FOxTROT Protocol

Fluoropyrimidine, **Ox**aliplatin & **T**argeted **R**eceptor pre-**O**perative **T**herapy for colon cancer

A randomised trial assessing whether preoperative chemotherapy and/or an anti-EGFR monoclonal antibody improve outcome in high-risk operable colon cancer

Postoperative chemotherapy improves survival for patients with stage III (node-positive) colorectal cancer. There is now also good evidence – from the QUASAR1 study and meta-analysis - that survival is improved in stage II (node-negative) disease. However, for many patients the current treatment strategy of surgical excision followed by adjuvant chemotherapy still fails either to clear locoregional spread or to eradicate distant micrometastases, leading to disease recurrence.

Preoperative chemotherapy has been shown to be more effective than postoperative chemotherapy in many other cancers and it has the potential to also improve outcome in colon cancer. Optimal systemic therapy at the earliest possible opportunity may be more effective at eradicating distant metastases than the same treatment given after the delay and immunological stress of surgery. Added to this, shrinking the primary tumour before surgery may reduce the risk of incomplete surgical excision, and the risk of tumour cell shedding during surgery.

FOxTROT is a randomised trial aiming to establish whether giving the first 6 weeks of combination chemotherapy prior to surgery improves the probability of cure for patients with high-risk operable colon cancer, and whether adding the anti-EGFR monoclonal antibody panitumumab to neoadjuvant therapy, in patients with *RAS*-wildtype tumours, improves response. In addition, **FOxTROT**'s neoadjuvant therapy evaluation provides a unique opportunity for translational research to identify tumour markers predictive of response to cytotoxic and anti-EGFR therapy.

Any patient whose standard treatment is likely to comprise surgery followed by adjuvant oxaliplatin/FU combination chemotherapy should be considered for inclusion in **FOxTROT**. Entry is based on a CT scan staging algorithm, which identifies patients whose disease is locoregionally advanced, and therefore at significant risk of relapse following standard treatment. If allocated pre-operative chemotherapy, the first 6 weeks are given preoperatively and the rest of the course is given postoperatively. If allocated standard chemotherapy, the whole course is given postoperatively. The recommended chemotherapy regimen is 24 weeks of oxaliplatin plus modified de Gramont infusional fluorouracil (OxMdG). Clinicians can, however, opt to use a shorter 12-week course of chemotherapy ('FOxTROT lite') for patients for whom 24 weeks is considered excessive (e.g. because of age/frailty or moderate recurrence risk). Patients with *RAS*-wildtype tumours allocated preoperative chemotherapy are also randomised to receive panitumumab with the first 6 weeks of chemotherapy or to control. For patients not eligible for the panitumumab randomisation, clinicians can opt to use oxaliplatin plus capecitabine (OxCap) chemotherapy instead of OxMdG.

The 150-patient **FOxTROT** pilot study shows that preoperative OxMdG chemotherapy is feasible, safe and well-tolerated with good pathological evidence of tumour down-staging. A parallel radiology/pathology study of patients included and excluded during this pilot phase shows that **FOxTROT** entry criteria can now reasonably be widened to include all patients with radiological breach of the muscularis propria: radiological T3 (rT3). FOxTROT now aims to randomise 1050 rT3 and rT4 patients between pre- plus post-operative and standard post-operative chemotherapy (in a 2:1 ratio). This will provide over 80% power to detect a 25% proportional reduction in the primary outcome, recurrence at 2 years (e.g. 32% reduced to 24%). The primary outcome measure for the panitumumab comparison is pathological down-staging following preoperative chemotherapy. The success of **FOxTROT** depends on the wholehearted support of the surgical, radiological, pathological and oncological communities and, to recognise this, publication of the main results will be in the names of all collaborators and not those of the central organisers.

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1. BACKGROUND

Rationale for neoadjuvant chemotherapy in colon cancer

After lung cancer, colorectal cancer (CRC) is the most common malignant disease in developed countries, with about a million new cases and 500,000 deaths worldwide each year.[1] The primary treatment is resectional surgery, which is possible in 80% of patients. But after apparently curative surgery, up to half of patients subsequently develop incurable recurrent disease. Adjuvant fluorouracil-based combination chemotherapy has been proven to produce a moderate but persistent improvement in survival for patients with stage III (node-positive) CRC. There is also good evidence – from the QUASAR1 study[2] and meta-analysis – that chemotherapy in stage II (node-negative) disease reduces the risk of recurrence and death from CRC. Nevertheless, for many patients the current treatment strategy of surgical excision followed by adjuvant chemotherapy fails either to clear locoregional spread or to eradicate distant micrometastases.

