FU dose may be consi dere d.**

Extravasation

- **In the event of extravasation, the local policy shoul d be followe d.**

Appendix I (B)

MdG (modified de Gramont) - (Regimen B)

Treatment schedule

Day 1 of treatment sche dule (14 day cycle)

0:00 iv bolus dexamethasone 8 mg

0:00 - 2:00 d,/-folinic aci d 350 mg OR /-folinic aci d 175 mg (flat dose) iv infusion in 250 ml 5% dextrose over 2 hours

2:00 - 2:05 5-fluorouracil 400 mg/m^2 iv bolus injection over 5 minutes

2:05 - 48:05 5-fluorouracil 2800 mg/m^2 iv infusion over 46 hours via ambulatory pump

48:05 disconnect pump an d flush line as per local protocol

Please note that the bolus 5FU must be given as a 5 minute injection an d not as a short 15 or 30 minute infusion.

Oral antiemetics (startingday 2)

- **Dexamethasone 2 mg b d x 1 day.**
- **Domperi done or metocloprami de prn.**

Notes on the use of dexamethasone

- **Emesis is insignificant with the M dG regimen, and dexamethasone is not necessary as an antiemetic. However, it has been included in the schedule in order to correct for the possible contribution of dexamethasone to the anticancer effect in the combination regimens.**
- **The dose of dexamethasone may be adjusted at the discretion of the investigator in patients with side effects attributable to steroids.**

Scheduled Tests

- **FBC and clinical assessment (NCI CTC grades) should be performed on the day of starting each cycle (or within 3 working days before) and the results available before starting.**
- **Biochemistry; U&Es, LFTs, magnesium and calcium are done at the same time as FBC.**

Toxicity and dose modifications for MdG

Haematological

- **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 <100 x 10^9/l. Only treat when neutrophils an d platelets are above these limits.

- **If >1 delay, or 1 delay of ≥2 weeks occurs, re duce the 5FU (bolus an d infusion) doses by 20% an d continue at the lower dose for subsequent cycles unless further toxicity occurs.**
- **If a further delay(s) for myelotoxicity occurs despite a 20% dose re duction, a further dose re duction may be ma de, at the discretion of the treating clinician.**
- **No un due inci dence of neutropenia has been observe d with this regimen, but if neutropenia is dose limiting in an in divi dual patient GCSF may be use d accor ding to local hospital policy.**

Renal function (see also Appendix V)

- **Check serum creatinine at each cycle. If this rises >25%, re-check EDTA clearance or 24-hour urinary creatinine.**
- **If GFR drops to below 30 ml/min, re duce 5FU (bolus an d infusion) by 20% until recovery.**

Hepatobiliary function (see also Appendix V)

- **LFTs shoul d be checke d before each treatment cycle.**
- **If serum bilirubin >1.5 x ULN during treatment, discuss with investigator as this may in dicate disease progression.**
- **If serum bilirubin >3 x ULN re duce 5FU (bolus an d infusion) by 50%.**
- **An isolate d rise in transaminase (either AST or ALT) >2.5 x ULN during treatment is likely to be treatment-relate d, 5FU (bolus an d infusion) shoul d be interrupte d until recovery.**

Stomatitis

- **Routine mouthcare (e.g. Corso dyl, nystatin) is recommen de d.**
- **If mouth ulcers occur despite this, re duce the 5FU doses (bolus an d infusion) by 20% an d continue at the lower dose for subsequent cycles unless further toxicity occurs.**
- **If further toxicity occurs re duce 5FU (bolus an d infusion) by a further 20%.**
- **Also refer to section on DPD deficiency below.**

Diarrhoea

- **For diarrhoea occurring between cycles, treat symptomatically initially: loperami de 2-4 mg q ds an d/or co deine phosphate 30-60 mg q ds as require d.**
- **If diarrhoea has not resolve d 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 require d, re duce the 5FU doses (bolus an d infusion) by 20% an d continue at the lower dose for subsequent cycles unless further toxicity occurs.**

- **If further toxicity occurs re duce 5FU doses (bolus an d infusion) by a further 20%.**

Hand-foot syndrome (HFS)

- **Treat symptomatically.**
- **If HFS is still a problem, re duce the 5FU doses (bolus an d infusion) by 20% for subsequent cycles.**

DPD deficiency

- **DPD is the initial an d rate-limiting enzyme for 5FU break down. DPD deficiency is an inherite d (pharmacogenetic) disorder in which in divi duals with absent or significantly decrease d DPD activity develop life-threatening toxicity following exposure to 5FU (in either iv or oral form). Re duce d drug clearance results in marke dly prolonge d exposure to 5FU so that a dministration of stan dar d doses of 5FU results in altere d 5FU pharmacokinetics an d severe toxicity inclu ding mucositis, granulocytopenia, neuropathy an d death. The onset of toxicity usually occurs twice as fast in patients with low DPD activity as compare d with patients with a normal DPD activity. Approximately 3-5% of the population has low DPD activity an d 0.1% has absent activity. We recommen d that (i) patients with a personal or family history suggestive of DPD deficiency shoul d not be enrolle d onto FOCUS 3, an d (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.**

Card iotoxicity

- **5FU may provoke angina attacks or even MI in patients with ischaemic heart disease. Continue d treatment with upgra de d antianginal me dication an d re duce d 5FU dose may be consi dere d.**

Extravasation

- **In the event of extravasation, the local policy shoul d be followe d.**

Appendix I (C)

IrOx MdG (irinotecan + oxaliplatin + modified de Gramont) - (Regimen C)

Please check you are using the correct dose for the status of your patient.

- **Patients 70 years or less with PS = 0-1** — **Treatment Sche dule 1**
- **Patients 70 years or less with PS = 2** — **Treatment Sche dule 2**
- **Patients over 70 years with PS = 0-1** — **Treatment Sche dule 2**
- **Patients over 70 years with PS = 2** — **Treatment Sche dule 3**

Treatment Schedule 1 - (for Patients 570 years with PS = 0-1)

Day 1 of treatment sche dule (14 day cycle)

0:00 iv bolus granisetron 3 mg (or equivalent)

iv bolus dexamethasone 8 mg

0:00 - 0:30 irinotecan 180 mg/m² iv infusion in 250 ml normal saline over 30 minutes

0:30 flush line with 5% dextrose

0:30 - 2:30 d,/-folinic aci d 350 mg OR /-folinic aci d 175 mg (flat dose) iv infusion in 250 ml 5% dextrose over 2 hours

Concurrently with (via a Y site connector or other appliance according to hospital policy): 0:30 - 2:30 oxaliplatin 85 mg/m² iv infusion in 250 ml 5% dextrose over 2 hours

2:30 flush line with 5% dextrose

2:30 - 2:35 5-fluorouracil 400 mg/m² iv bolus injection over 5 minutes

2:35 - 48:35 5-fluorouracil 2400 mg/m² iv infusion over 46 hours via ambulatory pump

48:35 disconnect pump an d flush line as per local protocol

Treatment Schedule 2 - (for Patients >70 years with PS = 0-1 *OR* Patients 570 years with PS = 2)

These patients receive 80% of the full dose, with the possibility of dose escalation to 100% after 6 weeks of treatment as per FOCUS 2 trial[35].

Day 1 of treatment schedule (14 day cycle)

0:00 iv bolus granisetron 3 mg (or equivalent)

iv bolus dexamethasone 8 mg

0:00 - 0:30 irinotecan 144 mg/m² iv infusion in 250 ml normal saline over 30 minutes

0:30 flush line with 5% dextrose

0:30 - 2:30 d,/-folinic acid 350 mg OR /-folinic acid 175 mg (flat dose) iv infusion in 250 ml 5% dextrose over 2 hours

Concurrently with (via a Y site connector or other appliance according to hospital policy): 0:30 - 2:30 oxaliplatin 68 mg/m² iv infusion in 250ml 5% dextrose over 2 hours

2:30 flush line with 5% dextrose

2:30 - 2:35 5-fluorouracil 320 mg/m² iv bolus injection over 5 minutes

2:35 - 48:35 5-fluorouracil 1920 mg/m² iv infusion over 46 hours via ambulatory pump

48:35 disconnect pump an d flush line as per local protocol

Treatment Schedule 3 - (for Patients >70 years with PS = 2)

These patients receive 60% of the full dose, with the possibility of dose escalation to 80% after 6 weeks of treatment.

Day 1 of treatment sche dule (14 day cycle)

0:00 iv bolus granisetron 3 mg (or equivalent)

iv bolus dexamethasone 8 mg

0:00 - 0:30 irinotecan 108 mg/m² iv infusion in 250 ml normal saline over 30 minutes

0:30 flush line with 5% dextrose

0:30 - 2:30 d,/**-folinic aci d 350 mg OR** /**-folinic aci d 175 mg (flat dose) iv infusion in 250 ml 5% dextrose over 2 hours**

Concurrently via a Y site connector or other appliance accor ding to hospital policy with: 0:30 - 2:30 oxaliplatin 51 mg/m² iv infusion in 250 ml 5% dextrose over 2 hours

2:30 flush line with 5% dextrose

2:30 - 2:35 5-fluorouracil 240 mg/m² iv bolus injection over 5 minutes

2:35 - 48:35 5-fluorouracil 1440 mg/m² iv infusion over 46 hours via ambulatory pump

48:35 disconnect pump an d flush line as per local protocol

Summary of IrOx MdG Treatment Schedules

Schedule	Starting level	Ir mg/m2	Ox mg/m2	FU bolus mg/m2	FU infn mg/m2
1	100%: L70 yrs and PS=0-1	180	85	400	2400
2	80%: >70 years or PS=2	144	68	320	1920
3	60%: >70 years and PS=2	108	51	240	1440

For all IrOx MdG schedules:

- **Please note that the bolus 5FU must be given as a 5 minute injection, and not as a short 15 or 30 minute infusion.**
- **A prophylactic dose of atropine s/c may be given before irinotecan according to local standard practice.**

Oral antiemetics (startingday 2)

- **Dexamethasone 2 mg b d x 1 day.**
- **Domperi done or metocloprami de prn.**

Note on the use of dexamethasone

- **The dose of dexamethasone may be adjusted at the discretion of the investigator in patients with side effects attributable to steroids.**

Other supportingmedication

- **Ensure patient has supplies of loperami de and ciprofloxacin, and knows how to use them.**

Scheduled Tests

- **FBC and clinical assessment (NCI CTC grades) should be performed on the day of starting each cycle (or within 3 working days before) and the results available before starting.**
- **Biochemistry; U&Es, LFTs, magnesium and calcium are done at the same time as FBC.**

Toxicity and dose modifications for IrOx MdG

Acute cholinergic syndrome

- **Irinotecan may provoke an acute cholinergic syndrome with diarrhoea, sweating, salivation, bra dycar dia, 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 more common with IrOxM dG (incidence grade 3/4 neutropenia 50%) than with IrM dG (incidence grade 3/4 neutropenia 28%) though febrile neutropenia was similar in incidence (5% v 3%).**
- **Check FBC on (or up to 3 working days before) day 1 of each cycle. Delay 1 week if neutrophils $<1.5 \times 10^9$/l or platelets $<100 \times 10^9$/l. Only treat when neutrophils and platelets are above these limits.**

- **If >1 delay, or 1 delay of ≥2 weeks occurs, reduce the irinotecan, oxaliplatin 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.**
- **An increased incidence of neutropenia has been observed in patients on this regimen. We encourage investigators to use GCSF as per local hospital policy.**

Renal function (see also Appendix V)

- **Oxaliplatin, like carboplatin, is not nephrotoxic but is renally cleared.**
- **Before starting oxaliplatin, ensure patient fulfils eligibility for renal function described in Section 5.**
- **Check serum creatinine at each cycle. If this rises >25%, re-check EDTA clearance or 24-hour urinary creatinine.**
- **If GFR drops to below 30 ml/min, omit oxaliplatin, reduce 5FU (bolus and infusion) by 20% and irinotecan by 50% until recovery.**

Hepatobiliary function (see also Appendix V)

- **Irinotecan and its metabolites are cleared by biliary excretion and patients with cholestasis have delayed clearance. Oxaliplatin is not principally cleared by the liver, but there is evidence of delayed clearance in patients with marked hepatic dysfunction.**
- **LFTs should be checked before each treatment cycle.**
- **If serum bilirubin 1.5 - 3 x ULN reduce irinotecan by 50%.**
- **If serum bilirubin >3 x ULN omit irinotecan and reduce oxaliplatin and 5FU (bolus and infusion) by 50%.**
- **An isolated rise in transaminase (either AST or ALT) >2.5 x ULN during treatment is likely to be treatment-related, irinotecan, oxaliplatin and 5FU (bolus and infusion) should be interrupted until recovery.**

Stomatitis

- **Routine mouthcare (e.g. Corso dyl, nystatin) is recommended.**
- **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) by a further 20%.**
- **Also refer to section on DPD deficiency below.**

Diarrhoea

- In the IrOxM dG trial, grade 3/4 diarrhoea occurred in 20% patients compared with 12% on IrM dG.
- Irinotecan may produce delayed diarrhoea which, if untreated, may become severe. Early intervention with high-dose loperami de is highly effective. An upfront prescription of this should be provided. Patients must be carefully instructed and given the written information sheet, telephone contact numbers and supplies of loperami de and ciprofloxacin. Care should be taken that out-of-hours staff answering patient queries are familiar with the protocol.
- Patients should start loperami de 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 b d should be added. If it lasts >48 hours, or if the patient reports symptoms of dehydration, admit acutely for rehy dration and further management (e.g. octreoti de).
- After an episode of severe diarrhoea (grade 3-4), delay chemotherapy until full recovery then resume at 20% reduced doses of all three drugs.
- 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 further toxicity occurs reduce irinotecan & 5FU (bolus & infusion) by a further 20%.

Hand-foot syndrome (HFS)

- Treat symptomatically.
- If HFS is still a problem, reduce the 5FU doses (bolus and infusion) by 20% for subsequent cycles (no need to reduce irinotecan).

DPD deficiency

- DPD is the initial and rate-limiting enzyme for 5FU 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 5FU (in either iv or oral form). Reduced drug clearance results in markedly prolonged exposure to 5FU so that administration of standard doses of 5FU results in altered 5FU 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 FOCUS 3, 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.

Cardiotoxicity

- **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.**

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.**

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 irinotecan and 5FU. When symptoms have resolved to grade 1, oxaliplatin should be restarted at a 20% reduced dose.**

Extravasation

- **In the event of extravasation, the local policy should be followed.**

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 corticosteroi d and antihistamine.**
- **After full recovery, the patient may continue with irinotecan and 5FU.**

- **At the investigator's discretion, the patient may be rechallenge d with oxaliplatin at the next cycle. In this case, premedication is recommended as follows:**
  - **Dexamethasone 4 mg p.o. 6 hourly starting 24 hours pre-treatment + 8 mg iv 30 minutes pre-dose chlorphenamine 10 mg (or equivalent) + raniti dine 50 mg (or equivalent) iv 30 minutes pre-dose. Continue dexamethasone, chlorphenamine and raniti dine for 24-48 hours after treatment with oxaliplatin.**

Appendix I (D)

Ir MdG + cetuximab (irinotecan + modified de Gramont + Cetuximab) - (Regimen D)

Please note a physician must be present in the unit or ward, or immediately available by emergency bleep, during the first infusion of cetuximab and for one hour thereafter. Adrenaline an d emergency resuscitation equipment must be imme diately available. . Vital signs shoul d be checke d before, during, post an d 1 hour after the cetuximab infusion an d recor de d. There must be at least one hour between completion of the cetuximab infusion an d the start of chemotherapy.

ode of administration

- **1st dose:**
  500 mg/m² cetuximab administered by i.v. infusion over 120 minutes, directly followed by chemotherapy
- **2nd dose:**
  500 mg/m² cetuximab administered by i.v. infusion over 90 minutes, directly followed by chemotherapy
- **Subsequent doses:**
  500 mg/m² cetuximab administered by i.v. infusion over 60 minutes, directly followed by chemotherapy

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 1 hour afterwards, i.e. either during chemotherapy or without further therapy, if applicable. Availability of resuscitation equipment must be ensured.

Prophylactic premedication

Before the first three cetuximab administrations, appropriate anti-allergic prophylaxis with a corticosteroi d (at a dose equivalent to 8mg dexamethasone intravenous or oral) and an appropriate antihistamine (standard H1 blocker, intravenous or oral, at standard dosage) is mandatory. Pretreatment with a corticosteroi d (at a dose equivalent to 8mg dexamethasone intravenous or oral) and an antihistamine (standard H1 blocker, intravenous or oral, at standard dosage) is also recommended before all subsequent infusions of cetuximab. Paracetamol and raniti dine can also be administered as part of the prophylactic premedication.

Treatment Schedule

Day 1 of treatment schedule (14 day cycle)

0:00 iv chlorphenamine 10 mg (or equivalent H1 blocker)
paracetamol 1 g p.o., raniti dine 150 mg p.o - Optional 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 over 2 hours, (in subsequent cycles reduce infusion time to 1 hour)
Observe for delayed hypersensitivity reaction.

2:00 - 4:00 d,/-folinic acid 350 mg OR /-folinic acid 175 mg (flat dose) iv infusion in 250 ml 5% dextrose over 2 hours.

4:00 - 4:30 irinotecan 180 mg/m^2 iv infusion in 250 ml normal saline over 30 minutes.

4:30 - 4:35 5-fluorouracil 400 mg/m^2 iv bolus injection over 5 minutes

4:35 - 50:35 5-fluorouracil 2400 mg/m^2 iv infusion over 46 hours via ambulatory pump

50:35 disconnect pump and flush line as per local protocol

Notes

- From cycle 3 onwards the cetuximab dose is to continue at 500 mg/m^2 every two weeks and the duration of infusion shortened to 1 hour. Observations continue as on day 1 and the one hour gap between cetuximab and irinotecan should be maintained. Folinic Acid can be administered during the observation period. Please also note that changes to the infusion time for cetuximab may be necessary due to allergic or hypersensitivity reactions to cetuximab (please see the appropriate section below).
- Please note that the bolus 5FU must be given as a 5 minute injection and not as a short 15 or 30 minute infusion.
- A prophylactic dose of atropine s/c may be given before irinotecan according to local standard practice.

Oral antiemetics (startingday 2)

- Dexamethasone 2 mg b d x 1 day.
- Domperi done or metocloprami de prn.

Other supportingmedication

- Ensure patient has supplies of loperami de and ciprofloxacin, and knows how to use them.

Note on the use of dexamethasone

- **The dose of dexamethasone may be a djuste d at the discretion of the investigator in patients with si de effects attributable to steroi ds.**

Scheduled Tests

- **FBC an d clinical assessment (NCI toxicity scores) shoul d be performe d on the day of starting each cycle (or within 3 working days before) an d the results available before starting.**
- **Biochemistry; U&Es, LFTs, magnesium an d calcium are done at the same time as FBC.**

Toxicity and dose modifications for Ir MdG + cetuximab

Acute cholinergic syndrome

- **Irinotecan may provoke an acute cholinergic syndrome with diarrhoea, sweating, salivation, bra dycar dia, 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

- **Check FBC on (or up to 3 working days before) day 1 of each cycle. Delay 1 week if neutrophils $<1.5 \times 10^9$/l or platelets $<100 \times 10^9$/l. Only treat when neutrophils and platelets are above these limits.**
- **If >1 delay, or 1 delay of $\geq$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.**
- **No undue incidence of neutropenia has been observed with this regimen, but if neutropenia is dose limiting in an individual patient GCSF may be used according to local hospital policy.**

Renal function (see also Appendix V)

- **Check serum creatinine at each cycle. If this rises >25%, re-check EDTA clearance or 24-hour urinary creatinine.**
- **If GFR drops to below 30 ml/min, reduce 5FU (bolus and infusion) by 20% and irinotecan by 50% until recovery.**

Hepatobiliary function (see also Appendix V)

- **Irinotecan and its metabolites are cleared by biliary excretion and patients with cholestasis have delayed clearance.**
- **LFTs should be checked before each treatment cycle.**
- **If serum bilirubin 1.5 - 3 x ULN reduce irinotecan by 50%.**
- **If serum bilirubin >3 x ULN omit irinotecan and reduce 5FU (bolus and infusion) by 50%.**
- **An isolated rise in transaminase (either AST or ALT) >2.5 x ULN during treatment is likely to be treatment-related, irinotecan and 5FU (bolus and infusion) should be interrupted until recovery.**

Stomatitis

- **Routine mouthcare (e.g. Corso dyl, nystatin) is recommended.**
- **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) by a further 20%.**
- **Also refer to section on DPD deficiency below.**

Diarrhoea

- **Irinotecan may produce delayed diarrhoea which, if untreated, may become severe. Early intervention with high-dose loperami de is highly effective. An upfront prescription of this should be provided. Patients must be carefully instructed and given the written information sheet, telephone contact numbers and supplies of loperami de and ciprofloxacin. Care should be taken that out-of-hours staff answering patient queries are familiar with the protocol.**
- **Patients should start loperami de 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 b d should be added. If it lasts >48 hours, or if the patient reports symptoms of dehydration, admit acutely for rehy dration and further management (e.g. octreoti de).**
- **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 further toxicity occurs reduce irinotecan and 5FU (bolus and infusion) by a further 20%.**

Hand-foot syndrome (HFS)

- **Treat symptomatically.**
- **If HFS is still a problem, re duce the 5FU doses (bolus an d infusion) by 20% for subsequent cycles (no nee d to re duce irinotecan).**

DPD deficiency

- **DPD is the initial an d rate-limiting enzyme for 5FU break down. DPD deficiency is an inherite d (pharmacogenetic) disorder in which in divi duals with absent or sig nificantly decrease d DPD activity develop life-threatening toxicity following exposure to 5FU (in either iv or oral form). Re duce d drug clearance results in marke dly prolonge d exposure to 5FU so that a dministration of stan dar d doses of 5FU results in altere d 5FU pharmacokinetics an d severe toxicity inclu ding mucositis, granulocytopenia, neuropathy an d death. The onset of toxicity usually occurs twice as fast in patients with low DPD activity as compare d with patients with a normal DPD activity. Approximately 3-5% of the population has low DPD activity an d 0.1% have absent activity. We recommen d that (i) patients with a personal or family history suggestive of DPD deficiency shoul d not be enrolle d onto FOCUS 3, an d (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.**

Card iotoxicity

- **5FU may provoke angina attacks or even MI in patients with ischaemic heart disease. Continue d treatment with upgra de d antianginal me dication an d re duce d 5FU dose may be consi dere d.**

Extravasation

- **In the event of extravasation, the local policy shoul d be followe d.**

Cetuximab-specific Toxicities

Allergic/Hypersensitivity reactions

- **Severe grade 3/4 hypersensitivity reactions have occurred in 2.2% of patients treated with cetuximab. One death from angio-oe dema 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.**
- **A nurse must be present in the immediate area during the first infusion of cetuximab and for one hour thereafter, and a physician within close proximity**

or immediately available by emergency bleep. Adrenaline, glucocorticoi ds an emergency resuscitation equipment must be imme diately available.

- **Treatment depen ds on the gra de 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% an d monitor closely for any worsening. 1st dose:** • **decrease infusion rate by 50% resulting in an infusion duration 4 hours 2n d dose:** • **decrease infusion rate by 50% resulting in an infusion duration of 3 hours, if allergic/hypersensitivity reaction persists decrease infusion rate by another 25% to an infusion duration of 4 hours Subsequent doses:** • **decrease infusion rate by 50% resulting in an infusion duration of 2 hours, if allergic/hypersensitivity reaction persists decrease infusion rate by another 50% to an infusion duration of 4 hours** **The total infusion time for cetuximab shoul d not excee d 240 minutes.**
Grade 2 **Rash; flushing; urticaria; dyspnea; drug fever .38°C**	**Stop cetuximab infusion.** **A dminister broncho dilators, oxygen etc. as me dically in dicate d.** **Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolve d or decrease d to gra de 1 in severity, an d monitor closely for any worsening. Prolongation of infusion duration shoul d be performe d as describe d for gra de 1 reactions, as applicable.** **The total infusion time for cetuximab at 500mg/m^2 shoul d not excee d 4 hours.**
Grade 3 or Grade 4 **Gra de 3: Symptomatic bronchospasm, with or without urticaria; parenteral me dication(s) in dicate d; allergy-relate d oe dema/angioe dema; hypotension** **Gra de 4: Anaphylaxis**	**Stop cetuximab infusion imme diately an d disconnect infusion tubing from the patient.** **A dminister a drenaline, broncho dilators, antihistamines, glucocorticoi ds, intravenous flui ds, vasopressor agents, oxygen etc., as me dically in dicate d.** **Patients have to be with drawn imme diately from treatment an d 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 CI should be contacted immediately to discuss and grade the reaction.**

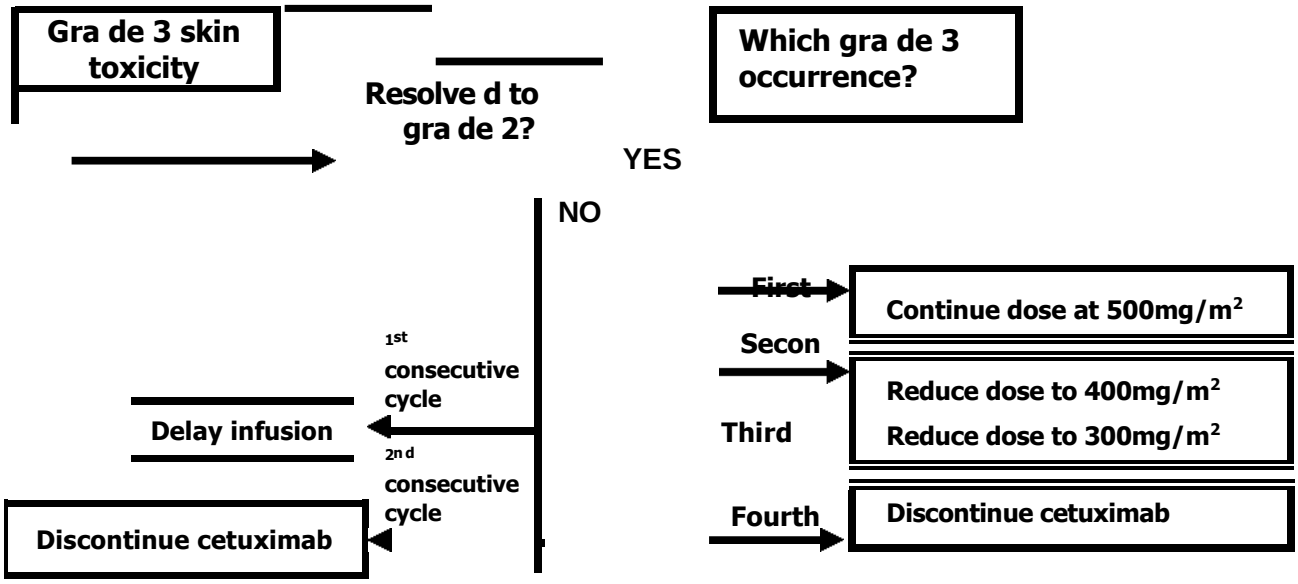
Skin toxicity

- **The acneiform skin rash associated with cetuximab occurs in over 70% of patients. About 12% have grade reactions. On longer-term therapy, paranychia occur 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 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 1 consecutive infusion is 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 metroni dazole or erythromycin). Systemic antibiotics (e.g. a second generation tetracycline such as doxycycline 100 mg po daily) should be considered for grade 2 acneiform eruption, and are mandatory for grade reactions. The threshold for referral to the dermatology clinic should be planned locally but all patients with grade 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, avoi dance of hot water for baths or showers an d use of emollient creams are beneficial; topical corticosteroi ds are not recommen de d. Fissures may occur in dry skin an d topical dressings (e.g. hy drocolloi d dressings an d as a dvise d by your dermatologist) are helpful.

- Nail toxicities occur in 8% of patients with cetuximab, characterise d by a paronychial inflammation with associate d swelling of the lateral skin fol ds of toes an d fingers, especially great toes an d thumbs, which may be painful. It may persist for up to three months after cessation of cetuximab therapy. Dermatological a dvice shoul d be sought. Use of daily salt baths an d local antiseptic / astringent ointments have been foun d to be helpful. Anti-inflammatory drugs may help to ease the pain.

Treatment adjustments for cetuximab-related skin toxicity:



Hypomagnesemia

- Hypomagnesemia 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, carpope dal 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 VI for details).

Other reasons for cetuximab discontinuation:

- **If a subject develops an intercurrent illness (e.g., infection) that, in the opinion of the investigator mandates interruption of cetuximab therapy, that intercurrent illness must resolve within a time frame such that no more than one infusion is withheld. After the interruption of treatment, the subject will continue with cetuximab at the dose received before the interruption.**
- **If therapy must be withheld for a longer period of time, the subject will be discontinued from cetuximab treatment. In special cases, the investigator may request that the subject continues to receive cetuximab with permission of the FOCUS 3 TMG via the trial manager at the MRC CTU.**
- **Cetuximab therapy will not be withheld for chemotherapy-related toxicities. Therefore, in the event that the next infusion of chemotherapy is delayed, the subject will receive cetuximab as planned.**

Appendix I (E)

Ir MdG + bevacizumab (irinotecan + modified de Gramont + bevacizumab) - (Regimen E)

Treatment Schedule

Day 1 of treatment schedule (14 day cycle)

0:00 iv bolus granisetron 3 mg (or equivalent)

iv bolus dexamethasone 8 mg

0:00 - 1:30 bevacizumab 5 mg/kg iv infusion in 100 ml normal saline over 90 minutes 1:30 - 2:00 irinotecan 180 mg/m^2 iv infusion in 250 ml normal saline over 30 minutes 2:00 - 4:00 d,/-folinic acid 350 mg OR /-folinic acid 175 mg (flat dose) iv infusion in 250 ml

5% dextrose over 2 hours

4:00 - 4:05 5-fluorouracil 400 mg/m^2 iv bolus injection over 5 minutes

4:05 - 50:05 5-fluorouracil 2400 mg/m^2 iv infusion over 46 hours via ambulatory pump

50:05 disconnect pump and flush line as per local protocol

Notes

- **If the first bevacizumab infusion is well tolerated, especially without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over a 60 minute period. If the 60 minute infusion is well tolerated, all subsequent infusions may be delivered over a 30 minute period.**
- **Bevacizumab infusions should not be administered or mixed with dextrose or glucose solutions.**
- **The dose for bevacizumab will be calculated as milligrams per kilogram body weight (mg/kg). The patient's weight at baseline will be used to determine the dose of bevacizumab to be used for the duration of the study. If a patient's weight changes by .10% during the course of the study, the dose of bevacizumab should be recalculated, if a patient's weight changes by <10% the dose can be adjusted according to the local policy/clinician's discretion, but this is not an absolute requirement.**
- **Please note that the bolus 5FU must be given as a 5 minute injection, and not as a short 15 or 30 minute infusion.**
- **A prophylactic dose of atropine s/c may be given before irinotecan according to local standard practice.**

Oral antiemetics (startingday 2)

- **Dexamethasone 2 mg b d x 1 day.**
- **Domperi done or metocloprami de prn.**

Other supportingme dication

- **Ensure patient has supplies of loperami de an d ciprofloxacin, an d knows how to use them.**

Note on the use of dexamethasone

- **The dose of dexamethasone may be a djuste d at the discretion of the investigator in patients with si de effects attributable to steroi ds.**

Scheduled Tests

- **FBC an d clinical assessment (NCI CTC gra des) shoul d be performe d on the day of starting each cycle (or within 3 working days before) an d the results available before starting.**
- **Biochemistry; U&Es, LFTs, magnesium an d calcium are done at the same time as FBC.**
- **A 24 hour urine collection shoul d be performe d before starting cycle 1. Proteinuria by dipstick urinalysis must be assesse d before each bevacizumab a dministration.**
- **Bloo d pressure shoul d be measure d before each cycle. If BP is raise d at baseline, patient shoul d commence anti-hypertensive me dication until controlle d, prior to receiving bevacizumab treatment**

Toxicity and dose modifications for Ir MdG + bevacizumab

Acute cholinergic syndrome

- **Irinotecan may provoke an acute cholinergic syndrome with diarrhoea, sweating, salivation, bra dycar dia, 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

- **Check FBC on (or up to 3 working days before) day 1 of each cycle. Delay 1 week if neutrophils $<1.5 \times 10^9$/l or platelets $<100 \times 10^9$/l. Only treat when neutrophils and platelets are above these limits.**
- **If >1 delay, or 1 delay of $\geq$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 for myelotoxicity occurs despite a 20% dose reduction, a further dose reduction may be made, at the discretion of the treating clinician.**
- **No undue incidence of neutropenia has been observed with this regimen, but if neutropenia is dose limiting in an individual patient GCSF may be used according to local hospital policy.**

Renal function (see also Appendix V)

- **Check serum creatinine at each cycle. If this rises >25%, re-check EDTA clearance or 24-hour urinary creatinine.**
- **If GFR drops to below 30 ml/min, reduce 5FU (bolus and infusion) by 20% and irinotecan by 50% until recovery.**

Hepatobiliary function (see also Appendix V)

- **Irinotecan and its metabolites are cleared by biliary excretion and patients with cholestasis have delayed clearance.**
- **LFTs should be checked before each treatment cycle.**
- **If serum bilirubin 1.5 - 3 x ULN reduce irinotecan by 50%.**
- **If serum bilirubin >3 x ULN omit irinotecan and reduce 5FU (bolus and infusion) by 50%.**
- **An isolated rise in transaminase (either AST or ALT) >2.5 x ULN during treatment is likely to be treatment-related, irinotecan and 5FU (bolus and infusion) should be interrupted until recovery.**

Stomatitis

- **Routine mouthcare (e.g. Corso dyl, nystatin) is recommended.**
- **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) by a further 20%.**
- **Also refer to section on DPD deficiency below.**

Diarrhoea

- **Irinotecan may produce delayed diarrhoea which, if untreated, may become severe. Early intervention with high-dose loperami de is highly effective. An upfront prescription of this should be provided. Patients must be carefully instructed and given the written information sheet, telephone contact numbers and supplies of loperami de and ciprofloxacin. Care should be taken that out-of-hours staff answering patient queries are familiar with the protocol.**
- **Patients should start loperami de 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 b d should be added. If it lasts >48 hours, or if the patient reports symptoms of dehydration, admit acutely for rehy dration and further management (e.g. octreoti de).**
- **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 resolve d by the time the next cycle is due, delay 1 week.**
- **If further toxicity occurs re duce irinotecan an d 5FU (bolus an d infusion) by a further 20%.**

Hand-foot syndrome (HFS)

- **Treat symptomatically.**
- **If HFS is still a problem, re duce the 5FU doses (bolus an d infusion) by 20% for subsequent cycles (no nee d to re duce irinotecan).**

DPD deficiency

- **DPD is the initial an d rate-limiting enzyme for 5FU break down. DPD deficiency is an inherite d (pharmacogenetic) disorder in which in divi duals with absent or significantly decrease d DPD activity develop life-threatening toxicity following exposure to 5FU (in either iv or oral form). Re duce d drug clearance results in marke dly prolonge d exposure to 5FU so that a dministration of stan dar d doses of 5FU results in altere d 5FU pharmacokinetics an d severe toxicity inclu ding mucositis, granulocytopenia, neuropathy an d death. The onset of toxicity usually occurs twice as fast in patients with low DPD activity as compare d with patients with a normal DPD activity. Approximately 3-5% of the population has low DPD activity an d 0.1% have absent activity. We recommen d that (i) patients with a personal or family history suggestive of DPD deficiency shoul d not be enrolle d onto FOCUS 3, an d (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.**

Card iotoxicity

- **5FU may provoke angina attacks or even MI in patients with ischaemic heart disease. Continue d treatment with upgra de d antianginal me dication an d re duce d 5FU dose may be consi dere d.**
- **Please also refer to the bevacizumab specific cardiotoxicities below.**

Extravasation

- **In the event of extravasation, the local policy shoul d be followe d.**

Bevacizumab-specific Toxicities

Gastrointestinal perforation

- **Bevacizumab has been associated with serious cases of gastrointestinal perforation in patients with metastatic carcinoma of the colon or rectum.**
- **If any patient develops gastrointestinal perforation then permanently discontinued bevacizumab.**

Wound healing complications

- **Bevacizumab therapy may adversely affect wound healing, it should not be initiated for at least 28 days following major surgery, or until the surgical wound has fully healed.**
- **If patients experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed.**
- **Should surgery be required for any reason during bevacizumab treatment, bevacizumab should be withheld and not restarted for at least 28 days post-operatively or until the surgical wound is fully healed. Non-emergency surgery should be delayed if possible until at least 28 days after the last dose of bevacizumab. The time period of omitting bevacizumab for at least 28 days before, or after, major surgery is based on the calculated half-life of bevacizumab being approximately 20 days.**
- **If any wound dehiscence requiring medical therapy occurs then permanently discontinue bevacizumab.**

Fistula

- **Fistula formation is a recognised side effect of bevacizumab. Fistulae are most often gastrointestinal in origin, but may originate from other sites including the genitourinary system and rarely the trachea and/or oesophagus.**
- **If any grade 4 fistula or any grade of tracheosophageal fistula occurs then permanently discontinue bevacizumab.**
- **If any grade of fistula possibly, probably or definitely related to bevacizumab occurs then permanently discontinue bevacizumab.**
- **If a patient develops a fistula unrelated to bevacizumab, discontinue bevacizumab until fistula resolves completely. At this point, if it is thought to be in the patient's best interest to continue with bevacizumab, then this must be discussed on a case by case basis with the Chief Investigator.**

Proteinuria

- **Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence that grade 1 proteinuria may be related to dose.**

- **Proteinuria by dipstick urinalysis must be assessed before each bevacizumab administration.**
- **Proteinuria 1+ on dipstick is acceptable and does not require interruption of treatment.**

1st occurrence of proteinuria

- **1+ (dipstick) - bevacizumab should be administered as scheduled. No additional evaluation is required.**
- **.2+ (dipstick) - bevacizumab should be administered as scheduled. The following additional evaluation is required: 24-hour urine collection required in the 3 days prior to next dose.**
    - **If 24 hour protein .2 g: bevacizumab should be administered as scheduled.**
    - **If 24 hour protein >2 g: omit bevacizumab. Do 24- hour urine collection within 3 days prior to next dose.**
        - **If repeat 24 hour urine protein .2 g: bevacizumab should be administered as scheduled. 24 hour protein should be further monitored prior to each administration of bevacizumab until it has decreased to .1 g/24 hours.**
        - **If repeat 24 hour protein >2 g: omit bevacizumab until 24 hour protein .2 g. 24-hour protein should be further monitored prior to each administration of bevacizumab until it has decreased to .1 g/24 hours.**
- **Nephrotic syndrome (grade 4 proteinuria) - permanently discontinue bevacizumab.**

2nd and subsequent occurrence of proteinuria

- **.2+ (dipstick) - bevacizumab should be administered as scheduled. No additional evaluation is required.**
- **.3+ (dipstick) - bevacizumab should be administered as scheduled. The following additional evaluation is required: 24 hour urine collection required in the 3 days prior to next dose.**
    - **If 24 hour protein .2 g: bevacizumab should be administered as scheduled.**
    - **If 24 hour protein >2 g: omit bevacizumab. Do 24 hour urine collection within 3 days prior to next dose.**
        - **If repeat 24 hour urine protein .2 g: bevacizumab should be administered as scheduled. 24 hour protein should be further monitored prior to each administration of bevacizumab until it has decreased to .1 g/24 hours.**
        - **If repeat 24 hour protein >2 g: omit bevacizumab until 24 hour protein .2 g. 24 hour protein should be further monitored prior to each administration of bevacizumab until it has decreased to .1 g/24 hours.**
- **Nephrotic syndrome (grade 4 proteinuria) - permanently discontinue bevacizumab.**

Hypertension

- **An increased incidence of hypertension has been observed in patients treated with bevacizumab. Hypertension is generally treated with oral anti-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. Only 0.7% of all patients treated with bevacizumab were required to discontinue therapy due to uncontrolled hypertension. A hypertensive encephalopathy was reported in one case only. The risk of bevacizumab associated hypertension has not been found to correlate with the patient's baseline characteristics, underlying disease or concomitant therapy.**
- **Monitoring of blood pressure is recommended during bevacizumab therapy.**
- **Grade 1 - Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 mmHg if previously within normal range. Intervention is not indicated.**
- **Grade 2 - Recurrent or persistent (>24 hr) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 mmHg if previously within normal range. Interrupt bevacizumab therapy. Treatment with monotherapy antihypertensive may be indicated. Once controlled to <150/100 mmHg, patients may continue bevacizumab.**
- **Grade 3 - Requiring more than one anti-hypertensive or more intensive therapy than previously. Bevacizumab should be interrupted for persistent or symptomatic hypertension and should be permanently discontinued if blood pressure is not controlled by medication.**
- **Grade 4 - Life-threatening consequences e.g. hypertensive crisis. Permanently discontinue bevacizumab.**

Congestive heart failure

- **Events consistent with congestive heart failure (CHF) have been reported in clinical trials. The symptoms ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF, such as pre-existing coronary heart disease or concomitant car diotoxic therapy.**
- **Caution should be exercised when treating patients with clinically significant cardiovascular disease or pre-existing congestive heart failure with bevacizumab.**

Reversible posterior leukoencephalopathy syndrome (RPLS)

- **There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with reversible posterior leukoencephalopathy syndrome (RPLS), a rare neuralgic disorder, which can present with the following signs and**

symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of RPLS requires confirmation by brain imaging. In patients developing RPLS, treatment of specific symptoms including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of re-initiating bevacizumab therapy in patients previously experiencing RPLS is not known.