Preoperative ('neoadjuvant') chemo- and radiotherapy are more effective than the same or similar therapy given postoperatively in a number of GI and other cancers. This may be because earlier treatment is more effective at eradicating micrometastatic disease than chemotherapy three months later, the typical period between the initial diagnosis of cancer and starting post-operative chemotherapy. CRC metastases have a short doubling time[3,4] and tumour growth may be further accelerated after surgery due to the immunological stress of surgery and enhanced growth factor activity in the early post-operative period.[5-7] Thus, pre-operative therapy, started within days of the diagnostic and staging investigations, could potentially eradicate micrometastases that would become irreversibly established with the current standard surgery then chemotherapy treatment sequence.

Preoperative therapy may also have beneficial effects on the primary tumour and regional spread. Only 10% of colon cancer recurrence is primarily confined to the resection site, but the proportion of metastases that subsequently develop because of incomplete local clearance is far higher, and locoregional recurrences may subsequently have a more aggressive phenotype.[8] Preoperative therapy could potentially reduce tumour cell shedding at the time of surgery, a process thought to contribute to dissemination of tumour cells.[9] This may be particularly important for coelomic spread: peritoneal metastases are present in around 50% of patients with recurrent disease and, once established, have a poor response to systemic therapy.[10] Other potential practical benefits exist: by giving drug therapy at a time when its effects are observable, an assessment of response may be made, which could potentially guide decisions about postoperative therapy. It is also possible that, as in oesophageal cancer, the preoperative setting may allow drug benefits to be achieved with relatively brief exposures, which would have both quality of life and cost benefits.

Although an attractive concept, preoperative chemotherapy has not, until now, been evaluated in operable colon cancer. There are several reasons for this: drug therapy until recently gave low response rates, raising concerns that tumour growth during the neoadjuvant treatment phase could result in bowel obstruction, necessitating emergency surgery with its high associated morbidity and mortality. Another concern was that inaccurate radiological staging might result in inappropriate chemotherapy for patients who would be better managed with surgery alone. But, recent advances in radiology and in chemotherapy mean it is now possible and timely to investigate neoadjuvant therapy for patients with colon cancer.

Advances in radiology

It is now established that CT scan staging of CRC can identify a subset of patients with locally advanced, poor prognosis disease who under current standard management will require postoperative chemotherapy and who are also most appropriate for evaluation of a novel neoadjuvant strategy. High-quality CT scanning is now routinely available, making a large national multi-centre trial of neoadjuvant therapy in poor prognosis disease feasible.

In a pilot study for this proposal,[11] CT scan evaluation criteria were developed for scoring “good” or “poor” prognosis (radiological T4 disease (rT4) or rT3 disease with ≥5mm extramural extension), defining groups with 87% vs 53% 3-year cancer-specific survival, with high inter-observer concordance and excellent exclusion value for early stage cancers.

These radiological risk stratification criteria are readily taught and have now undergone multicentre validation as part of the **FOxTROT** pilot study. We compared radiological (r) and pathological (p) staging in the 150-patient **FOxTROT** pilot together with a parallel audit of patients in FOxTROT centres who were not included in the study. The CT criteria were shown to have selected a high-risk population (93% pT3 and above), and to have successfully excluded patients with low-risk cancers. The **FOxTROT** pilot study included 99 patients randomised to preoperative chemotherapy and 51 to standard surgery then chemotherapy. Eight of the 150 patients had pT2 tumours at the time of surgery, but 7/8 had been in the pre-operative chemotherapy arm. Only 1 of 51 patients in the standard arm had a pT2 tumour and had therefore been radiologically misclassified. The audit of patients not included in the FOxTROT pilot showed that among those with rT3 but <5 mm extramural extension ('intermediate risk'), 93% had pathological features indicating a requirement for chemotherapy. Based on these findings, the entry criteria for the **FOxTROT** main study have been widened to include all rT3 (≥1mm extramural extension) tumours.