Haemorrhage

- **The haemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumour-associated haemorrhage and minor mucocutaneous haemorrhage.**
- **Tumour-associated haemorrhage was observed in phase 1 and 2 bevacizumab studies. Six serious events, of which four had fatal outcome, were observed in patients with non-small cell lung cancer receiving bevacizumab. These events occurred suddenly and presented as major or massive haemoptysis in patients with either squamous cell histology and/or tumours located in the centre of the chest in close proximity to major blood vessels. In five of these cases, these haemorrhages were preceded by cavitation and/or necrosis of the tumour.**
- **Tumour-associated haemorrhage was also seen rarely in other tumour types and locations, including central nervous system (CNS) bleeding in a patient with hepatoma with occult CNS metastases and continuous oozing of blood from a thigh sarcoma with necrosis.**
- **Five haemorrhagic events in IFL + bevacizumab (three rectal haemorrhages, one gastrointestinal haemorrhage and one melaena) were assessed as tumour-associated. The addition of bevacizumab did not result in a significant increase in the incidence or severity of grade 3/4 haemorrhagic events in this study.**
- **Mucocutaneous haemorrhage has been seen in 20-40% of patients treated with bevacizumab. These were most commonly grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention, and did not require any changes in the bevacizumab treatment regimen. There have also been less common events of minor mucocutaneous haemorrhage in other locations, such as gingival bleeding and vaginal bleeding.**
- **The risk of CNS haemorrhage in patients with CNS metastases receiving bevacizumab could not be evaluated, as patients with a history or evidence of CNS metastases were excluded from all clinical trials.**
- **There is no information on the safety profile of bevacizumab in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting bevacizumab treatment, as such patients were excluded from all clinical trials. However, patients**

who developed venous thrombosis while receiving bevacizumab did not appear to have an increased rate of serious bleeding when treated with full dose warfarin and bevacizumab concomitantly.

- **If grade pulmonary or CNS haemorrhage then permanently discontinue bevacizumab.**
- **If grade haemorrhagic event other than pulmonary or CNS haemorrhage then permanently discontinue bevacizumab.**

Venous thromboembolism

- **Venous thromboembolic events, including deep vein thrombosis, pulmonary embolism and thrombophlebitis, occurred in 15.2% and 16.4% of patients in the IFL + placebo and IFL + bevacizumab arms respectively. It could not be determined if these events were due to the patients' underlying cancer, their cytotoxic chemotherapy, bevacizumab or other risk factors.**
- **The incidence of venous thromboembolic events was lower in the 5FU/LV + bevacizumab arm compared to that in the control (9.0% vs 13.5%).**
- **Patients who developed venous thrombosis while receiving bevacizumab did not appear to have an increased rate of serious bleeding when treated with full dose warfarin and bevacizumab concomitantly.**

<u>Grade 3 or incidentally discovered pulmonary embolus first occurrence</u>

- **Hold bevacizumab treatment. If the planned duration of therapeutic-dose anticoagulant therapy is .2 weeks, bevacizumab should be held until the period of therapeutic-dose anticoagulant therapy is over.**
- **If the planned duration of therapeutic-dose anticoagulant therapy is >2 weeks, bevacizumab should be held for 2 weeks and then may be resumed during the period of therapeutic-dose anticoagulant therapy as soon as all of the following criteria are met:**
    - **The subject must be on a stable dose of anticoagulant and, if on warfarin, have an INR within the target range (usually between 2 and 3) prior to restarting study drug treatment.**
    - **The subject must not have had a Grade 3 or 4 haemorrhagic event since entering the study.**
    - **The subject must not have had any evidence of tumour invading or abutting major blood vessels on any prior CT scan.**

<u>Grade 3 or incidentally discovered pulmonary embolus second occurrence, Grade 4 first occurrence</u>

- **Discontinue bevacizumab.**

Arterial thromboembolism

- **The incidence of arterial thromboembolic events (including CVAs, MIs, TIAs and other arterial thromboembolic events) was higher in patients receiving IFL + bevacizumab (3.3%) compared to patients receiving IFL + placebo (1.3%). The incidence of arterial thromboemolic events was also reported to be higher in the 5FU/LV + bevacizumab arm (10.0%) compared to the control arm (4.8%).**
- **Patients receiving bevacizumab plus chemotherapy, with a history of arterial thromboembolic events or age >65 years have an increased risk of developing arterial thromboembolic events during bevacizumab therapy. Caution should be taken when treating these patients with bevacizumab.**
- **In the case of an arterial thromboembolic event (e.g. angina, MI), treatment with bevacizumab must be discontinued.**

Hypersensitivity reaction

- **Hypersensitivity reactions to bevacizumab are extremely rare (<1 in 1000).**
- **If hypersensitivity reaction attributable to bevacizumab, treat with hydrocortisone, antihistamines and adrenaline if required.**
- **If grade 1 reaction, no interruption of bevacizumab is required.**
- **If grade 2 reaction, treatment should be stopped and not restarted on the same day.**
- **If grade 3/4 reaction, permanently discontinue bevacizumab.**

Appendix II - Dose Capping in Obese Patients

For patients who are obese, doses of drugs base d on surface area (SA) (5FU, irinotecan, oxaliplatin an d cetuximab) will be cappe d using the following scheme:

Patient's height in cm:	Cap surface area at:
un der 150cm	1.5 m_2
150-159 cm	1.7 m_2
160-169 cm	1.9 m_2
170-179 cm	2.1 m_2
180 cm or taller	2.3 m_2

To use this system, calculate the patient's SA in the normal way, then check on this table. If the calculated SA is higher than the cap value indicated for that patient's height, use the cap value instead.

Example 1: **an obese patient 153 cm tall has a calculated SA of 1.95 m^2. This is more than the SA cap of 1.7 m^2, therefore prescribe using 1.7 m^2.**

Example 2: **a large patient 185 cm tall has a calculated SA of 2.25 m^2. This is lower than the SA cap of 2.3 m^2, therefore prescribe using 2.25 m^2.**

Please note that this system results in "capped" doses being used for patients of BMI >30 on average, although within each height band shorter patients (e.g. 170-173 cm) are capped at BMI 32-34, and taller patients (e.g. 177-179) are capped at BMI 27-28. Overall, the cap will apply to around 5% of patients in an average oncology practice.

Reference:

- **Dubois D & Dubois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med, 1916; 17: 863-871 .**

APPENDIX III - Capecitabine Dosing

The routine use of capecitabine in place of 5FU is not permitte d. The reason is that although several of the 5FU-base d regimens on test in FOCUS 3 have well-vali date d capecitabine alternatives, others do not.

However, for patients who enter FOCUS 3 but subsequently develop a relative or absolute contra-in dication to infusional 5FU-base d treatment, capecitabine may be offere d as an alternative, using a 9- day-on, 5- days-off sche dule an d keeping the other drugs (irinotecan, oxaliplatin, cetuximab, bevacizumab) as in the patient's allocate d FOCUS 3 sche dule. In this situation, please contact either the FOCUS 3 trial team at the MRC CTU or the Chief Investigator to discuss crossover before treatment with capecitabine commences.

There is a well- documente d potential for increase d toxicity of capecitabine when changing from 5FU to capecitabine (most probably due to interaction with retaine d polyglutamate d folates) [34]. For this reason, patients crossing over from a 5FU-base d FOCUS 3 regimen to its capecitabine alternative must receive a re duce d starting dose of capecitabine, an d increase to the full- dose regimen only if well-tolerate d after 2 cycles (4 weeks).

FU doses before change-over (bolus+infusion, mg/m^2)	Starting dose of capecitabine (mg/m^2 b.d. days 1-9)	….increased after 2 cycles if no toxicity (mg/m^2 b.d. days 1-9)
400+2800 (full dose single-agent)	1000	1250
400+2400 (full- dose combinations)	800	1000
320+1920 (80% combinations)	640	800
240+1440 (60% combination)	480	600

Additional Dose Reductions

The doses shown in this table must be further re duce d un der the following circumstances:

- **Impaired renal function: If calculate d or measure d GFR is in the range 30-50 ml/min, re duce capecitabine by 25%. E.g. a patient on IrM dG whose GFR is 45 ml/min will receive [800-25% =] 600 mg/m^2 capecitabine starting dose, increasing to 750 mg/m^2 if well tolerate d.**
- **Previous need for 5FU dose-reduction: If the patient's dose of 5FU has alrea dy been re duce d for toxicity, age or frailty prior to converting to capecitabine, then this re duction shoul d be carrie d forwar d proportionately. For example a patient on IrOxM dG who has been receiving it at 80% dose level, either because of a dvance d age or because of toxicity, woul d receive [800 x 80% =] 640 mg/m^2 starting dose.**

issed Doses

Missed doses are a compliance issue and should be documented on the patient's capecitabine diary card which will be supplied by the MRC CTU once it has been confirmed that the patient can switch to capecitabine. Patients should be shown how to document missed doses on the capecitabine diary card. Completed diary cards should be checked at subsequent visits.

Contraindications of Capecitabine

If there has been an allowed crossover to capecitabine for line related problems the following may be contraindicated medications:

- **Brivudine or sorivudine may produce a dangerous interaction with capecitabine. These medications are not licensed in the UK but may be prescribed for viral infections in other countries.**

In addition, extra care should be taken with:

- **Warfarin: INR (International normalised ratio) control may be affected by capecitabine. If a patient requiring warfarin is taking capecitabine, more frequent INR monitoring is required.**
- **Phenytoin: blood phenytoin levels may increase with capecitabine. If a patient is taking phenytoin concomitantly with capecitabine, they should be monitored regularly for increased phenytoin plasma concentrations.**

Capecitabine dose banding:

First calculate the patient's surface area accurately to 2 decimal places.

- **Calculate the exact (not roun de d) target dose of capecitabine.**

  For example, a patient on XELOX requiring 800 mg/m^2, whose S.A is 1.59 m^2, has an exact target dose of 1.59 x 800 = 1272 mg.

- **Use the table to fin d the roun de d dose an d the number of tablets per dose:**

Exact dose (mg)	Roun de d dose (mg)	Number of tablets per dose	
		500mg	+ 150mg
576 - 725	650	1	1
726 - 875	800	1	2
876 - 975	950	1	3
976 - 1075	1000	2	0
1076 - 1225	1150	2	1
1226 - 1375	1300	2	2
1376 - 1475	1450	2	3
1476 - 1575	1500	3	0
1576 - 1725	1650	3	1
1726 - 1875	1800	3	2
1876 - 1975	1950	3	3
1976 - 2075	2000	4	0
2076 - 2225	2150	4	1
2226 - 2400	2300	4	2
2401 - 2575	2500	5	0
2576 - 2725	2650	5	1
2726 - 2900	2800	5	2

- **Complete the patient's diary sheet for the cycle, including the patient's name, the numbers of each tablet to take (at the top) and the day and date of each dose due (in the table). Give the diary sheet to the patient together with their tablets.**

APPENDIX IV - Cockcroft & Gault Formula

The estimate d GFR is given by:

Males: $\frac{1.23 \times (140 - age) \times weight\ (kg)}{serum\ creatinine\ (\mu mol/l)}$

Females: $\frac{1.04 \times (140 - age) \times weight\ (kg)}{serum\ creatinine\ (\mu mol/l)}$

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.30 ml/min is accepted as evidence of adequate renal function.**
- **Patients with a Cockcroft & Gault estimate of <30 ml/min prior to randomisation should have formal GFR measurement with EDTA or 24 urinary creatinine, which must be within the centre's normal range. The corrected EDTA clearance should be.30 ml/min.**
- **After the start of treatment, if the Cockcroft & Gault estimate falls by >25% from baseline or to below 30 ml/min, the EDTA or 24 hour urinary creatinine measurement should be re-checked.**

APPENDIX V - Renal & Hepatic Function

		5FU dose	irinotecan dose	oxaliplatin dose	cetuximab & bevacizumab doses
Renal function	GFR 30ml/min	Full	Full	Full	Full
	GFR <30 ml/min	Re duce by 20%	Re duce by 50%	Do not give	Full
Hepatic function	Bili .1.5 x ULN an d AST/ALT .2.5 x ULN	Full	Full	Full	Full
	Bili 1.5 - 3 x ULN	Full	Re duce by 50%	Full	Full
	Bili >3 x ULN	Re duce by 50%	Withhol d until recovery	Re duce by 50%	Full
	AST/ALT >2.5 x ULN	Re duce by 50%	Withhol d until recovery	Full	Full

Notes:

- **Organ function at the time of enrolment must meet the eligibility criteria (see Section 5) i.e. GFR.30 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).**

- **If patient experiences more than one of the toxicities above, the largest dose reduction should be used. E.g. If a patient has GFR <30ml/min and bilirubin >3x ULN, then reduce the 5FU dose by 50%.**

- **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 consultant oncologist.**

- **GFR: see notes in Appendix IV for the use of Cockcroft & Gault formula to estimate GFR. For patients with a Cockcroft & Gault estimate <30 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 & Gault estimate.**

- **Patients with GFR <30 ml/min should not receive capecitabine.**

APPENDIX VI - Hypomagnesaemia

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 standardised replacement. Other drugs include diuretics, digoxin and prolonged aminoglycosi de 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 hypokalaemia should be undertaken during and for eight weeks after cetuximab therapy (http://www.fda.gov/c der/ d rug/infopage/erbitux/ d efault.htm).

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, carpope dal 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 be considered as a SAE/SUSAR to be reported to the MRC 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 an d duration of infusion an d the dose shoul d be re duce d in renal impairment" (BNF 56, Sept 2008).

There appears to be no stan dard gui delines, with respect to magnesium a dministration 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 divi de d doses; suitable preparations are magnesium glycerophosphate tablets or liqui d [not license d, available from specialist importing companies an d special-order manufacturers]" (BNF 56, Sept 2008).

Monitoring

It is recommen de d by the FOCUS 3 trial TMG that magnesium levels are measure d:

- **at baseline**
- **prior to each chemotherapy cycle**
- **for all symptomatic patients**
- **for any patient with hypocalcaemia**

After completion of cetuximab therapy, magnesium shoul d be measure d at 6-8 weeks after the last dose of cetuximab an d at intervals until hypomagnesemia has resolve d. This information will be collecte d on the amen de d CRFs an d recorde d as per toxicity gra ding criteria below.

Please refer to Appendix IX for NCI CTC grading of hypomagnesemia

References:

- **Schrag. D, Flombaum.C, Chung.K, Saltz. L; Cetuximab therapy may occasionally cause profoun d hypomagnesemia an d hypocalcemia. Abstract no. 264; ASCO GI 2005**

- **Carson. E, Novak. A, Stella. P; Hypomagnesemia in patients with stage IV colorectal cancer treate d with cetuximab as a single agent; Abstract no. 3655; ASCO GI 2005.**

- **BNF (British National Formulary) 56, Sept 2008 (E d)**

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 - RECIST Response Definitions (V1.1)[1]

- **RECIST (Response Evaluation Criteria In Solid Tumours) v1.1 has now superseded RECIST v1.0.**
- **The key amendments are:**
  - **a maximum of five measurable non-nodal lesions should be measured, with a maximum of two per organ.**
  - **Lymph node measurement rules have changed.**
  - **The definition of progressive disease has changed.**

easurable 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 two measurable lesions per organ, and up to a maximum of five lesions in total. These should be representative of all involved organs.**
- **Target lesion (non-nodal) must be accurately measurable in at least 1 dimension, with the longest diameter ≥10 mm (assuming CT slice thickness is no greater than 5mm). 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 5 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 then 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.**

Lymph Node Measurement Rules

- **Measure short axis**
  - **Target lesion if short axis 15mm**
  - **Non-target lesion is short axis 10 to < 15mm**
  - **Normal if short axis < 10mm**

- **Add ACTUAL short axis measurements to sum of longest diameters of non-nodal lesions.**
- **When considered normal if < 10mm, for CR the sum may not be zero if nodes are included as target lesions.**
- **The implication of this is that patients previously considered PR because of residual nodes <10mm may now be considered CR.**

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 4 weeks apart. All lymph nodes must be non-pathological in size (<10mm short axis). (In FOCUS 3 the 12-week assessment should be used as the confirmatory assessment; there is no need for additional confirmatory scans).**
- **Partial response (PR): 30°/13 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°/13 increase in the sum of longest diameters of target lesions compared to smallest sum longest diameter recorded. In addition, the sum must also demonstrate an absolute increase of at least 5mm. Unequivocal progression of non-target lesions, or the appearance of new lesions is also considered progression. Unequivocal progression means the patient has overall status of progressive disease at that time point. Modest increases in the size of one or more non-target lesions is usually not sufficient.**

Reminders:

- **New lesions must be unequivocal and not attributable to a different scanning technique or non-tumour (e.g. "new" bone lesions may be flare). When in doubt continue treatment and repeat evaluation.**
- **If a scan shows a new lesion in anatomical region which was not included in the baseline scans, this is still PD.**
- **Response is judged against baseline, but progression is judged against the smallest recorded score.**

Examples:

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

Time point response: patients with target (+/- non-target) disease

Target Lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluate d	No	PR
PR	Non-PD or not all evaluate d	No	PR
SD	Non-PD or not all evaluate d	No	SD
Not all evaluate d	Non-PD	No	NE
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD

References:

1. **Eisenhauer EA, Therasse, P *et al*. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009, 45, 228-247.**
2. **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 IX - NCI Common Toxicity Criteria V3.0

Toxicity	0	1	2	3	4	5
NAUSEA	None	Loss of appetite without alteration in eating habits	Oral intake decrease d without significant weight loss, dehydration or malnutrition; IV flui ds in dicate d <24hrs	Ina dequate oral caloric or flui d intake; IV flui ds, tube fee dings or TPN in dicate d 24hrs	Life-threatening consequences	Death
VO MITING	None	1 episo de in 24 hours	2-5 episo des in 24 hours; IV flui ds in dicate d <24hrs	6 episo des in 24 hours; IV flui ds, or TPN in dicate d 24hrs	Life-threatening consequences	Death
ANOREXIA	None	Loss of appetite without alteration in eating habits	Oral intake altere d without significant weight loss or malnutrition; oral nutritional supplements in dicate d	Associate d with significant weight loss or malnutrition; IV flui ds, tube fee dings or TPN in dicate d	Life-threatening consequences	Death
ALOPECIA	Normal	Thinning or patchy	Complete	-	-	-
RASH: ACNE/ ACNEIFORM	None	Intervention not in dicate d	Intervention in dicate d	Associate d with pain, disfigurement, 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, blee ding, oe dema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain, interfering with function	-	-
NAIL CHANGES	None	Discoloration; ri dging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbe d(s)	Interfering with ADL	_	-
PAIN	None	Mil d pain not interfering with function	Mo derate pain: pain or analgesics interfering with function, but not interfering with ADL	Severe pain: pain or analgesics severely interfering with ADL	Disabling	-
MUCOSITIS/ STO MATITIS (clinical exam)	None	Erythema of the mucosa	Patchy ulcerations or pseu domembranes	Confluent ulcerations or pseu domembranes; blee ding with minor trauma	Tissue necrosis; significant spontaneous blee ding; life-threatening consequences	Death
MUCOSITIS/ STO MATITIS (functional/ symptomatic)	None	Minimal discomfort, intervention not in dicate d	Symptomatic, me dical intervention in dicate d but not interfering with ADL	Stool incontinence or other symptoms interfering with ADL	Symptoms associate d 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 flui ds in dicate d <24hrs	Increase of 7 stools/day; incontinence; IV flui ds 24hrs; hospitalisation	Life-threatening consequences (e.g., haemo dynamic collapse)	Death
DIARRHOEA (patients with a colostomy)	None	Mil d increase in ostomy output compare d with baseline	Mo derate increase in ostomy output compare d with baseline, not interfering with ADL	Severe increase in ostomy output compare d to baseline interfering with ADL	Life-threatening consequences (e.g., haemo dynamic collapse)	Death
LETHARGY	None	Mil d fatigue over baseline	Mo derate or causing difficulty performing some activities	Severe fatigue interfering with ADL	Disabling	-
HAE MO-GLOBIN	Within normal limits	10.0 g/dl - normal	8.0 - 9.9 g/dl	6.5 - 7.9 g/dl	<6.5 g/dl	Death
PLATELETS	Within normal limits	75x109/1 - normal	50 - 74x109/1	25 - 49x109/1	<25x109/1	Death
WBC	Within normal limits	3.0x109/1-normal	2.0 - 2.9x109/1	1.0 - 1.9x109/1	<1.0x109/1	Death
NEUTROPHILS	Within normal limits	1.5x109/l - normal	1.0 - 1.4x109/1	0.5 - 0.9x109/1	<0.5x109/1	Death

Toxicity	0	1	2	3	4	5
ALT	Within normal limits	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5 - 20.0 ULN	>20 x ULN	-
AST	Within normal limits	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5 - 20.0 ULN	>20 x ULN	-
BILIRUBIN	Within normal limits	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3 - 10 x ULN	>10 x ULN	-
SENSORY NEUROPATHY	Normal	Asymptomatic; loss of deep ten don reflexes or paresthesia (inclu ding tingling) but not interfering with function	Sensory alteration or paresthesia (inclu ding 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 in dicate d	Life-threatening; disabling (e.g., paralysis)	Death
ALLERGIC REACTION/ HYPER-SENSITIVITY (INCLUDING DRUG FEVER)	Normal	Transient flushing or rash; drug fever <3£3°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever 3£3°C (104°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) in dicate d; allergy-relate d edema/ angioe dema; hypotension	Anaphylaxis	Death
MAGNESIU M, SERU M-LOW/ HYPO MAGNESE MIA	Within normal limits	<LLN-1.2 mg/dL <LLN-0.5mmol/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
HYPERTENSION	None	Asymptomatic, transient(<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not in dicate d	Recurrent or persistent (24 hrs) or symptomatic Increase by >20mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be in dicate d	Requiring more than one drug or more intensive therapy than previously	Life-threatening consequences (e.g., hypertensive crisis)	Death
CARDIAC ISCHE MIA/ INFARCTION	None	Asymptomatic arterial narrowing without ischemia	Asymptomatic an d testing suggesting ischemia; stable angina	Symptomatic an d testing consistent with ischemia; unstable angina; intervention in dicate d	Acute myocardial infarction	Death
BRONCHOSPAS M WHEEZING	None	Asymptomatic	Symptomatic not interfering with function	Symptomatic interfering with function	Life-threatening	Death
DYSPNEA (SHORTNESS OF BREATH)	None	Dyspnoea on exertion, but can walk 1 flight of stairs without stopping	Dyspnoea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1km) without stopping	Dyspnoea with ADL	Dyspnoea at rest; intubation/ ventilator in dicate d	Death
PNEU MONITIS/ PULMONARY INFILTRATES	None	Asymptomatic, ra diographic fin dings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O2 in dicate d	Life - threatening; ventilatory support in dicate d	Death
PULMONARY FIBROSIS (RADIOGRAPHIC CHANGES)	None	Minimal ra diographic fin dings (or patchy or bibasilar changes) with estimate d ra diographic proportion of total lung volume that is fibrotic of <25%	Patchy or bi-basilar changes with estimate d ra diographic proportion of total lung volume that is fibrotic of 25-<50%	Dense or wi desprea d infiltrates/consoli dat ion with estimate d ra diographic proportion of total lung volume that is fibrotic of 50-<75%	Estimate d ra diographic proportion of total lung volume that is fibrotic is 75%; honeycombing	Death

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

APPENDIX X - LIST OF EXPECTED TOXICITIES

Toxicities/si de effects that have previously occurre d an d are liste d in the SPC are liste d here. Please recor d all si de effects on the toxicity section of the treatment form. If the outcome of the si de effect is serious (see FOCUS 3 protocol for definitions), the SAE form in the CRF booklet shoul d also be complete d. Any toxicity not describe d below, i.e. a toxicity that is unexpecte d, will be reporte d as a SUSAR.

Toxicity	5-Fluorouracil	Irinotecan	Capecitabine	Oxaliplatin	Cetuximab	Bevacizumab
Haemapoeitic:						
Anaemia	✓	✓	✓	✓	✓	
Febrile neutropenia	✓	✓	✓	✓		✓
Gra de 3 or 4 lab abnormalities	✓	✓	✓	✓		✓
Leukopenia	✓	✓	✓		✓	✓
Neutropenia	✓	✓	✓	✓		✓
Thrombocytopenia	✓	✓	✓	✓	✓ (rare)	✓
Coagulation disorders					✓	✓
Gastrointestinal:						
Ab dominal pain	✓	✓	✓	✓	✓	✓
Constipation		✓	✓	✓	✓	✓
Diarrhoea	✓	✓	✓	✓	✓	✓
Dry mouth	✓		✓			
Dyspepsia	✓		✓	✓	✓	
Flatulence			✓			
Loose stools	✓	✓	✓	✓		
Nausea	✓	✓	✓	✓	✓	✓
Oral pain	✓		✓			
Stomatitis / mucositis	✓		✓	✓	✓	✓
Taste disturbance	✓		✓	✓		

Toxicity	5-Fluorouracil	Irinotecan	Capecitabine	Oxaliplatin	CetuxiMab	Bevacizu Ma b
Gastrointestinal (contd):						
Upper ab dominal pain	✓	✓	✓			
Vomiting	✓	✓	✓	✓	✓	✓
Intestinal obstruction			✓	✓	✓ (rare)	✓
Oesophagitis	✓		✓			
Gastritis/ duo denitis	✓		✓			
Colitis	✓	✓	✓			
Gastro-intestinal haemorrhage	✓	✓	✓		✓	✓
Gastro-intestinal perforation						✓ ✓
Hiccups				✓		
Neurotoxicity:						
Acute neurosensory manifestations				✓		
Dizziness	✓		✓		✓	
Dysarthria (rare)	✓ (cerebellar symptoms)	✓	✓ (cerebellar symptoms)	✓		
Hea dache			✓	✓	✓	
Hyperaesthesia			✓	✓		
Hypoaesthesia			✓	✓		
Insomnia			✓		✓	
Ototoxicity (uncommon)				✓		
Paraesthesia	✓		✓	✓		✓
Pharyngolaryngeal dysaesthesia				✓		
Sensory peripheral neuropathy				✓		✓
Confusion			✓		✓	✓
Visual disturbance		✓		✓		✓
Convulsions					✓	

Toxicity	5-Fluorouracil	Irinotecan	Capecitabine	Oxaliplatin	Cetuximab	Bevacizu ma b
Biochemistry:						
Gra de 3 or 4 alkaline phosphatase (CTC v3.0)		✓	✓	✓		
Gra de 3 or 4 ALT (CTC v3.0)		✓	✓	✓		
Gra de 3 or 4 AST (CTC v3.0)		✓	✓	✓		
Gra de 3 or 4 bilirubin increase (CTC v3.0)	✓	✓	✓	✓		
Hyperglycaemia			✓		✓	
Cardiovascular:						
Lower limb oe dema			✓			
Peripheral oe dema					✓	
Angina / MI / Arrhythmia	✓		✓		✓	
Hypotension		✓			✓	
Hypertension		✓			✓	✓
Thrombosis					✓	✓
Syncope			✓		✓	✓
Cutaneous:						
Acneform rash					✓	
Alopecia	✓	✓	✓	✓	✓	
Dermatitis	✓		✓		✓	✓
Dry skin	✓		✓	✓	✓	
Exfoliative dermatitis	✓		✓		✓	✓
Han d-foot syn drome or palmar-plantar erythro dysaesthaesia	✓		✓	✓		✓
Localise d exfoliation	✓		✓	✓	✓	
Nail disor ders	✓		✓		✓	
Pigmentation disor der	✓		✓		✓	
	✓		✓		✓	

Toxicity	5-Fluorouracil	Irinotecan	Capecitabine	Oxaliplatin	CetuxiMab	Bevacizu Ma b
Cutaneous (contd.):						
Pruritis			✓		✓	
Rash erythematous	✓	✓	✓		✓	
Skin discolouration	✓		✓		✓	✓
Skin disorder		✓			✓	
Skin fissures	✓		✓		✓	
Skin hyperpigmentation	✓		✓		✓	
Respiratory effects:						
Pulmonary fibrosis (rare)		✓		✓		
Pleural effusion					✓	
General undesirable effects:						
Acute cholinergic syn drome		✓				
Anorexia	✓	✓	✓	✓	✓	✓
Arthralgia			✓	✓		
Asthenia	✓	✓	✓	✓	✓	✓
Back pain			✓	✓	✓	
Conjunctivitis	✓	✓	✓	✓	✓	
Cough			✓	✓		
Vertigo	✓		✓			
Deafness (rare)				✓		
Dehy dration	✓	✓	✓		✓	✓
Depression			✓	✓	✓	
Disturbance of renal function		✓		✓		✓
Dyspnoea		✓	✓	✓	✓	✓
Dysuria				✓		
Epistaxis	✓		✓	✓		✓
	✓	✓	✓		✓	

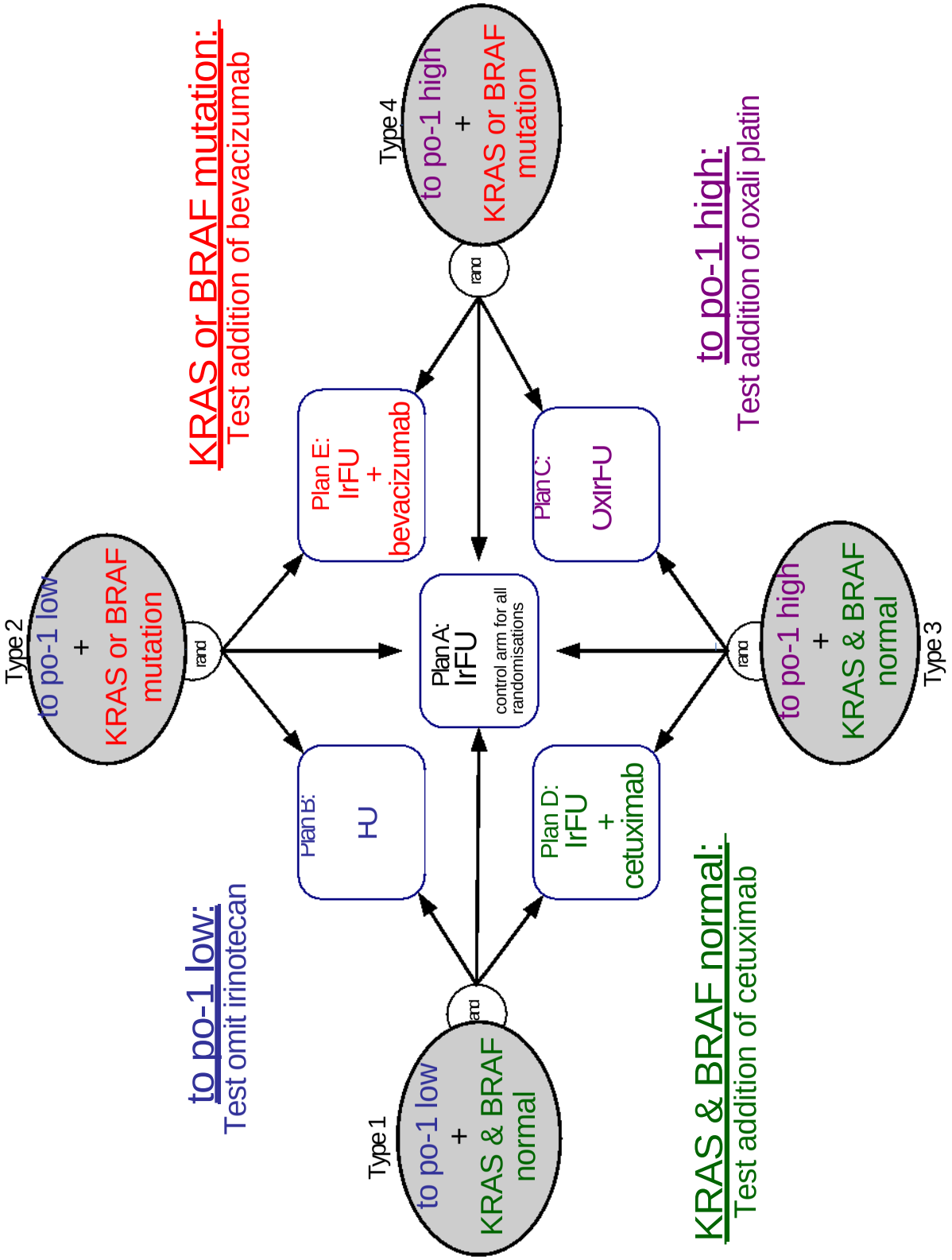
Toxicity	5-Fluorouracil	Irinotecan	Capecitabine	Oxaliplatin	CetuxiMab	Bevacizu Ma b
General undesirable effects (contd):						
Fatigue	✓	✓	✓	✓	✓	✓
Fever	✓		✓	✓	✓	✓
Haematuria				✓		✓
Haemorrhage (rectum, nose)	✓		✓	✓	✓	✓
Increase d cough					✓	
Increase d lacrimation	✓		✓			
Infection	✓	✓	✓	✓	✓	✓
Infusion reaction (characterise d by		✓		✓	✓	✓
Lethargy	✓	✓	✓	✓	✓	✓
Malaise	✓	✓	✓	✓	✓	✓
Micturition, abnormal frequency				✓		
Myalgia		✓	✓		✓	
Pain in limb		✓	✓	✓		
Pyrexia	✓	✓	✓	✓	✓	✓
Rigors	✓	✓	✓	✓	✓	
Weakness	✓	✓	✓		✓	
Weight decrease	✓		✓	✓	✓	
Weight increase	✓			✓	✓	
Chest Pain	✓		✓	✓	✓	
Renal Failure			✓		✓	
Abscess formation					✓	✓

APPENDIX XI - Patient Information Sheets

Version 3.0, November 2010

Information Sheets are provided by the trials office in Microsoft Word format. Please complete your contact details at the end of each of the information sheets. They should then be printed on local hospital headed notepaper.

This diagram will be included i n the patient folder as a reference



PIS Stage 1 :

<Print on hospital headed paper>

Patient Information Sheet

(Stage 1)

FOCUS 3 - A study to determine the feasibility of molecular selection of therapy using ICRAS, BRAF and topo-1 in patients with metastatic or locally advanced colorectal cancer.

Version 3.0, November 2010

> **When cancer of the bowel is not completely removable by surgery or when it has spread to elsewhere in your body, chemotherapy may be given. This is a form of drug treatment which aims to kill cancer cells.**

> **You have been invited to think about taking part in a clinical trial, because you an your doctors are considering a course of chemotherapy for colorectal (bowel) cancer.**

> **Participation is entirely voluntary. If after considering it, you decide not to participate, this will not affect your care in any way and your doctor will explain the best alternative standard treatment available.**

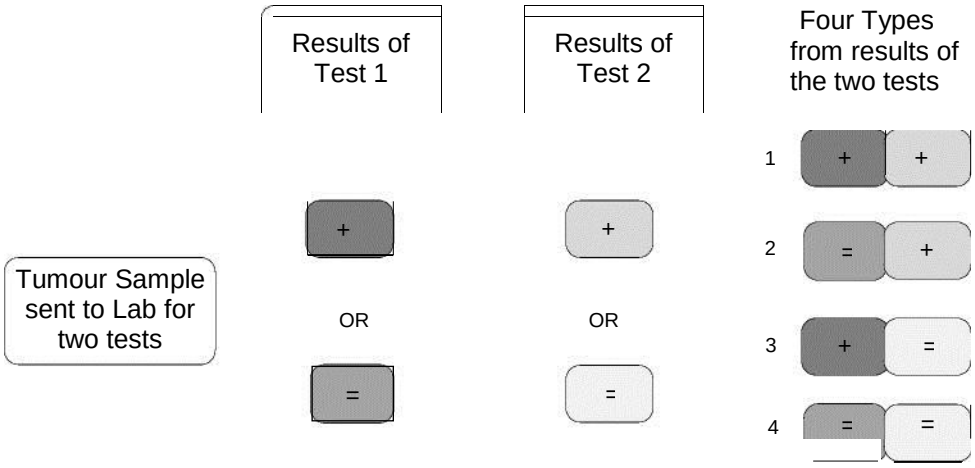
> **Usually, the type of chemotherapy that is offered to a patient depends on how well it works on average in patients with the same cancer as you have.**

> **However, there are now some tests that can be done on the tumour which may help us to choose more accurately which sort of chemotherapy would be best for you as an individual.**

> **You will be asked to consent to the two parts of this clinical trial separately. The first step, explained here, asks that you give us permission to send a piece of your tumour (already stored in the hospital where your cancer was diagnosed) to a laboratory where special tests (known as "molecular markers") will be run on the tumour sample.**

> **These tests will identify your cancer as one of four 'types'. This process will take approximately two weeks. The diagram below demonstrates this process.**

What happens to my tumour sample?



> **Your tumour sample will be one of the four types shown above. We will then ask you to consent to the main study, where you will be randomly allocated to one of three appropriate treatments based on your tumour type.**

> **One of these treatments is the usual course of treatment that you would be offered, which is the same regardless of the tumour type. In the other two treatment plans, we are trying to find out if they will be more suitable than the usual treatment for those with a particular tumour type.**

> **We know that the tests do not give us an answer for some people. So there will be a few patients for whom we cannot allocate a tumour type. If this happens in your case, you will receive the standard treatment off trial. Your oncology doctor will discuss your options if this happens.**

> **We will give full information about the main trial and treatments at your next visit to clinic, or further information is available now if you would like it. A folder will be provided for you to store all of your information**

> **By consenting to tumour testing, you are under no obligation to consent to the main trial. If you decide not to consent to the main trial, your tumour test results will not be given to anyone else or used in any way.**

Please use this space below to record any questions you might have for your oncology doctor at your next visit.

PIS Stage 2 :

<PRINT ON HOSPITAL HEADED PAPER>

Patient Information Sheet
(Stage 2)

FOCUS 3 — A study to determine the feasibility of molecular selection of therapy using ICRAS, BRAF and topo-1 in patients with metastatic or locally advanced colorectal cancer.

You have been invited to consider taking part in a clinical trial, because you and your doctors are considering a course of chemotherapy for colorectal (bowel) cancer. We would like a total of 240 patients to join this clinical trial in the UK.

Participation is entirely voluntary. If, after considering it, you decide not to participate, this will not affect your care in any way and your doctor will explain the best alternative standard treatment available.

This sheet explains the background to the research and is intended to support your discussions with your doctors and nurses. Please ask the doctor or nurses if you are unclear over any of the points raised.

When you have read this information sheet you should take time to consider whether you wish to take part and you may want to discuss it with your GP, family or others before deciding.

1. What is chemotherapy?

When cancer of the bowel is not completely removable by surgery, or when the cancer has spread to somewhere else in your body, chemotherapy, a form of drug treatment which aims to kill cancer cells, may be given.

Although it does not completely cure bowel cancer, chemotherapy can shrink or control it for a period. We have found that, on average, patients who receive chemotherapy live for a longer period of time, and have better control of their symptoms, than if they had not had chemotherapy.

2. Why is this research being done?

Unfortunately, chemotherapy can produce unwanted effects ("side effects") as well as benefits, and it does not help every patient. Even when chemotherapy works well, it may not control cancer indefinitely. Usually, the specific chemotherapy that is offered to a patient is selected by how well it works on average in patients with the same cancer as you have, in this case, colorectal cancer.

However, there are now some tests that can be done on the tumour which may help us to choose more accurately which sort of chemotherapy would be best for you as an individual. To prove that these tests can reliably tell us who would benefit the most from specific types of chemotherapy is a very big project and, before we start it, we need to check whether this approach would work in practice.

This trial is a way of checking all those practical issues as well as beginning to compare the benefits of selecting treatment for you as an individual.

3. How is the research done?

You have already agreed to have a sample of your tumour tested. We asked the pathology laboratory in the hospital where your cancer was diagnosed to send a previously stored sample of your cancer to a central laboratory for special molecular tests.