Advances in Chemotherapy

Trials of chemotherapy in metastatic CRC have now established that it is a relatively chemo-sensitive disease. In two large UK phase III trials, FOCUS[12] (n= 2135 patients) and COIN[13] (n= 2445 patients), the "OxMdG" regimen of fluorouracil (FU) oxaliplatin gave objective major responses (PR or CR) in 56% and 53% of patients respectively. Of particular relevance to **FOxTROT** only 14% and 9% of patients, respectively, had disease progression in the first 12 weeks of chemotherapy.[12-13] Even higher response rates can be achieved by adding EGFR-targeted monoclonal antibody (mAb) therapies to combination chemotherapy (see below).[13-20]

Another relevant factor is that lymph node positivity (Dukes' C) is no longer the unique indication for adjuvant chemotherapy. Data from QUASAR1,[2] supported by meta-analyses of other trials, indicates that the proportional reduction in risk of recurrence with adjuvant chemotherapy is similar in node-positive and negative disease. QUASAR found a 22% (p=0.004) reduction in recurrence in Dukes' B patients. This is important information for a neo-adjuvant trial, where preoperative therapy will downstage a proportion of node-positive patients, so operative stage is less reliable as a determinant of postoperative treatment.

The oral fluoropyrimidine capecitabine has been shown to have equivalent efficacy to FU in advanced CRC and is well established in the adjuvant setting, both as a single agent[21] and in combination with oxaliplatin ("OxCap").[22] This is a welcome option for some patients. The toxicity of capecitabine-based regimens differs somewhat from the FU-based equivalents, with generally more GI and skin toxicity but less myelotoxicity. The increase in GI toxicity is however, a concern when EGFR-targeted therapy is added to OxCap,[13] and this combination is, therefore, not recommended.

Epidermal growth factor targeted therapies

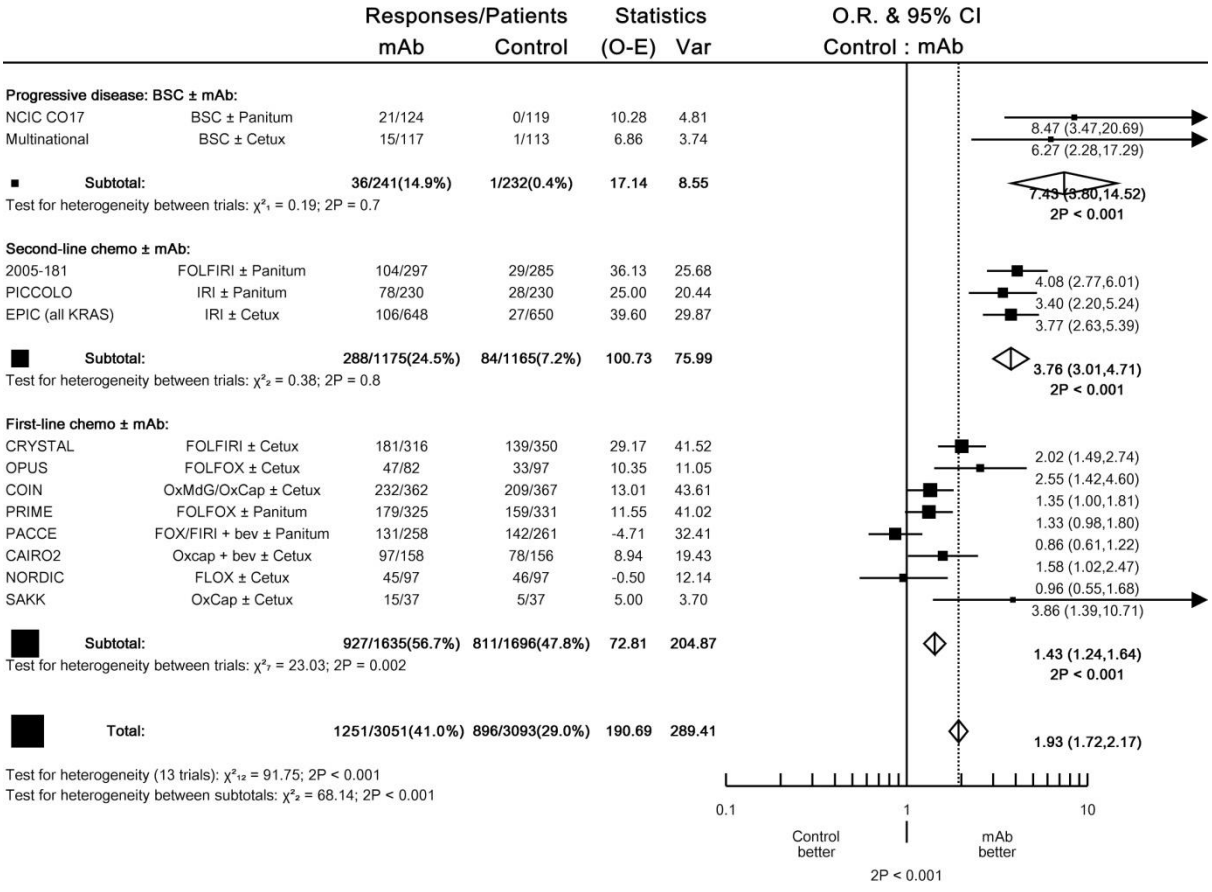
Targeted therapies, directed at vascular endothelial growth factor (VEGF) and epithelial growth factor receptor (EGFR), are now of established efficacy in colon and other cancers. EGFR is a transmembrane glycoprotein that, in response to binding of ligand, generates intracellular tyrosine kinase activity, stimulating an intra-cellular cascade leading to cell cycle progression. EGFR expression is seen in over 70% of colorectal cancer cells. Therapeutic inhibition of EGFR can be achieved with monoclonal antibodies (mAbs, e.g. cetuximab, panitumumab), or small molecule inhibitors (e.g. gefitinib, erlotinib). To date, only mAbs are established in CRC, where around 10% of unselected patients with chemoresistant disease will have a major response to single-agent cetuximab[14] or panitumumab.[15,16] Benefits are confined to patients with normal (wildtype) *RAS* tumours (*RAS*-wt) with no benefit for *RAS*-mutant tumours. Surprisingly, there is no proven association with immunohistochemical EGFR expression, but several other putative predictive biomarkers are under evaluation.