Two tests were done, which will be described later. Those tests identified your cancer as one of four 'types'. Information about your cancer 'type' has been forwarded to the MRC Clinical Trials Unit, which is the organisation co-ordinating this research.

The next step in this research is to confirm that you are well enough to receive the treatments and that you agree to join the trial. All of the treatments in the trial have been shown to be effective in the treatment of colorectal cancer.

The best way of weighing up the advantages and disadvantages of different treatments for a particular type of cancer is in a randomised controlled trial (or RCT). "Randomised" means that if you decide to participate in the trial, a central computer will allocate your treatment at random. Neither your oncology doctor nor you will choose which treatment you prefer. Using the computer to choose the treatment ensures that the groups of patients with each type of cancer receiving each treatment are similar. In this way, a fair comparison can be made between treatments at the end of the trial.

4. What tests were done on the tumour?

Two sorts of tests were performed on the tumour. The first is a test of a protein called topo-1 and the second is a test of two of the genes which are often altered in colorectal cancer (the

genes are calle d KRAS an d BRAF). About half of patients with colorectal cancer have low levels of topo-1 an d half have high levels. Similarly, about half of patients with colorectal cancer have a change (mutation) in either the KRAS or the BRAF gene an d about half have no change in either gene. When these two tests were complete d, we were able to divi de the cancer into one of four molecular types:

- Type 1: low topo-1, Both KRAS an d BRAF normal
- Type 2: low topo-1, Either KRAS or BRAF mutation
- Type 3: high topo-1, Both KRAS an d BRAF normal
- Type 4: high topo-1, Either KRAS an d BRAF mutation

5. Will the results of my tests delay my treatment?

We expect that the tests will be available within two weeks of you giving us your permission to enter the trial and request the samples. It normally takes about two weeks to make the arrangements to start any chemotherapy.

Occasionally, there can be a delay getting the sample from the hospital to the central laboratory. If the molecular test results are not available within 2 weeks from registration but the results are expected within the next two weeks, we will delay your randomisation and you will be able to have one cycle of FU as detailed in Plan B below. If after one cycle of FU, the molecular test results are still not available you will be offered standard treatment off trial and your oncology doctor will discuss these options with you. If the results are available after your one cycle of FU, you will then be randomised to the trial and allocated a treatment.

6. Which treatments are being studied?

There are five types of medicine which have been shown to work in colorectal cancer. The new thing in this trial is the allocation of treatment combinations to individual patients according to their molecular type. The five treatment combinations are:

1. **IrFU (Irinotecan & FU) — Plan (Regimen) A**

   FU (fluorouracil) is the drug most commonly used for colorectal cancer. FU is usually given with another drug called irinotecan. This combination is abbreviated to IrFU. Currently IrFU is one of the standard therapies for patients with colorectal cancer.

2. **FU (Fluorouracil) — Plan B**

   FU can be used alone (without irinotecan). When FU is used alone, a higher dose is given. Research suggests that in some types of tumour FU is at least as good at fighting the cancer but has fewer side effects than IrFU.

3. IrFU with oxaliplatin — Plan C

This treatment is similar to IrFU but a dds the drug oxaliplatin an d uses a lower dose of irinotecan. Previous research suggests that this combination may be of extra benefit in some tumour types. This combination is abbreviate d to OxIrFU.

4. IrFU with cetuximab — Plan D

Cetuximab (which is also known as Erbitux) is a new type of drug calle d a monoclonal antibo dy. Research has shown that it works best with patients who have the normal KRAS an d BRAF gene in the tumour. In this trial, we will be using cetuximab with IrFU.

5. IrFU with bevacizumab — Plan E

Bevacizumab (which is also known as Avastin) is also a monoclonal antibo dy drug. It works by affecting the bloo d supply to the tumour. In this trial, we will be using bevacizumab with IrFU.

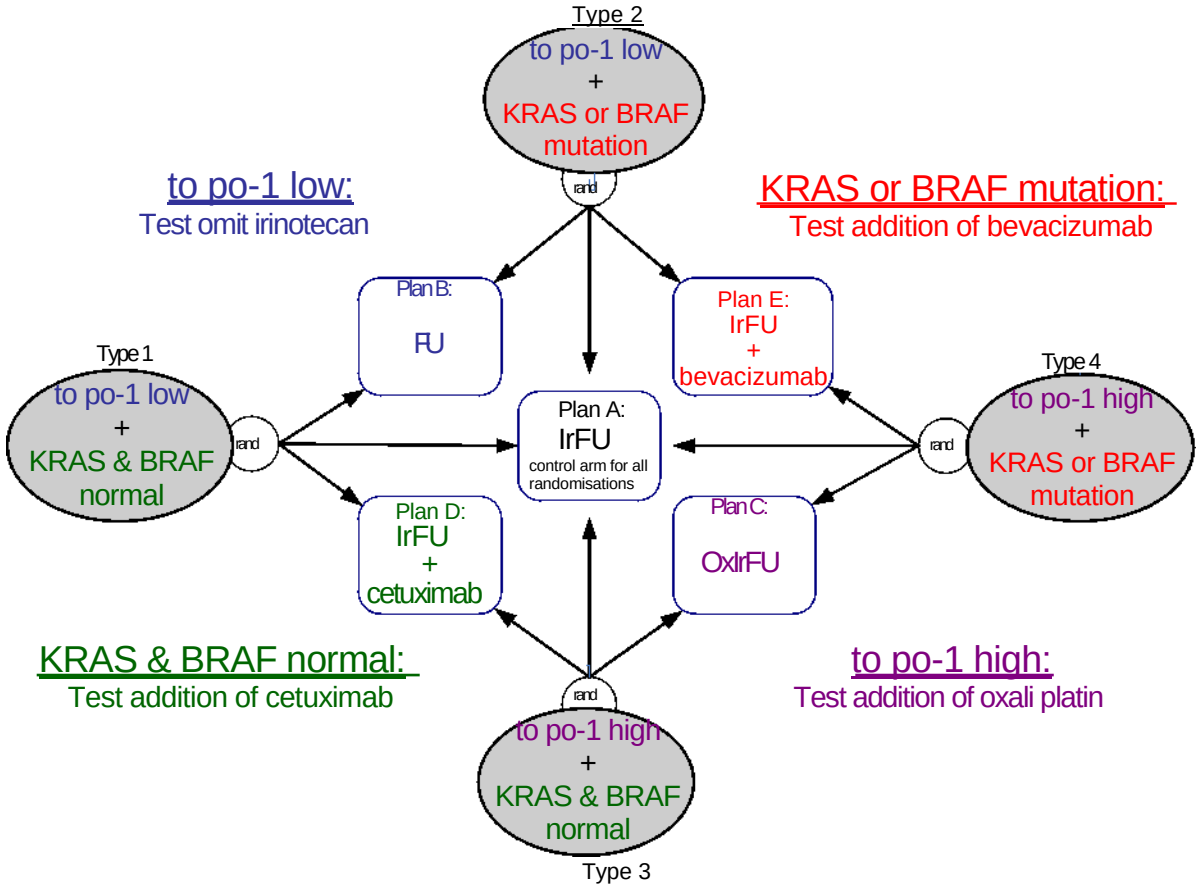
All of these treatments are given along with a vitamin calle d folinic aci d.

For each type of cancer we will be comparing the effects of three different treatment plans. One of these plans is the usual course of treatment that you woul d routinely be offere d (Plan A). The other two plans are those which the tumour sample tests suggest might be more appropriate than the usual treatment for your particular type of colorectal cancer.

7. Which treatment might I receive if I take part?

This will depen d on the result of the tests we do on your tumour sample. When the result of the tests is receive d by the trial office, they will inform your oncology doctor. Your oncology doctor will speak with you an d discuss the molecular type of cancer you have an d can give you more information about the three different treatment plans which you are now eligible to receive if you deci de to take part. As explaine d earlier, allocation to one of these three different treatment plans is ma de by a ran dom process, so it is important before you consent to participate that you an d your oncology doctor woul d be happy for you to follow any one of the plans.

The diagram below shows how this works.



This diagram shows the standard treatment in the centre rectangle. The 4 tumour types are shown in ovals. For each tumour type there are three possible treatment combinations you might receive.

For example, if your tumour is topo-1 low and KRAS or BRAF mutation, you can see that you are Type 2 and the three treatments you are most suited to receive are:

- **IrFU (standard)**
- **FU**
- **IrFU + bevacizumab**

You will be allocated to one of these treatments.

We know that in a few patients the tests do not give us an answer. So there will be a few patients in whom we cannot define their tumour type. This may be because only a very small amount of tumour was taken as a biopsy and there is none remaining for these extra tests, or because the test fails for a technical reason. It is important for us to find out how often this happens in real life, to see whether the large trial will work. If we have the results from one tumour test, but not the other, you will be randomised between two treatment allocations, and not three. Your oncology doctor will explain more about this to you if it happens. Again, we need to know how often this. If we have not been able to get a result from either test, you will be offered standard treatment off trial.

8. What happens during treatment?

Chemotherapy treatment involves numerous visits to the hospital. Whilst on any of the treatments you are allocated to, your progress will be monitored carefully. You will have a blood test once a fortnight. At this time you will also be asked about any side-effects you have experienced. It is important that you tell us about any problems, as it is often possible to deal with side-effects with minor adjustments to the treatment.

You will need to have a number of CT scans during your treatment in order for the doctors to assess your response. CT stands for computerised tomography. The CT scanner uses X-rays to take a series of very detailed pictures of the body and is a painless procedure. The pictures are taken while you lie on a couch, which moves backwards and forwards through the hole of the machine. This procedure involves some exposure to ionising radiation. Like all medical procedures, this does entail some risk, but in this case the benefits outweigh any such risk. The number of scans required is the same number that we normally request in routine clinical practice for patients in your condition.

9. How are the treatments given?

Whichever treatment you are allocated to receive, the treatment is given on a regular basis, every two weeks. This continues for at least six months, provided the cancer remains under good control and you are not getting any side effects that you cannot cope with.

All of the treatments are given as a 'drip' into one of your veins through a thin, flexible tube (called a 'cannula'). The drip is given once each fortnight and lasts for 48 hours. However, in most hospitals it is now possible to receive the treatment as an outpatient using a small portable pump, which you can take home with you.

If you have pump treatment at home, you will need to be fitted with a different type of tube known as a 'central line'. Central lines may be placed in the arm, shoulder or chest. The central line leads into one of the big veins in your chest and provides a place for the chemotherapy pump to be attached. Once this is fitted you will still need to attend the hospital for a day each fortnight, but it is not necessary to stay in overnight.

There are several different designs of tube and pump and your oncology doctor will explain which is to be used and what is involved. You will be given full details of the treatment for whichever combination you are allocated to.

10. What are the unwanted effects of treatment?

As well as its benefits, chemotherapy can also produce some unwanted effects. One important part of the trial is to compare the side effects of the different treatment plans, so that we can weigh up their advantages and disadvantages. The potential side-effects of the chemotherapy schedules are described in more detail in separate information sheets which will be given to you when we know your cancer type. Please ask your doctor or research nurse if you would like to read these now.

You will be given a Patient Card to carry around with you at all times. In case of an emergency, the card will inform the doctors that you are on a Clinical Trial and let then know what drugs you are being treated with. The card also lists the side effects that you might expect to experience from your allocated treatment. On the back of the card are the details of the people you should contact if you fell unwell.

11. What if my treatment doesn't work for me?

The trial treatment will continue if the CT scan shows that cancer has been stabilised or is shrinking. This treatment will be offered for as long as you are benefiting from it. If your cancer does not stabilise or shrink, then normally you will stop the treatment you are on, as there is no benefit. If this happens your clinic doctor will talk to you about other treatment options.

12. Confidentiality and safety

If you choose to enter this study, you may withdraw at any time and will still receive the best treatment your doctor can offer you.

Participation in this trial does not affect your normal rights to complain about any aspect of your treatment and care. If you wish to make a complaint about being approached for this trial, or about any aspect of the trial, the normal NHS complaints procedure is in place.

It is important that women of child-bearing age do not become pregnant while on this trial as the effects of these treatments on the baby are unknown. We would therefore ask that effective contraceptive measures are taken.

If you have private medical insurance you should consult with your insurer before agreeing to take part.

This trial is being sponsored by the Medical Research Council, which undertakes public sector research. If you decide to participate in this trial, information will be collected by the Medical Research Council Clinical Trials Unit. Your GP will be informed, but otherwise all information

about you and your treatment will remain strictly confidential and no individual patients will be identified when the results of the trial are published.

We will ask if we can flag your records with the NHS Information Centre so that if you move away or decide not to continue with the trial we will still be able to find out how you are doing. You will be asked a question about this on the consent form that you will have to sign before you are entered into the study.

During the course of the trial, which is expected to last one year, the progress of the research will be considered at regular intervals by an expert committee. Sometimes during the course of a research project, new information becomes available about the treatment that is being studied or the tests we are doing. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

The results of the study and the additional research described below will be presented after the completion of the trial at international scientific meetings and published in a leading medical journal. At no point in the analysis or publication will any information about the identity of participants be revealed. A copy of the results will be available to you or your family from your clinic on request. The regulatory authorities have given their permission for this trial to be undertaken and we will report to them in confidence any unexpected side effects which occur.

13. Will this trial help patients in the future?

The main purpose of this trial is to see whether this approach to testing the cancer tumour first, then allocating treatment depending on the tumour type, will work well in practice. So, we will be checking how long it takes for the sample to get to the central laboratory and how quickly and reliably the tests can be performed.

We also want to find out what you think about this approach to choice of treatment and the information we have given you, so at the end of this information sheet you will be given an optional response questionnaire with a few questions for you to answer.

If this trial is successful, we hope to expand the trial to a total of 3000 patients with colorectal cancer to prove which treatments are the best for the different cancer types.

14. Optional additional research

- **In asking you to take part in this trial, we will also ask you for a blood sample for research purposes. Each person's genetic makeup influences the way they respond to any medical treatment - how well it works and what side effects occur.**

  We plan to test a range of genes and proteins from your blood and from your cancer which may influence this. We would also like to test for any things in your genetic make up that might have given you an increased risk of getting the cancer in the first place. These studies will involve extracting DNA or other material from the tumour and blood. This research is based in UK Universities but may involve collaboration with commercial companies or other institutions.

  All such work is anonymous: your specimens will be identified by your unique trial number, not your name, and neither you nor your relatives will be identified or contacted. These additional studies will not affect your treatment in any way, and you are free to withhold this permission without affecting your participation in FOCUS 3 or your relationship with your doctor.

  Any unused part of the samples taken will be stored for as long as possible, in case further investigations are developed which may help us understand more about the response of cancer to these therapies. Please note that if any inventions resulting in commercial gain emerge from any of the above research, you will not be eligible to benefit financially from these discoveries.

- **We would be very interested in collecting your opinion on the kind of information we have given you about the trial. We realise that what happens on the trial may be difficult for many people to understand and we are trying to make the information sheets we give you as clear as possible. Your opinions would be very helpful in telling us where we could improve the information that we have given you. If you decide not to take part we would still like to receive this information. . This information will be collected on a very short response questionnaire, which you can complete yourself without giving your name.**

- **We would also like to talk to around 20 patients about the timings of starting treatment while we get the results of the tests. If you are approached and agree to take part, a member of the research team will arrange to meet with you for a research interview, a time that would be convenient for you during one of your clinic visits. We would like to tape record this discussion using a small portable voice recorder.**

15. What if there is a problem?

In the event that something does go wrong and you are harmed during this study there are no special compensation arrangements, other than the following standard arrangements for trials sponsored by the MRC:

- **If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation but you may have to pay your legal costs.**
- **If you have a concern about any aspect of the way you have been approached or treated during the course of this study, you should speak with your doctor. If you remain unhappy or would rather complain formally, you can do this through the NHS Complaints Procedure E. Participation in this study does not affect your normal rights to complain about any aspect of your treatment and care. (Contact number Details can be obtained from the hospital.)**
- **The MRC will give sympathetic consideration to claims for non-negligent harm suffered by a person as a result of a trial or other work supported by MRC. This does not extend to liability for non-negligent harm arising from conventional treatment where this is one arm of a trial. MRC acts as its own insurer and does not provide cover for non-negligent harm in advance for participants in MRC-fun de d studies.**
- **Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within the hospital, whether or not the patient is participating in an MRC-supporte d study. MRC does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is a NHS Trust or not.**
- **In addition, Merck, the company that manufactures and is supplying cetuximab, and Roche, the company that manufactures bevacizumab are responsible for ensuring that these drugs are manufactured in accordance with international standards for drug manufacture.**

Funding

This research is funded by Medical Research Council, with support from Health departments across the UK.

Further information

This study has been reviewed and approved by the Wales Research Ethics Committee. There is an information sheet with some further details about each of the types of treatment used in this trial. You will be given the appropriate one at the time of starting treatment, but if you would like to see all of them at this point please ask.

If you have any further questions about your illness or clinical trials, please discuss them with your doctor. You may also find it helpful to contact Cancerbackup, an independent patient advisory group (Freephone: 0808 800 1234; website: http://www.cancerbackup.org.uk;

Thank you for taking the time to read this information and for considering taking part in this study.

Contact names and telephone numbers:

Local PI

Research Nurse

PIS Stage 3 :

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Patient Information Sheet

(Stage 3)

FOCUS 3 - A study to determine the feasibility of molecular selection of therapy using KRAS, BRAF and topo-1 in patients with metastatic or locally advanced colorectal cancer.

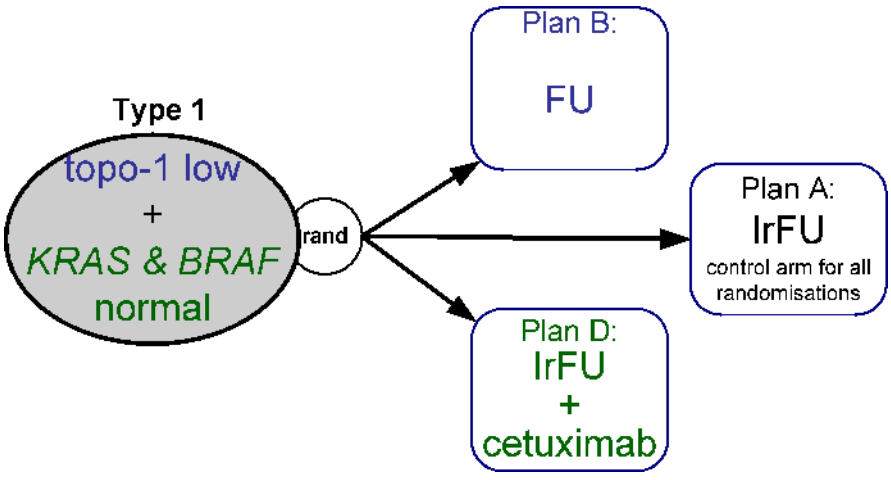
Randomisation 1

Information for patients whose tumour type is low topo-1 and KRAS and BRAF normal

The results of your tumour tests have shown that your tumour is Type 1 (See Stage 2 sheet diagram and the diagram in your folder). This means that the cancer has been confirmed as low topo-1 and KRAS and BRAF normal. This sheet gives some information about the chemotherapy you might now be receiving.

Which treatment will I receive if I take part?

There are three different treatment plans for your tumour type which we have called plans or regimens A, B, and D. Allocation to one of these treatment plans is made by a random process, so it is important before you join that both you and your doctor would be happy for you to accept any one of these plans. The diagram below and the diagram in your folder will help you to understand this. Your doctor/nurse will cross through any treatments which will not apply.



`Plan A' is the standard treatment IrFU.

Chemotherapy (IrFU) is given every two weeks, and this would continue for at least 6 months, provided the cancer remains under good control and you are not getting unpleasant side effects. You will have a CT scan after 12 weeks treatment to see how the cancer is responding and the treatment will continue if the cancer has been stabilised or is shrinking. This treatment will be offered as long as you are benefiting from it.

`Plan B' is FU alone.

FU is given every two weeks and this would continue for at least 6 months, provided the cancer remains under good control and you are not getting unpleasant side effects. As in Plan A, you will have a CT scan after 12 weeks to see how the cancer is responding and the treatment will continue if the cancer has been stabilised or is shrinking. This treatment would be offered as long as you are benefiting from it.

`Plan D' is IrFU plus cetuximab.

In addition to chemotherapy as in Plan A, you would receive a treatment with cetuximab every two weeks. As in Plan A, you will have a CT scan after 12 weeks to see how the cancer is responding and the treatment will continue if the cancer has been stabilised or is shrinking. This treatment will be offered as long as you are benefiting from it.

Whichever treatment you receive, the aim is to shrink or control your cancer and help you feel well for as long as possible. If at any stage your consultant feels that you would be better helped by an alternative form of treatment (e.g. surgery or radiotherapy), your participation in this research will not prevent that being offered.

Unfortunately, even at its best, chemotherapy may not control this form of cancer indefinitely. If your cancer starts to grow despite the full treatment plan your doctor will discuss further treatment options. Not every patient benefits from second-line treatment and the decision whether to recommend it depends on a careful individual assessment by your doctor, of its possible benefits and side effects.

Your contact numbers are:

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Patient Information Sheet

(Stage 3)

FOCUS 3 - A study to determine the feasibility of molecular selection of therapy using KRAS, BRAF and topo-1 in patients with metastatic or locally advanced colorectal cancer.

Version 3.0, November 2010

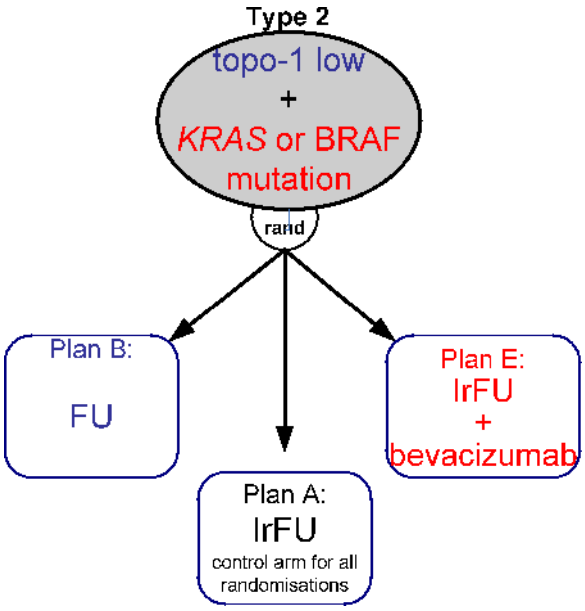
Randomisation 2

Information for patients whose tumour type is low topo-1 and KRAS or BRAF mutant

The results of your tumour tests have shown that your tumour is Type 2 (See Stage 2 sheet diagram). This means that the cancer has been confirmed as low topo-1 and either KRAS or BRAF mutant. This sheet gives some information about the chemotherapy you might now be receiving.

Which treatment might I receive if I take part?

There are three different treatment plans for you tumour type which we have called plans or regimens A, B, and E. Allocation to one of these treatment plans is made by a random process, so it is important before you join that both you and your doctor would be happy for you to accept any one of these plans. The diagram below and the diagram in your folder will help you to understand this. Your doctor/nurse will cross through any treatments which will not apply.



`Plan A' is the standard treatment IrFU.

Chemotherapy (IrFU) is given every two weeks, and this would continue for at least 6 months, provided the cancer remains under good control and you are not getting unpleasant side effects. You will have a CT scan after 12 weeks treatment to see how the cancer is responding and the treatment will continue if the cancer has been stabilised or is shrinking. This treatment will be offered as long as you are benefiting from it.

`Plan B' is FU alone.

FU is given every two weeks and this would continue for at least 6 months, provided the cancer remains under good control and you are not getting unpleasant side effects. As in Plan A, you will have a CT scan after 12 weeks to see how the cancer is responding and the treatment will continue if the cancer has been stabilised or is shrinking. This treatment will be offered as long as you are benefiting from it.

`Plan E' is IrFU plus bevacizumab.

In addition to chemotherapy as in Plan A, you would receive a treatment with bevacizumab every two weeks. As in Plan A, you will have a CT scan after 12 weeks to see how the cancer is responding and the treatment will continue if the cancer has been stabilised or is shrinking. This treatment will be offered as long as you are benefiting from it.

Whichever treatment you receive, the aim is to shrink or control your cancer and help you feel well for as long as possible. If at any stage your consultant feels that you would be better helped by an alternative form of treatment (e.g. surgery or radiotherapy), your participation in this research will not prevent that being offered.

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Patient Information Sheet

(Stage 3)

FOCUS 3 - A study to determine the feasibility of molecular selection of therapy using KRAS, BRAF and topo-1 in patients with metastatic or locally advanced colorectal cancer.

Version 3.0, November 2010

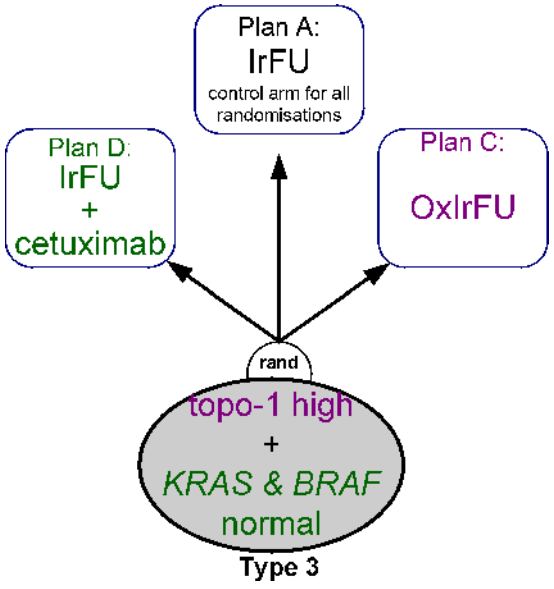
Randomisation 3

Information for patients whose tumour type is high topo-1 and both KRAS and BRAF normal

The results of your tumour tests have shown that your tumour is Type 3 (See Stage 2 sheet diagram). This means that the cancer has been confirmed as high topo-1, and both KRAS and BRAF normal. This sheet gives some information about the chemotherapy you might now be receiving.

Which treatment might I receive if I take part?

There are three different treatment plans for you tumour type which we have called plans (or regimens) A, C, and D. Allocation to one of these treatment plans is made by a random process, so it is important before you join that both you and your doctor would be happy for you to accept any one of these plans. The diagram below and the diagram in your folder will help you to understand this. Your doctor/nurse will cross through any treatments which will not apply.



'Plan A' is the standard treatment IrFU.

Chemotherapy (IrFU) is given every two weeks, and this would continue for at least 6 months, provided the cancer remains under good control and you are not getting unpleasant side effects. You will have a CT scan after 12 weeks treatment to see how the cancer is responding and the treatment will continue if the cancer has been stabilised or is shrinking. This treatment will be offered as long as you are benefiting from it.

'Plan C' is OxIrFU.

Chemotherapy (OxIrFU) is given every two weeks, and this would continue for at least 6 months, provided the cancer remains under good control and you are not getting unpleasant side effects. As in Plan A, you will have a CT scan after 12 weeks to see how the cancer is responding and the treatment will continue if the cancer has been stabilised or is shrinking. This treatment will be offered as long as you are benefiting from it.

'Plan D' is IrFU plus cetuximab.

In addition to chemotherapy as in Plan A, you would receive a treatment with cetuximab every two weeks. As in Plan A, you will have a CT scan after 12 weeks to see how the cancer is responding and the treatment will continue if the cancer has been stabilised or is shrinking. This treatment will be offered as long as you are benefiting from it.

Whichever treatment you receive, the aim is to shrink or control your cancer and help you feel well for as long as possible. If at any stage your consultant feels that you would be better helped by an alternative form of treatment (e.g. surgery or radiotherapy), your participation in this research will not prevent that being offered.

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Patient Information Sheet

(Stage 3)

FOCUS 3 - A study to determine the feasibility of molecular selection of therapy using KRAS, BRAF and topo-1 in patients with metastatic or locally advanced colorectal cancer.

Version 3.0, November 2010

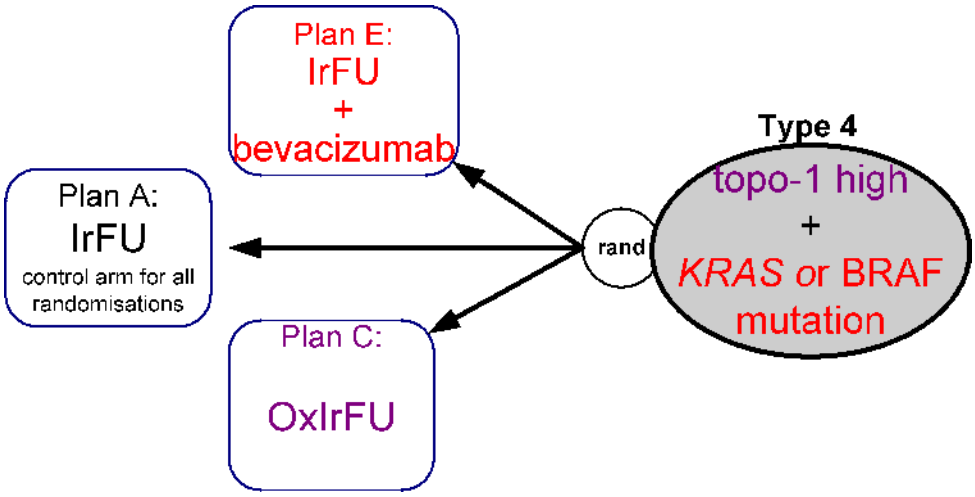
Randomisation 4

Information for patients whose tumour type is high topo-1 and KRAS or BRAF mutant

The results of your tumour tests have shown that your tumour is Type 4 (See Stage 2 sheet diagram). This means that the cancer has been confirmed as high topo-1 and either KRAS or BRAF mutant. This sheet gives some information about the chemotherapy you might now be receiving.

Which treatment might I receive if I take part?

There are three different treatment plans for you tumour type which we have called plans (or regimens) A, C, and E. Allocation to one of these treatment plans is made by a random process, so it is important before you join that both you and your doctor would be happy for you to accept any one of these plans. The diagram below and the diagram in your folder will help you to understand this. Your doctor/nurse will cross through any treatments which will not apply.



'Plan A' is the standard treatment IrFU.

Chemotherapy (IrFU) is given every two weeks, and this would continue for at least 6 months, provided the cancer remains under good control and you are not getting unpleasant side effects. You will have a CT scan after 12 weeks treatment to see how the cancer is responding and the treatment will continue if the cancer has been stabilised or is shrinking. This treatment will be offered as long as you are benefiting from it.

'Plan C' is OxIrFU.

Chemotherapy (OxIrFU) is given every two weeks, and this would continue for at least 6 months, provided the cancer remains under good control and you are not getting unpleasant side effects. As in Plan A, you will have a CT scan after 12 weeks to see how the cancer is responding and the treatment will continue if the cancer has been stabilised or is shrinking. This treatment will be offered as long as you are benefiting from it.

'Plan E' is IrFU plus bevacizumab.

In addition to chemotherapy as in Plan A, you would receive a treatment with bevacizumab every two weeks. As in Plan A, you will have a CT scan after 12 weeks to see how the cancer is responding and the treatment will continue if the cancer has been stabilised or is shrinking. This treatment will be offered as long as you are benefiting from it.

Whichever treatment you receive, the aim is to shrink or control your cancer and help you feel well for as long as possible. If at any stage your consultant feels that you would be better helped by an alternative form of treatment (e.g. surgery or radiotherapy), your participation in this research will not prevent that being offered.

Unfortunately, even at its best, chemotherapy may not control this form of cancer indefinitely. If your cancer starts to grow despite the full treatment plan your doctor will discuss further treatment options. Not every patient benefits from second-line treatment and the decision whether to recommend it depends on a careful individual assessment by your doctor, of its possible benefits and side effects.

Your contact numbers are:

PIS Stage 4 :

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Patient Information Sheet

(Stage 4)

FOCUS 3 — A study to determine the feasibility of molecular selection of therapy using KRAS, BRAF and topo-1 in patients with metastatic or locally advanced colorectal cancer.

IrFU Information Sheet — Plan A
Information for patients receiving IrFU chemotherapy

This sheet gives some information about the chemotherapy you will be receiving. 'IrFU' is short for 'Irinotecan + Fluorouracil'.

How is the treatment given?

IrFU chemotherapy is given each fortnight. The treatment starts with an anti-sickness injection then a 2-3 hour 'drip', into a vein, of a chemotherapy drug (irinotecan) and a vitamin called folinic acid (FA). This is followed by an injection of the chemotherapy drug, 'FU' (fluorouracil). The injection, also into the vein, takes about five minutes.

After that, you receive more FU, this time given very slowly into the vein, over the next 46 hours. There are several different methods of doing this and your oncology doctor or nurse will discuss with you the way that suits you best. Generally this is given at home, using a portable pump, however there may be times when you need to stay in hospital.

Depending upon which method is used, you may need to have a thin flexible tube fitted in either your arm or your chest. This leads into one of your veins, and chemotherapy is given through it. Once fitted, it can stay in for the duration of your treatment. You may also be asked to take warfarin, a tablet which reduces the risk of blood clots.

Unwanted effects of chemotherapy

For most patients the side effects of IrFU are only mild. However, you may find it helpful to be forewarned about some of the things which could occur.

During the first couple of hours of the chemotherapy you may notice sweating or watering eyes, and feel stomach cramps or have a bout of diarrhoea. If you are affected, tell the nurse on the chemotherapy unit: these symptoms are easily stopped by an injection. If this happens to you, you may receive the injection in advance for future treatments. If the

symptoms occur after you have got home from the hospital, during the 24 hours after your irinotecan infusion, rest quietly and telephone the ward for advice.

Occasionally, more severe diarrhoea can occur as a side effect of IrFU chemotherapy. If left untreated this could be dangerous, but it usually responds well to prompt treatment, therefore you will be given tablets (loperami de) to take if necessary. If you have diarrhoea (except within the first 24 hours after the irinotecan infusion)

- **Take 2 of the loperami de tablets provided, immediately after the first liquid stool, then another tablet every two hours until 12 hours after the diarrhoea has stopped.**
- **Drink plenty of water, fizzy drinks or soups for as long as the diarrhoea lasts.**
- **If the diarrhoea hasn't settled within 24 hours, you should contact the hospital. You will be asked to start a course of an antibiotic called ciprofloxacin. However, if the diarrhoea is severe, or if you can't drink plenty of liquid or if you also have a temperature, you may need to be admitted for a period of observation.**

Other side-effects

Some people feel more tired than usual for a few days. You may notice a change in taste for certain foods, or soreness in the mouth. Some patients find they feel sick, although actual vomiting is unusual. In the longer term, usually after several months of treatment, your hands and feet may become rather dry or sore, and you may have some have hayfever-like symptoms such as a runny nose or sore eyes.

All these side-effects can be helped by medication, so if you are affected please talk to your oncology team. If medication has been tried but the side effects persist, it is usually possible to get rid of them by slightly reducing the dose of chemotherapy. This does not compromise the effectiveness of treatment.

It is possible, though not inevitable, that your hair will thin during this treatment. If you find that you are losing hair, talk it through with your oncology nurses who will be able to help you cope. Hair loss, if it occurs, is temporary - it will grow back when IrFU treatment stops.

Rare side-effects

Just occasionally, we meet someone who is unusually sensitive to the effects of FU chemotherapy, and the side effects described above occur more quickly and severely than for others. The reason for this is an unusual metabolism which means that the FU stays in the bloodstream for longer after it has been given. If this happens, treatment is stopped until the problems have resolved, and it is then usually possible to restart at a lower dose. This does not compromise the effectiveness of treatment.

Very rarely, chemotherapy can cause heart palpitations, chest pain, or poor co-ordination. It is most unlikely that you will be affected, but if you suspect you have one of these problems, please discuss it with your oncology doctor.

Other complications

If you have had a tube fitted for receiving chemotherapy at home, there is a possibility of a problem related to the tube. If you notice any problems such as redness, pain or discharge around the tube, or swelling of one arm, please speak to the oncology doctor or nurse.

What about my other medications?

Most other medications (though not all) can be taken safely alongside IrFU treatment. If you are on regular medications (including non-prescribed drugs such as complementary therapies and herbal drugs), please make sure your oncology doctor knows about them before you start your treatment so that they can be checked.

After starting your IrFU treatment, if any new medication is required it is important that any doctor prescribing it knows you are on IrFU.

Finally, if you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering fits or severe diarrhoea, please seek advice immediately, either from your hospital team or from your GP.

Your contact numbers are:

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Patient Information Sheet

(Stage 4)

FOCUS 3 — A study to determine the feasibility of molecular selection of therapy using KRAS, BRAF and topo-1 in patients with metastatic or locally advanced colorectal cancer. Version 3.0, November 2010

FU Information Sheet — Plan B
Information for patients receiving FU chemotherapy

This sheet gives some information about the chemotherapy you will be receiving now that you have been allocated to this treatment plan.

How is the treatment given?

FU chemotherapy is given each fortnight. The treatment starts with a two hour drip, into a vein, of a vitamin called folinic acid (FA). This is followed by an injection of the chemotherapy drug, fluorouracil. The injection, also into the vein, takes about five minutes.

After that, you receive more fluorouracil, this time given very slowly into the vein, over the next 46 hours. There are several different methods of doing this and your oncology doctor or nurse will discuss with you the way that suits you best. Generally this is given at home, using a portable pump, however there may be times when you need to stay in hospital.

Depending upon which method is used, you may need to have a thin flexible tube fitted in either your arm or your chest. This leads into one of your veins, and chemotherapy is given through it. Once fitted, it can stay in for the duration of your treatment. You may also be asked to take a tablet called warfarin, to reduce the risk of a blood clot forming on the tube in your vein.

Unwanted effects of chemotherapy

Any chemotherapy can cause side effects. For most patients the side effects of FU are mild, and some have no side effects at all. However, you may find it helpful to be forewarned about some of the side effects that could occur.

- **FU can cause diarrhoea. You will be given anti-diarrhoea tablets to use if this is mild, but if you have severe diarrhoea (more than 4 watery stools in a day) please telephone the hospital for advice.**

- **Some patients find they feel a little sick for a few days after the FU treatment, but vomiting is unusual. You will be provided with some anti-sickness tablets to take if you start feeling sick. If you vomit more than once in a 24-hour period, please telephone the hospital for advice.**

Occasionally, more severe diarrhoea can occur as a side effect of IrFU chemotherapy. If left untreated this could be dangerous, but it usually responds well to prompt treatment, therefore you will be given tablets (loperami de) to take if necessary. If you have diarrhoea (except within the first 24 hours after the irinotecan infusion)

- **Take 2 of the loperami de tablets provided, immediately after the first liquid stool, then another tablet every two hours until 12 hours after the diarrhoea has stopped.**
- **Drink plenty of water, fizzy drinks or soups for as long as the diarrhoea lasts.**
- **If the diarrhoea hasn't settled within 24 hours, you should contact the hospital. You will be asked to start a course of an antibiotic called ciprofloxacin. However, if the diarrhoea is severe, or if you can't drink plenty of liquid or if you also have a temperature, you may need to be admitted for a period of observation.**

Other side-effects

Some people feel more tired than usual for a few days. You may notice a change in taste for certain foods, or soreness in the mouth. You will be provided with a mouthwash which may help. If you develop ulcers or pain in the mouth, please telephone the hospital for advice.
Some patients find they feel sick, although actual vomiting is unusual. In the longer term, usually after several months of treatment, your hands and feet may become rather dry or sore, with redness or dryness of the skin and you may have some have hayfever-like symptoms such as a runny nose or sore eyes.

All these side-effects can be helped by medication, so if you are affected please talk to your oncology team. If medication has been tried but the side effects persist, it is usually possible to get rid of them by slightly reducing the dose of chemotherapy. This does not compromise the effectiveness of treatment.

Rare side-effects

Very rarely, FU chemotherapy can cause heart palpitations, chest pain (angina), or poor co-ordination. It is most unlikely that you will be affected, but if you suspect you have one of these problems, please discuss it with your oncology doctor or nurse.

Other complications

If you have had a tube fitted for receiving chemotherapy at home, there is a possibility of a problem related to the tube. If you notice any problems such as redness, pain or discharge

around the tube, or swelling of one arm, please speak to the oncology doctor or nurse as soon as possible.

What about my other medications?

Most other medications (though not all) can be taken safely alongside FU treatment. If you are on regular medications (including non-prescribed drugs such as complementary therapies and herbal drugs), please make sure your oncology doctor knows about them before you start your treatment so that they can be checked.

After starting your FU treatment, if any new medication is required it is important that any doctor prescribing it knows you are on FU.

Finally, if you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering fits or severe diarrhoea, please seek advice immediately, either from your hospital team or from your GP.