Cetuximab and panitumumab are both licensed for use in patients with advanced, *RAS*-wt colorectal cancer in combination with FOLFOX or after failure of chemotherapy. Panitumumab is a high affinity (K_d= 5 x10^{-11}M) IgG_2 mAb which differs from cetuximab in being fully human. It blocks the binding of ligands to EGFR and inhibits EGFR-mediated tyrosine phosphorylation, *in vitro* cell proliferation and xenograft tumour growth.[23] It does not cause the immuno-allergic side effects that are possible with murine or chimeric antibodies. Panitumumab has a clearance rate of <5 mL/day/kg, similar to that of endogenous IgG_2, with low interpatient variability allowing infrequent administration. Several thousand patients with cancer have now been enrolled in clinical trials of panitumumab, receiving doses ranging from 0.01 mg/kg to 5 mg/kg once weekly, 6 mg/kg fortnightly, and 9 mg/kg three

weekly.[16] Panitumumab has been studied as monotherapy in metastatic colorectal cancer (mCRC) and other solid tumours (renal, prostate, pancreatic, non small-cell lung, oesophageal and head and neck). It has also been studied in mCRC in combination with chemotherapy and with chemotherapy plus bevacizumab.

Clinical trials of anti-EGFR mAbs

For patients with *RAS*-wt mCRC who had failed standard chemotherapy, anti-EGFR mAbs used as single agents halve the rate of progression when compared with best supportive care alone.[14-16] Most trials assessing EGFR-targeted mAbs in addition to cytotoxic chemotherapy for mCRC have also found improved PFS and increased response rates in the *RAS*-wt population with no effect in *RAS*-mut patients. Of most relevance to FOxTROT, highly significant improvements in the objective response rate were seen in the trials of anti-EGFR therapy when added to second-line irinotecan-based chemotherapy (25% v 7%: p<0.001), and when added to first-line, usually oxaliplatin-based chemotherapy (57% v 48%: p<0.001).



Thus, although questions remain whether anti-EGFR targeted therapies are harmful in patients with *RAS*-mut tumours – as suggested by the OPUS,[18] PRIME,[19] PACCE[24] and CAIRO2[25] trials – there is no doubt that response rates of *RAS*-wt tumours are increased by adding anti-EGFR therapies to chemotherapy. It is possible that patients with other, less common sources of *RAS-RAF-AKT* pathway activation (e.g. *BRAF* V600E mutation) may also not benefit and this will be investigated in the FOxTROT biomarker study (see below).

Panitumumab Clinical Safety Experience (please refer to the current panitumumab Investigator's Brochure for up-to-date details.)

Panitumumab has generally been well tolerated with most treatment-related toxicities mild to moderate in severity. The panitumumab Investigator's Brochure[16] describes 48 cases (5%) of treatment-related serious adverse events among patients receiving panitumumab monotherapy. The most frequently-reported serious, treatment-related adverse event was hypomagnesaemia, reported in eight patients (1%). Hypomagnesaemia AEs and SAEs (with or without concomitant hypocalcaemia) have been reported in clinical studies of panitumumab (and cetuximab given as a single agent or in combination with various chemotherapy regimens with 41% of patients experiencing Grade 1 or 2 severity and 7% Grade 3 or 4.[16] Therefore, routine magnesium monitoring is mandated for patients receiving panitumumab. All other treatment-related serious adverse events were reported in <1% of patients.

The most common side effect of panitumumab, and other EGFR inhibitors, is a dose-related, reversible, acneiform, or maculopapular skin rash, which occurs in over 90% of patients, but reaches NCTC Grade 3 in under 15%.[16] Reported less frequently (~20%) are fingertip or nail bed infection and inflammation. Beyond these skin effects, the side effects, of any grade, that were significantly increased in the randomised comparison of panitumumab with supportive care were diarrhoea (21% vs 11%), constipation (19% vs 9%), nausea (22% vs 15%), and vomiting (18% vs 12%).[16] Other AEs that have been reported as related to panitumumab are asthenia, pain, fever, back pain, abdominal pain, anorexia, arthralgia, dizziness, increased cough, dyspnoea, upper respiratory infection, throat irritation alopecia and myalgia. Grade 3 events were reported for fatigue (3%), diarrhoea, nausea and vomiting (reported at 1% each). No evidence of cardiotoxicity has been observed despite intensive monitoring.[16] Allergy is uncommon with any infusion-related reaction (anaphylactoid reaction, chills, fever, dyspnoea, or urticaria) reported in 3% and severe (grade 3 and 4) reactions in <1% of panitumumab-treated patients.[16] Although most infusion reactions are mild to moderate in intensity they can, rarely, be fatal. As of January 2012, three fatal infusion-related reactions have been reported in over 75,000 patients with mCRC treated with panitumumab. These three patients had previously experienced angioedema, and hypersensitivity reactions to cetuximab and oxaliplatin, respectively, and panitumumab is now contraindicated in patients with a history of severe or life-threatening hypersensitivity reactions. Pulmonary toxicity also occurs rarely but because of a known association between EGFR-directed therapy and interstitial lung disease, evidence of interstitial pneumonitis or pulmonary fibrosis is another contraindication to panitumumab.

To date, using a very sensitive methodology for antibody detection, the immunogenicity of panitumumab has been low. Pre-existing anti-panitumumab antibodies have been detected in <5% of patients and <5% have showed increased anti-panitumumab antibody titres after receiving panitumumab, of which ~1% were able to neutralise the biological activity.

In trials of panitumumab in combination with the irinotecan-based IFL regimen, diarrhoea was more frequently reported than in monotherapy trials. When the trial was amended with the bolus IFL regimen switched to the infusional FOLFIRI regimen, diarrhoea, asthenia and nausea rates were approximately halved. In COIN, adding cetuximab to OxCap (but not OxMdG) produced unacceptable toxicity and led to reduction in the chemotherapy doses,[13] and hence OxCap is only allowable in the FOxTROT trial for patients excluded from the panitumumab randomisation (e.g. patients with *RAS-mut* tumours or at centres not taking part in the panitumumab randomisation).