Your contact numbers are:

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Patient Information Sheet

(Stage 4)

FOCUS 3 — A study to determine the feasibility of molecular selection of therapy using KRAS, BRAF and topo-1 in patients with metastatic or locally advanced colorectal cancer.

Version 3.0, November 2010

Ox Ir FU Information Sheet — Plan C
Information for patients receiving Ox Ir FU chemotherapy

This sheet gives some information about the chemotherapy you will be receiving. 'OxIrFU' is short for 'Oxaliplatin + Irinotecan + Fluorouracil'.

How is the treatment given?

OxIrFU chemotherapy is given each fortnight. The treatment starts with an anti-sickness injection then a 30 minute 'drip' into a vein with the first chemotherapy drug (irinotecan), followed by another 2-3 hour 'drip', into a vein, of a chemotherapy drug (oxaliplatin) and a vitamin (FA). This is followed by an injection of the chemotherapy drug, 'FU' (fluorouracil). The injection, also into the vein, takes about five minutes.

After that, you receive more FU, this time given very slowly into the vein, over the next 46 hours. There are several different methods of doing this and your oncology doctor or nurse will discuss with you the way that suits you best. Generally this is given at home, using a portable pump, however there may be times when you need to stay in hospital.

Depending upon which method is used, you may need to have a thin flexible tube fitted in either your arm or your chest. This leads into one of your veins, and chemotherapy is given through it. Once fitted, it can stay in for the duration of your treatment. You may also be asked to take warfarin, a tablet which reduces the risk of blood clots.

Unwanted effects of chemotherapy

You may find it helpful to be forewarned about some of the side effects which could occur with OxIrFU.

During the first couple of hours of the chemotherapy you may notice sweating or watering eyes, and feel stomach cramps or have a bout of diarrhoea. If you are affected, tell the nurse

on the chemotherapy unit: these symptoms are easily stopped by an injection. If this happens to you, you may receive the injection in advance for future treatments. If the symptoms occur after you have got home from the hospital, during the 24 hours after your irinotecan infusion, rest quietly and telephone the ward for advice.

Occasionally, more severe diarrhoea can occur as a side effect of OxIrFU chemotherapy. If left untreated this could be dangerous, but it usually responds well to prompt treatment, therefore you will be given tablets (loperami de) to take if necessary. If you have diarrhoea (except within the first 24 hours after the irinotecan infusion)

- **Take 2 of the loperami de tablets provided, immediately after the first liquid stool, then another tablet every two hours until 12 hours after the diarrhoea has stopped.**
- **Drink plenty of water, fizzy drinks or soups for as long as the diarrhoea lasts.**
- **If the diarrhoea hasn't settled within 24 hours, you should contact the hospital. You will be asked to start a course of an antibiotic called ciprofloxacin. However, if the diarrhoea is severe, or if you can't drink plenty of liquid or if you also have a temperature, you may need to be admitted for a period of observation.**

For a few hours or days after starting treatment, you may feel pins and needles in the hands and feet if you touch cold things or go out in the cold. You may also feel tingling in the throat. This is quite normal and not harmful. If affected, you may wish to wear gloves and avoid cold places for the periods when you are affected.

After several months of treatment, some patients find that the temporary tingling sensations, instead of lasting just a few hours or days, persist for longer. As a general rule, if this symptom persists right through the 2 weeks until your next treatment is due, and especially you have numbness as well as tingling, it is time to drop one of the drugs - oxaliplatin - from the chemotherapy. Please ensure you discuss this with your doctors if you are affected.

Some people feel discomfort or pain up their arm during the 2 hours that the oxaliplatin drip is running. If you are affected please tell the nurse on the chemotherapy unit straight away: this symptom can usually be relieved by placing a warm pad over the arm.

Just occasionally, people can become allergic to oxaliplatin, though usually only after several treatments. If, while the oxaliplatin drip is running, you develop palpitations, an itchy rash, wheezing or a swollen tongue, please tell the nurses immediately.

Other side-effects

Some people feel more tired than usual for a few days. You may notice a change in taste for certain foods, or soreness in the mouth. Some patients find they feel sick, although actual vomiting is unusual. In the longer term, usually after several months of treatment, your hands and feet may become rather dry or sore, and you may have some have hayfever-like symptoms such as a runny nose or sore eyes.

All these side-effects can be helped by medication, so if you are affected please talk to your oncology team. If medication has been tried but the side effects persist, it is usually possible to get rid of them by slightly reducing the dose of chemotherapy. This does not compromise the effectiveness of treatment.

It is possible, though not inevitable, that your hair will thin during this treatment. If you find that you are losing hair, talk it through with your oncology nurses who will be able to help you cope. Hair loss, if it occurs, is temporary - it will grow back when IrFU treatment stops.

Rare side-effects

Just occasionally, we meet someone who is unusually sensitive to the effects of FU chemotherapy, and the side effects described above occur more quickly and severely than for others. The reason for this is an unusual metabolism which means that the FU stays in the bloodstream for longer after it has been given. If this happens, treatment is stopped until the problems have resolved, and it is then usually possible to restart at a lower dose. This does not compromise the effectiveness of treatment.

Very rarely, chemotherapy can cause heart palpitations, chest pain, or poor co-ordination. It is most unlikely that you will be affected, but if you suspect you have one of these problems, please discuss it with your oncology doctor.

Other complications

If you have had a tube fitted for receiving chemotherapy at home, there is a possibility of a problem related to the tube. If you notice any problems such as redness, pain or discharge around the tube, or swelling of one arm, please speak to the oncology doctor or nurse.

What about my other medications?

Most other medications (though not all) can be taken safely alongside OxIrFU treatment. If you are on regular medications (including non-prescribed drugs such as complementary therapies and herbal drugs), please make sure your oncology doctor knows about them before you start your treatment so that they can be checked.

After starting your OxIrFU treatment, if any new medication is required it is important that any doctor prescribing it knows you are on OxIrFU.

Finally, if you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering fits or severe diarrhoea, please seek advice immediately, either from your hospital team or from your GP.

Your contact numbers are:

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Patient Information Sheet

(Stage 4)

FOCUS 3 - A study to determine the feasibility of molecular selection of therapy using KRAS, BRAF and topo-1 in patients with metastatic or locally advanced colorectal cancer.

Version 3.0, November 2010

Ir FU & cetuximab Information Sheet
Plan D

Information for patients receiving IrFU chemotherapy an d cetuximab

This sheet gives some information about the chemotherapy you will be receiving. 'IrFU' is short for 'Irinotecan + Fluorouracil'.

How is the treatment given?

IrFU & cetuximab chemotherapy is given each fortnight. The treatment starts with the first dose of cetuximab. A drip will be placed in your arm. Because cetuximab is an antibody, it can occasionally cause an allergic reaction. To begin with, an injection is given through the drip to reduce the risk of an allergic reaction. You will then receive the first dose of cetuximab as a drip over 2 hours. The nurse will monitor your pulse and blood pressure regularly before, during and after this treatment.

Following this you will have a 2-3 hour 'drip' of a vitamin called folinic acid (FA), into a vein, followed by a 'drip' of another chemotherapy drug (irinotecan) for another half an hour. This is followed by an injection of the chemotherapy drug, 'FU'. The injection, also into the vein, takes about five minutes.

After that, you receive more FU, this time given very slowly into the vein, over the next 46 hours. There are several different methods of doing this and your oncology doctor or nurse will discuss with you the way that suits you best. Generally this is given at home, using a portable pump, however there may be times when you need to stay in hospital.

Depending upon which method is used, you may need to have a thin flexible tube fitted in either your arm or your chest. This leads into one of your veins, and chemotherapy is given through it. Once fitted, it can stay in for the duration of your treatment. You may also be asked to take warfarin, a tablet which reduces the risk of blood clots.

Unwanted effects of chemotherapy

For most patients the side effects of IrFU and cetuximab are only mild. However, you may find it helpful to be forewarned about some of the things which could occur.

During the first couple of hours of the chemotherapy you may notice sweating or watering eyes, and feel stomach cramps or have a bout of diarrhoea. If you are affected, tell the nurse on the chemotherapy unit: these symptoms are easily stopped by an injection. If this happens to you, you may receive the injection in advance for future treatments. If the symptoms occur after you have got home from the hospital, during the 24 hours after your irinotecan infusion, rest quietly and telephone the ward for advice.

Occasionally, more severe diarrhoea can occur as a side effect of IrFU chemotherapy. If left untreated this could be dangerous, but it usually responds well to prompt treatment, therefore you will be given tablets (loperami de) to take if necessary. If you have diarrhoea (except within the first 24 hours after the irinotecan infusion)

- **Take 2 of the loperami de tablets provided, immediately after the first liquid stool, then another tablet every two hours until 12 hours after the diarrhoea has stopped.**
- **Drink plenty of water, fizzy drinks or soups for as long as the diarrhoea lasts.**
- **If the diarrhoea hasn't settled within 24 hours, you should contact the hospital. You will be asked to start a course of an antibiotic called ciprofloxacin. However, if the diarrhoea is severe, or if you can't drink plenty of liquid or if you also have a temperature, you may need to be admitted for a period of observation.**

Cetuximab causes a rash in most people that is like acne. This happens because it is blocking the action of the growth factor on the skin cells. It comes on gradually over the first three weeks and tends to affect the chest, front and back, and can affect the face. The treatments that are given for acne can help this rash including local and oral antibiotics. It can get quite bad in which case your oncology doctor may recommend interrupting the cetuximab treatment for 1 - 2 weeks to allow it to settle. In most patients it has settled down by 12 weeks of treatment.

Patients who have a longer course of treatment with cetuximab can find their skin gets dry and their eyelashes grow longer and curly. In addition some people develop a sore area alongside the nails (especially of the big toes and thumbs). Treatment can help all of these effects.

Cetuximab may cause an allergic reaction that may be life threatening. This occurs in 1 in 50 people receiving this treatment. You will be given medicines at each cycle to reduce this risk and emergency treatment will be available to treat the reaction if it occurs.

Cetuximab may cause a reduction in the level of magnesium salt in your blood. This may cause tiredness and unsteadiness and very rarely confusion and irregularity of heart rhythm.

FOCUS 3

The level of magnesium in the blood will therefore be monitored regularly and supplements provided if the

level falls below normal.

Other side-effects

Some people feel more tired than usual for a few days. You may notice a change in taste for certain foods, or soreness in the mouth. Some patients find they feel sick, although actual vomiting is unusual. In the longer term, usually after several months of treatment, your hands and feet may become rather dry or sore, and you may have some have hayfever-like symptoms such as a runny nose or sore eyes.

All these side-effects can be helped by medication, so if you are affected please talk to your oncology team. If medication has been tried but the side effects persist, it is usually possible to get rid of them by slightly reducing the dose of chemotherapy. This does not compromise the effectiveness of treatment.

It is possible, though not inevitable, that your hair will thin during this treatment. If you find that you are losing hair, talk it through with your oncology nurses who will be able to help you cope. Hair loss, if it occurs, is temporary - it will grow back when IrFU treatment stops.

Rare side-effects

Just occasionally, we meet someone who is unusually sensitive to the effects of FU chemotherapy, and the side effects described above occur more quickly and severely than for others. The reason for this is an unusual metabolism which means that the FU stays in the bloodstream for longer after it has been given. If this happens, treatment is stopped until the problems have resolved, and it is then usually possible to restart at a lower dose. This does not compromise the effectiveness of treatment.

Very rarely, chemotherapy can cause heart palpitations, chest pain, or poor co-ordination. It is most unlikely that you will be affected, but if you suspect you have one of these problems, please discuss it with your oncology doctor.

Other complications

If you have had a tube fitted for receiving chemotherapy at home, there is a possibility of a problem related to the tube. If you notice any problems such as redness, pain or discharge around the tube, or swelling of one arm, please speak to the oncology doctor or nurse.

What about my other medications?

Most other medications (though not all) can be taken safely alongside IrFU + cetuximab treatment. If you are on regular medications (including non-prescribed drugs such as

complementary therapies and herbal drugs), please make sure your oncology doctor knows about them before you start your treatment so that they can be checked.

After starting your IrFU + cetuximab treatment, if any new medication is required it is important that any doctor prescribing it knows you are on IrFU + cetuximab.

Finally, if you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering fits or severe diarrhoea, please seek advice immediately, either from your hospital team or from your GP.

Your contact numbers are:

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Patient Information Sheet

(Stage 4)

FOCUS 3 - A study to determine the feasibility of molecular selection of therapy using KRAS, BRAF and topo-1 in patients with metastatic or locally advanced colorectal cancer.

Version 3.0, November 2010

Ir FU & bevacizumab Information Sheet
Plan E

Information for patients receiving IrFU and bevacizumab chemotherapy.

This sheet gives some information about the chemotherapy you will be receiving. 'IrFU' is short for 'Irinotecan + Fluorouracil'.

How is the treatment given?

IrFU + bevacizumab treatment is given each fortnight. The treatment starts with an anti-sickness injection then a 90 minute 'drip', into a vein, of a the drug bevacizumab, followed by a 30 minute 'drip' of another drug called irinotecan. A vitamin called folinic acid (FA) is then given as a 'drip' over a further 2 hours. This is followed by an injection of the chemotherapy drug, 'FU' (fluorouracil). The injection, also into the vein, takes about five minutes.

After that, you receive more FU, this time given very slowly into the vein, over the next 46 hours. There are several different methods of doing this and your oncology doctor or nurse will discuss with you the way that suits you best. Generally this is given at home, using a portable pump, however there may be times when you need to stay in hospital.

Depending upon which method is used, you may need to have a thin flexible tube fitted in either your arm or your chest. This leads into one of your veins, and chemotherapy is given through it. Once fitted, it can stay in for the duration of your treatment. You may also be asked to take warfarin, a tablet which reduces the risk of blood clots.

Unwanted effects of chemotherapy

You may find it helpful to be forewarned about some of the side effects that could occur with IrFU + bevacizumab.

During the first couple of hours of the chemotherapy you may notice sweating or watering eyes, and feel stomach cramps or have a bout of diarrhoea. If you are affected, tell the nurse on the chemotherapy unit: these symptoms are easily stopped by an injection. If this happens to you, you may receive the injection in advance for future treatments. If the symptoms occur after you have got home from the hospital, during the 24 hours after your irinotecan infusion, rest quietly and telephone the ward for advice.

Occasionally, more severe diarrhoea can occur as a side effect of IrFU chemotherapy. If left untreated this could be dangerous, but it usually responds well to prompt treatment, therefore you will be given tablets (loperami de) to take if necessary. If you have diarrhoea (except within the first 24 hours after the irinotecan infusion)

- **Take 2 of the loperami de tablets provided, immediately after the first liquid stool, then another tablet every two hours until 12 hours after the diarrhoea has stopped.**
- **Drink plenty of water, fizzy drinks or soups for as long as the diarrhoea lasts.**
- **If the diarrhoea hasn't settled within 24 hours, you should contact the hospital. You will be asked to start a course of an antibiotic called ciprofloxacin. However, if the diarrhoea is severe, or if you can't drink plenty of liquid or if you also have a temperature, you may need to be admitted for a period of observation.**

Other side-effects

Some people feel more tired than usual for a few days. You may notice a change in taste for certain foods, or soreness in the mouth. Some patients find they feel sick, although actual vomiting is unusual. In the longer term, usually after several months of treatment, your hands and feet may become rather dry or sore, and you may have some have hayfever-like symptoms such as a runny nose or sore eyes.

All these side-effects can be helped by medication, so if you are affected please talk to your oncology team. If medication has been tried but the side effects persist, it is usually possible to get rid of them by slightly reducing the dose of chemotherapy. This does not compromise the effectiveness of treatment.

It is possible, though not inevitable, that your hair will thin during this treatment. If you find that you are losing hair, talk it through with your oncology nurses who will be able to help you cope. Hair loss, if it occurs, is temporary - it will grow back when IrFU treatment stops.

About one third of people receiving bevacizumab develop mild or moderate raised blood pressure (hypertension). We will monitor your blood pressure each time you attend before treatment and if your blood pressure goes up significantly (more than 20mmHg) then a blood pressure tablet will be prescribed for you.

It is rare to have an allergic reaction to bevacizumab. Signs of a reaction include skin rashes and itching, a feeling of swelling in the tongue or throat, irritation of the nasal passages, wheezing, a cough and breathlessness. You will be monitored closely during your treatment, but it is very important to tell your nurse or oncology doctor if you have any of these symptoms.

Wounds may also take longer to heal while you are having treatment with bevacizumab. Bevacizumab can also reduce the production of platelets (which help the blood to clot). Let your oncology doctor or GP know if you have any unexplained bruising or bleeding.

Rare side-effects

Just occasionally, we meet someone who is unusually sensitive to the effects of FU chemotherapy, and the side effects described above occur more quickly and severely than for others. The reason for this is an unusual metabolism which means that the FU stays in the bloodstream for longer after it has been given. If this happens, treatment is stopped until the problems have resolved, and it is then usually possible to restart at a lower dose. This does not compromise the effectiveness of treatment.

Very rarely, chemotherapy can cause heart palpitations, chest pain, or poor co-ordination. It is most unlikely that you will be affected, but if you suspect you have one of these problems, please discuss it with your oncology doctor. Your blood pressure will be checked regularly as bevacizumab can sometimes cause high blood pressure. If you have any headaches, nosebleeds or feelings of dizziness let your oncology doctor or GP know.

There have been some reports of an increased risk of blood clots (DVT), stroke and angina (heart pain) in people taking bevacizumab. There are also rare reports of gastro-intestinal perforation in people taking bevacizumab. It is important that you contact your doctor immediately if you suffer from severe stomach pain.

Other complications

If you have had a tube fitted for receiving chemotherapy at home, there is a possibility of a problem related to the tube. If you notice any problems such as redness, pain or discharge around the tube, or swelling of one arm, please speak to the oncology doctor or nurse.

What about my other medications?

Most other medications (though not all) can be taken safely alongside IrFU + bevacizumab treatment. If you are on regular medications (including non-prescribed drugs such as complementary therapies and herbal drugs), please make sure your oncology doctor knows about them before you start your treatment so that they can be checked.

After starting your IrFU + bevacizumab treatment, if any new medication is required it is important that any doctor prescribing it knows you are on IrFU + bevacizumab.

Finally, if you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering fits or severe diarrhoea, please seek advice immediately, either from your hospital team or from your GP.

Your contact numbers are:

<Delete this line an d print on hospital hea de d paper. Important Note: Capecitabine chemotherapy should only be administered to patients who have had line complications on MdG which must be discussed with MRC CTU prior to change.>

Patient Information Sheet

(Stage 4)

FOCUS 3 - A study to determine the feasibility of molecular selection of therapy using KRAS, BRAF and topo-1 in patients with metastatic or locally advanced colorectal cancer. Version 3.0, November 2010

Capecitabine Information Sheet

Information for patients receiving capecitabine chemotherapy

This sheet gives some information about one of the chemotherapy drugs you will be receiving now. Capecitabine (also known as Xelo da) comes in tablet form and will replace the FU which has been administered through the PICC line. Any other drugs you have been allocated to will remain the same.

At home, you will have a course of capecitabine tablets to take each morning and evening for 9 days, followed by a 5 day rest period with no capecitabine tablets. We call the whole two-week period one "cycle" of chemotherapy.

The dose of tablets is prescribed by your specialist, based on your body size and other factors. Different patients need different doses. The tablets come in two sizes, large (500 mg) and small (150 mg). The hospital pharmacist will work out how many large and small tablets you should take to give you the right dose, and will dispense one full cycle at a time (i.e. 9 days = 18 doses). You should take your first dose of capecitabine in the evening after you receive your other chemotherapy treatment at the hospital; the last dose of the cycle will be due on the morning 9 days later.

Take your dose of capecitabine tablets twice a day, approximately twelve hours apart (for example 8 a.m. and 8 p.m.). Try to stick to the same time each day, give-or-take two hours. It is best not to take capecitabine on an empty stomach, so have something to eat during the half-hour before your tablets are due. Swallow the tablets with water.

2. How will I remember the tablets?

It can be very difficult to remember to take tablets regularly. When you start each cycle of capecitabine you will be given a diary sheet with a space for each dose you are due. Please keep the sheet with your tablets, and make a note of the time you take each dose.

If you forget a dose but remember it within the next 6 hours, take it then and mark the time on the sheet. If you forget a dose completely, just write "forgot" in the box for that dose. Do not try to squeeze in extra doses the next day, and do not add on any missed doses at the end of the course, during your week's rest from treatment.