Patients receiving panitumumab in combination with bevacizumab and either oxaliplatin or irinotecan-based chemotherapy in the PACCE study,[24] experienced more severe adverse effects than those who did not get panitumumab. These effects included diarrhoea (leading to severe dehydration), severe infections and pulmonary embolism that in some cases were fatal. The safety profile of receiving panitumumab together with bevacizumab and oxaliplatin or irinotecan-based chemotherapy is not completely known - but combined EGF/VEGF therapy should not be used as it appears to increase the rate of progression.[24,25]

The need for FOxTROT: a large, multi-centre, randomised trial

Preoperative ("Neoadjuvant") chemotherapy is a promising and practical treatment for locally advanced colon cancer but the benefits and risks of this new approach have not yet been evaluated. What is needed is a large randomised trial to assess the value of neoadjuvant chemotherapy among different types of patient. **FOxTROT** ("**F**luoropyrimidine **Ox**aliplatin and **T**argeted **R**eceptor Pre-**O**perative **T**herapy") evaluates whether giving the first 6 weeks of an effective chemotherapy regimen pre-operatively improves disease-free survival compared with standard treatment where all chemotherapy is given postoperatively. It also assesses whether, in patients with *RAS*-wt tumours, the addition of an EGFR targeted mAb (panitumumab) achieves more effective preoperative tumour shrinkage than chemotherapy alone. For reliable results, **FOxTROT** aims to randomise more than one thousand patients and, to encourage widespread participation, trial procedures and documentation are kept to a minimum. Randomising one thousand patients is challenging but this is a small number compared to the many tens of thousands of future patients whose treatment may be guided by the results of **FOxTROT**.

Biomarker studies

FOxTROT also provides a unique opportunity for translational research to identify tumour markers predictive of response to chemotherapy and to anti-EGFR therapy. Cancer Research UK is supporting the collection of tissue and blood samples stored at the time of biopsy and surgery, which will be analysed for biomarkers of response to therapy.

It is already established that for EGFR-targeted therapy the oncogene *RAS* is one such biomarker with treatment benefit confined to patients with *RAS*-wt tumours. Collecting pre- and post-treatment tissue and blood samples from **FOxTROT** patients will allow us to detect and/or validate further markers to refine who benefits from panitumumab, while samples from all patients will contribute to understanding who benefits most from chemotherapy.

Such analyses may include morphological characteristics, immunohistochemistry, protein analysis, RNA analysis, DNA analysis including both specific and general (array-based) profiling methods. Tumour markers of potential relevance are:

- Detection of mutations in *KRAS, NRAS, BRAF, PIK3CA* and other relevant oncogenes
- Detection of cancer pathway genes such as p53
- Detection of EGFR expression and/or functional genetic polymorphisms
- Detection of EGFR copy number and gene amplification (by FISH)
- Detection of EGFR pathway activation (by IHC, Western blotting and/or gene expression microarray techniques)
- Proteomics and Epigenetics

The decision on which techniques will be selected will be dependent on sample specimen type, laboratory logistics, analysis timelines and emerging evidence.

Evaluating the influence of resectional quality on outcome

FOxTROT will build on the impressive advances in colorectal cancer radiology, surgery and pathology throughout the UK that have accrued from quality assured trials such as CR07, CLASICC and MERCURY, and from the PELICAN multidisciplinary advanced training programme. The **FOxTROT** study provides an excellent opportunity to prospectively evaluate resectional quality and its influence on outcome for colon cancer. Data from Yorkshire and Swedish cancer registries indicate that overall survival of colonic cancer is now inferior to that of rectal cancer.[26] It is apparent that this is partly due to the marked variation in the quality of colon cancer surgery. Data from CLASICC[27] show that, as in rectal cancer, there is marked and measurable variation in the quality of surgery of colon cancers, e.g. in the degree of removal of the mesocolon and its lymphatic supply, length of resection to the high tie lymph node, and clearance of the surgically created mesocolic resection, especially in the caecum and descending colon.[27-29] **FOxTROT** will include standardised, proforma-based pathology reporting (see appendix C), and external evaluation using duplicate sections and specimen photographs, to assess the quality of surgery. Major advances have been achieved in rectal cancer management through such methods and require application to colon cancer.

2. TRIAL DESIGN

Objectives

FOxTROT is a multi-centre randomised controlled trial (RCT) with the following objectives:

Primary objectives:

- To determine if neoadjuvant chemotherapy ± panitumumab followed by deferred surgery then completion of chemotherapy post-operatively reduces 2-year recurrence compared to standard surgery and postoperative chemotherapy
- To determine if, in patients with RAS-wt tumours, adding panitumumab to neoadjuvant therapy increases anti-tumour activity as measured by tumour shrinkage.