3. What about my other medications?

Most other medications (though not all) can be taken safely alongside capecitabine treatment. If you are on regular medications, please make sure your specialist knows about them before you start your treatment so that they can be checked. After starting your treatment, if any new medication is required it is important that the doctor prescribing it knows that you are receivign chemotherapy.

It is particularly important to tell your specialist about any of the following medications: warfarin, phenytoin, sorivu dine, brivu dine.

4. Will capecitabine chemotherapy have unwanted effects?

Any form of chemotherapy can cause side effects. On the whole the side effects of capecitabine are mild. However, you may find it helpful to be forewarned about some of the side effects that could occur.

- **Capecitabine can cause diarrhoea. You will be given anti-diarrhoea tablets to use if this is mild, but if you have severe diarrhoea (more than 4 watery stools in a day) please stop taking your capecitabine tablets and telephone the hospital for advice.**
- **Some patients feel a little sick for a few days after starting treatment. You will be provided with some anti-sickness tablets to take if you start feeling sick. If you vomit more than once in a 24-hour period please stop taking your capecitabine tablets and telephone the hospital for advice.**
- **Some people notice soreness in the mouth or a change in taste for some foods. You will be provided with a mouthwash that may help. If you develop ulcers or pain in the mouth, stop taking your capecitabine tablets and telephone the hospital for advice.**
- **Some people feel more tired than usual during chemotherapy treatment. There is no easy answer to this, but if you are affected you may find it helps to set aside a rest period in the middle of each day.**
- **In the longer term, usually after more than one cycle of treatment, your hands and feet may become rather tingly or sore, with redness or dryness of the skin. If you get pain, swelling or blistering/peeling of the skin, please stop taking your capecitabine tablets and telephone the hospital for advice.**

- **Chemotherapy can reduce the number of white cells in your blood. This can lead to increased vulnerability to infections. Your medical team will be monitoring your white cell count each time you come for treatment to make sure it is safe to continue.**
- **All these side effects can be helped by medication, so if you are affected please talk to your oncology team. If medication has been tried but the side effects persist, it is usually possible to get rid of them by slightly reducing the dose of chemotherapy. This does not compromise the effectiveness of treatment.**

If you have to stop taking your capecitabine tablets for any of these reasons, please make a note on the diary sheet. Do not add on the missed doses at the end of the course.

It is important to stop taking the capecitabine tablets if the side effects become troublesome. Some patients worry that this might reduce the effectiveness of the treatment, but research has shown this is not the case.

5. Rare side effects

Very rarely, capecitabine chemotherapy can cause heart palpitations, chest pain (angina), or poor co-ordination. It is most unlikely that you will be affected, but if you suspect you have one of these problems, please discuss it with your oncology doctor or nurse.

If you start suffering from any chest pain, please stop taking your capecitabine tablets and telephone the hospital for advice.

6. Are there any other precautions?

Please keep your capecitabine tablets well away from children, and do not let them become mixed up with anybody else's tablets. If there are any left over at the end of a cycle (for example if you forgot a dose, or missed some doses because of illness) please bring these along to your next hospital appointment and return them to the nurse or pharmacist along with your diary sheet - do not throw them away or store them at home.

Finally, if you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering fits or severe diarrhoea, please seek advice immediately, either from your hospital team or from your GP.

Your contact numbers are:

APPENDIX XII - Consent Forms

<Delete this line an d print on local hea de d paper>

Patient I dentification Number for this trial.....

affix patient ID sticker

REGISTRATION CONSENT FOR

Version 3.0, November 2010

FOCUS 3 - A STUDY TO DETERMINE THE FEASIBILITY OF MOLECULAR SELECTION OF THERAPY USING KRAS, BRAF AND TOPO-1 IN PATIENTS WITH METASTATIC OR LOCALLY ADVANCED COLORECTAL CANCER.

Name of Researcher .....

Please initial boxes to agree:

1. **I confirm that I have rea d an d un derstan d the information sheet, Stage 1 (Version 3.0 November 2010) for the above stu dy an d have ha d the opportunity to ask questions.** ☐

2. **I un derstan d that my participation is voluntary an d that I am free to with draw at any time, without giving any reason, without my me dical care or legal rights being affecte d.** ☐

3. **I give permission for a sample of the store d pathological specimens to be molecular teste d for topo-1 levels, an d KRAS an d BRAF mutation status, an d use d for other future bowel cancer research.** ☐

4. **I give permission for a copy of my consent form to be sent to the local pathology department to authorise the release of my pathology block an d to the MRC CTU where once checke d, the consent form will be destroye d.** ☐

5. **I agree to complete a response questionnaire which will document my un derstan ding of the trial. (This is optional and does not need to be completed to participate in the trial).** ☐

Boxes 1-4 must be initialled for consent to be valid I

agree to take part in the above study

Name of Patient	**Date**	**Signature**
Name of Person taking consent (if different from researcher)	**Date**	**Signature**
Researcher	**Date**	**Signature**

(1 copy for patient; 1 for researcher; 1 to be kept with hospital notes)

affix patient ID sticker

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Patient I dentification Number for this trial.....

RANDO MISATION CONSENT FOR M

Version 3.0, November 2010

FOCUS 3 - A STUDY TO DETERMINE THE FEASIBILITY OF MOLECULAR SELECTION OF THERAPY USING KRAS, BRAF AND TOPO-1 IN PATIENTS WITH METASTATIC OR LOCALLY ADVANCED COLORECTAL CANCER.

Name of Researcher .....

Please initial boxes to agree:

1. **I confirm that I have rea d an d un derstan d the information sheet Stages 2 & 3 (Version 3.0 November 2010) for the above stu dy an d have ha d the opportunity to ask questions.** ☐
2. **I un derstan d that my participation is voluntary an d that I am free to with draw at any time, without giving any reason, without my me dical care or legal rights being affecte d.** ☐
3. **I un derstan d that sections of any of my me dical notes may be looke d at by in divi duals from organisations involve d in developing an d running the trial (e.g. MRC CTU or Merck or Roche pharmaceutical companies) or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these in divi duals to have access to my records.** ☐
4. **I un derstan d that information hel d by the NHS an d records maintaine d by the NHS Information Centre an d the NHS Central Register or any applicable NHS information system may be use d to provi de information about my health status shoul d I lose contact with my hospital doctor** ☐
5. **I give permission for a copy of my consent form to be sent to the MRC CTU where once checke d, the consent form will be destroye d.** ☐
6. **I give permission for my GP to be informe d of my inclusion in this stu dy. All** ☐

6 boxes above must be initialled for consent to be valid.

7. **I give permission for a sample of my bloo d inclu ding the DNA to be use d for future bowel cancer research. (If you do not wish to give this permission, do not sign - you can still participate in the trial).** ☐

I agree to take part in the above study

Name of Patient	**Date**	**Signature**
Name of Person taking consent (if different from researcher)	**Date**	**Signature**
Researcher	**Date**	**Signature**

(1 copy for patient; 1 for researcher; 1 to be kept with hospital notes)

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Patient I dentification Number for this trial' .....

affix patient ID sticker

INTERVIEW CONSENT FOR

Version 2.0, October 2009

FOCUS 3 - A STUDY TO DETERMINE THE FEASIBILITY OF MOLECULAR SELECTION OF THERAPY USING KRAS, BRAF AND TOPO-1 IN PATIENTS WITH METASTATIC OR LOCALLY ADVANCED COLORECTAL CANCER.

Name of Researcher.....

Please initial boxes to agree:

1. **If requeste d, I agree to take part in an au dio-tape d interview an d give consent to the storage (inclu ding electronic) of personal information for the purposes of this stu dy. I un derstan d that any information that coul d i dentify me will be kept strictly confi dential an d that no personal information will be inclu de d in the stu dy report or other publication.** ☐

2. **If interviewe d, I give permission for some of my actual quotations to be use d anonymously in any future presentations or publications. (If you do not wish to give this permission, do not initial - you can still participate in the interview).** ☐

Box 1 must be initialled *and* the section below signed and dated for the supplementary consent to be valid.

I agree to take part in the interview

Name of Patient	**Date**	**Signature**
Name of Person taking consent (if different from researcher)	**Date**	**Signature**
Researcher	**Date**	**Signature**

(1 copy for patient; 1 for researcher; 1 to be kept with hospital notes)

APPENDIX XIII - Response Questionnaire

<PRINT ON HOSPITAL HEADED PAPER> **Version 1.0, March 2009**

Patient Response Questionnaire

Patient ID: ☐☐☐☐☐☐

To be completed after reading the Patient Information Sheet stage 2.
To give to patients with Stage 2 of Patient Information Sheet
Please answer all the questions by circling the number that best applies to you.

	I understood fully	I understood	I'm not sure if I understand	I didn't mostly understand	I didn't understand at all
1. To what extent do you think that you have un derstood the information containe d in the Patient Information Sheet stage 2?	1	2	3	4	5
2. To what extent do you feel you un derstoo d:					
a. Why your tumour was tested?	1	2	3	4	5
b. The differences between the treatments that you may be allocated to?	1	2	3	4	5
c. Why you have to wait for 2 weeks for treatment (inclu ding stan dard treatment)?	1	2	3	4	5
d. How you are allocate d (ran domised to) treatment?	1	2	3	4	5
e. What happens during treatment?	1	2	3	4	5
f. That you are aske d to give permission for a blood sample or this response questionnaire or, possibly an interview as part of further research stu dies?	1	2	3	4	5

	Yes	No
3. Are you going to consent to this stu dy?		

4. What other information helpe d you make your decision?

5. If you do not wish to participate in the study, we would appreciate if you could tell us your reason(s) why.

Thank you very much for completing this questionnaire.

APPENDIX XIV - GP Letter

FOCUS 3 Trial GP letter

< delete this line an d print on local hospital hea de d notepaper>

Version 2.0, October 2009

Dear. Dr......

Your patient ..... has been diagnose d with metastatic colorectal cancer. Following discussion of treatment options an d review of the trial information sheets, (s)he has consente d to enter the MRC FOCUS 3 trial.

Your patient has been allocate d to: (please see attache d trial schema)

- **Regimen A (Control): 5-fluorouracil + irinotecan (IrM dG)**
- **Regimen B: 5-fluorouracil alone (M dG)**
- **Regimen C: 5-fluorouracil + irinotecan + oxaliplatin (IrOxM dG)**
- **Regimen D: 5-fluorouracil + irinotecan + cetuximab**
- **Regimen E: 5-fluorouracil + irinotecan + bevacizumab**

The chemotherapy regimen for your patient will be:

- **Irinotecan + 5-fluorouracil: A combination of irinotecan, folinic acid plus bolus 5- fluorouracil followed by 46hour infusion of 5-fluorouracil repeated every 2 weeks OR**
- **5-fluorouracil: A combination of folinic acid plus bolus 5-fluorouracil followed by 46hour infusion of 5-fluorouracil repeated every 2 weeks OR**
- **5-fluorouracil + irinotecan + oxaliplatin: A combination of irinotecan, oxaliplatin, folinic acid plus bolus 5-fluorouracil followed by 46hour infusion of 5-fluorouracil repeated every 2 weeks OR**
- **5-fluorouracil + irinotecan + cetuximab: A combination of irinotecan, cetuximab (monoclonal antibody), folinic acid plus bolus 5-fluorouracil followed by 46hour infusion of 5-fluorouracil repeated every 2 weeks OR**
- **5-fluorouracil + irinotecan + bevacizumab: A combination of irinotecan, bevacizumab (monoclonal antibody), folinic acid plus bolus 5-fluorouracil followed by 46hour infusion of 5-fluorouracil repeated every 2 weeks**

Your patient has been given a Patient Information Sheet for this treatment regimen which gives information on the si de effects associate d with the regimen. A copy is attache d for your recor ds.

Patients may be change d to capecitabine instea d of 5FU if they are having line-relate problems.

The expecte d si de effects inclu de diarrhoea, neutropenia, mucositis, han d-foot syn drome (from the 5-fluorouracil), col d sensitive neuropathy (from the oxaliplatin), an acneiform rash (from the cetuximab), woun d healing complications, proteinuria, hypertension, reversible posterior leukoencephalopathy syn drome (RPLS), haemorrhage an d venous thromboembolism (from the bevacizumab).

If you have any questions about the trial or concerning specific toxicities arising in your patient, please contact

……

Please note that the following concomitant me dications shoul d be avoi de d while the patient is on this trial:

- **allopurinol**
- **cimeti dine**
- **metroni dazole**
- **St John's Wort (Hypericum perforatum)**
- **brivu dine/sorivu dine or derivatives are contra-in dicate d.**

Attached is a summary of the trial and a copy of the patient information sheets for your information.

Yours sincerely,

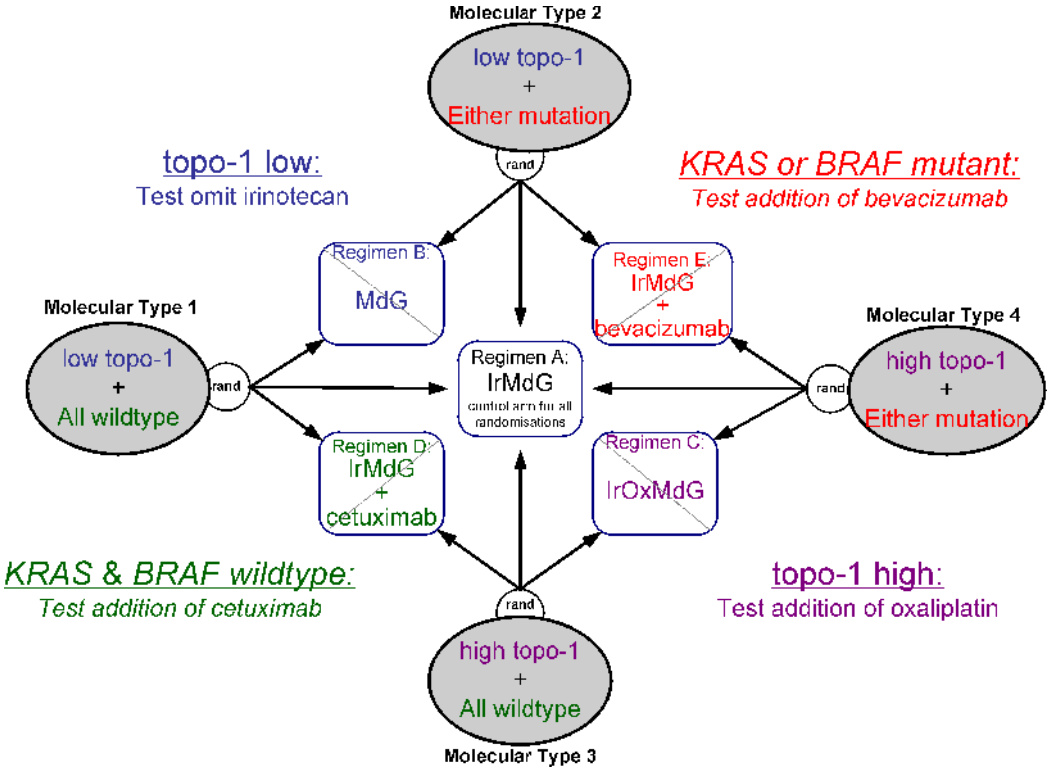
FOCUS 3 Investigator

Trial summary for GPs

FOCUS 3 is an open label, multi-arm, randomised controlled feasibility trial, involving 4 discrete 3-way ran domisations depending upon the results of molecular testing for KRAS mutation status, BRAF mutation status and topoisomerase-1 (topo-1) expression (IHC) from archival formalin fixed paraffin embedded tumour tissue. The results of these molecular tests will produce 4 subgroups of patient, and each patient will be randomised to one of 3 arms (see diagram below).

Recent data has demonstrated that the benefits of EGFR targeted monoclonal antibodies (e.g. cetuximab) are limited to patients with no mutations in their KRAS and BRAF oncogenes in the tumour, i.e. those patients who are both KRAS and BRAF wil dtype. In addition, data from the FOCUS trial, suggest that topo-1 levels in the tumour predict which patients benefit from use of irinotecan in combination with 5-fluorouracil in first line therapy. FOCUS 3 addresses the issue of individualisation of therapy for patients with metastatic colorectal cancer (mCRC) based on these biomarkers (molecular markers) in each patient's tumour. This feasibility trial tests a number of elements required for any future large scale and definitive trial of molecular selection in this disease setting. It is also structured to pose specific clinically relevant questions about optimal use of currently available agents, and the design is such that the randomised feasibility data can be included in the subsequent full trial. 240 patients with proven mCRC who are fit to receive any of the treatment regimens proposed and willing to consent to the release of a single tumour block for analysis of biomarkers will be entered into the trial.

The first trial intervention is the analysis of KRAS and BRAF mutation status and topo-1 expression from archival formalin-fixe d paraffin-embedded (FFPE) tumour blocks. This will be performed centrally in reference laboratories in Cardiff and Leeds. The control chemotherapy regimen for all four biomarker defined subsets is irinotecan plus infusional 5-fluorouracil and folinic acid as per the best arm of FOCUS (IrM dG). There are four research regimens: 5-fluorouracil alone (M dG); 5-fluorouracil, irinotecan plus oxaliplatin (IrOxM dG); IrM dG + cetuximab; IrM dG + bevacizumab. Capecitabine will not be allowed except for cases of venous access failure. Patients will continue on trial until at least 24 weeks of treatment have been received or until progression following their allocated treatment regimen. After 24 weeks of treatment, patients may have a break of up to 6 weeks before restarting trial treatment.



Patients are randomised according to molecular factors between one of arm A (control: IrM dG), and two other regimens depending on their molecular type. For example if the analysis of the tumour shows low topo-1 expression and a mutation in the KRAS or BRAF gene, then the patients will be randomly allocated between IrM dG (Control) v M dG (testing topo-1 hypothesis) v IrM dG + bevacizumab (testing KRAS and BRAF hypothesis).

The chemotherapy regimens are as follows:

- **Ir MdG: a combination of irinotecan 180mg/m^2 IV infusion over 30 minutes, followed by /-folinic acid (175 mg IV over 2 h) OR d,/-folinic acid (350 mg IV over 2 h), followed by bolus 5-fluorouracil (400 mg/m^2) followed by a 46 h IV infusion of 5-fluorouracil 2400 mg/m^2 repeated every 2 weeks.**
- **5-fluorouracil: /-folinic acid (175 mg IV over 2 h) OR d,/-folinic acid (350 mg IV over 2 h), followed by bolus 5-fluorouracil (400 mg/m^2) followed by a 46 h IV infusion of 5- fluorouracil 2800 mg/m^2 repeated every 2 weeks.**
- **IrOx MdG: This regimen will vary depending on the patient's age and WHO performance status (PS).**
    - **Patients <70 years, PS =0-1 will receive a combination of irinotecan 180mg/m^2 IV infusion over 30 minutes, followed by /-folinic acid (175 mg IV over 2 h) OR d,/-folinic acid (350 mg IV over 2 h), concurrently with oxaliplatin 85mg/m^2,**

followed by bolus 5FU (400 mg/m^2) followed by a 46 h IV infusion of 5- fluorouracil 2400 mg/m^2 repeated every 2 weeks.

- **Patients >70 years, PS=2 and patients <70 years, PS=2 receive 80% of the full dose with the possibility of dose escalation to 100% after 6 weeks of treatment.**
- **Patients >70 years, PS=1 do not receive irinotecan but will receive oxaliplatin and 5-fluorouracil at 100% of the dose.**
- **Patients >70 years, PS=2 do not receive irinotecan and receive oxaliplatin and 5- fluorouracil at 80% of the dose above.**

- **Ir MdG + cetuximab: Cetuximab 500mg/m^2 over 2h, followed by irinotecan 180mg/m^2 IV infusion over 30 minutes. This is followed by /-folinic acid (175 mg IV over 2 h) OR d,/-folinic acid (350 mg IV over 2 h), followed by bolus 5-fluorouracil (400 mg/m^2) followed by a 46 h IV infusion of 5-fluorouracil 2400 mg/m^2 repeated every 2 weeks.**
- **Ir MdG + bevacizumab: Bevacizumab 5mg/kg over 90min, followed by irinotecan 180mg/m^2 IV infusion over 30 minutes. This is followed by /-folinic acid (175 mg IV over 2 h) OR d,/-folinic acid (350 mg IV over 2 h), followed by bolus 5-fluorouracil (400 mg/m^2) followed by a 46 h IV infusion of 5-fluorouracil 2400 mg/m^2 repeated every 2 weeks.**

Appendix XV: Trial Management Group

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