Secondary objectives:

- To assess the accuracy of pre-treatment CT scan staging
- To assess the tolerability of the neoadjuvant therapies
- To assess the nature and frequency of surgical complications
- To measure the impact of the treatments on patient's quality of life and resource usage
- To assess whether adding panitumumab to neoadjuvant CT reduces 2-year recurrence
- To assess the prognostic and predictive value of tumour biomarkers
- To assess the influence of resectional quality on outcome

Randomised comparisons

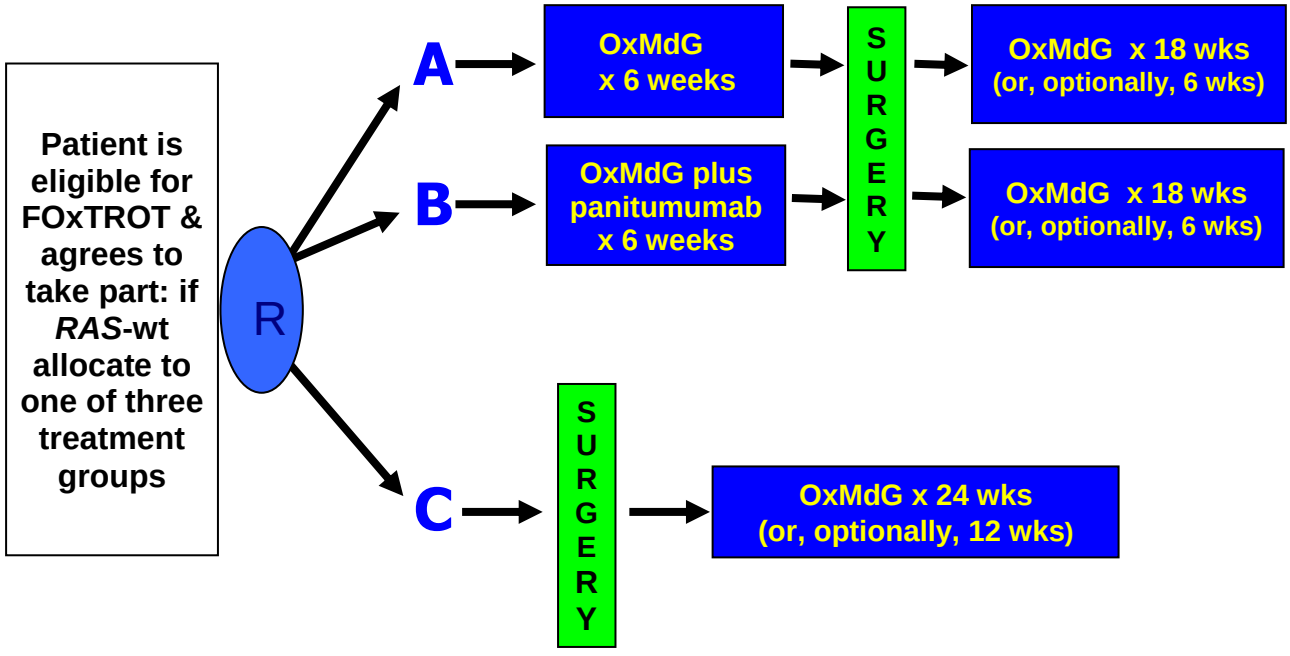
FOxTROT can be considered for all patients with potentially operable colon cancer, of radiological stage rT4 or rT3 (extramural extension ≥1mm) and no overt metastases (M0), for whom a course of oxaliplatin/fluoropyrimidine combination therapy is considered appropriate. **Every patient in FOxTROT** is randomised, in a 2:1 ratio, to receive either pre- plus post-operative therapy (6 weeks preoperative; remainder postoperative) or the same total duration given as standard post-operative chemotherapy. In addition, following *RAS* testing of the primary tumour, patients established to have *RAS*-wt tumours who are allocated preoperative CT are randomised, in a 1:1 ratio, to receive panitumumab with the first 6 weeks of chemotherapy or to control.

Thus, the three treatment arms for patients with *RAS*-wt tumours are:

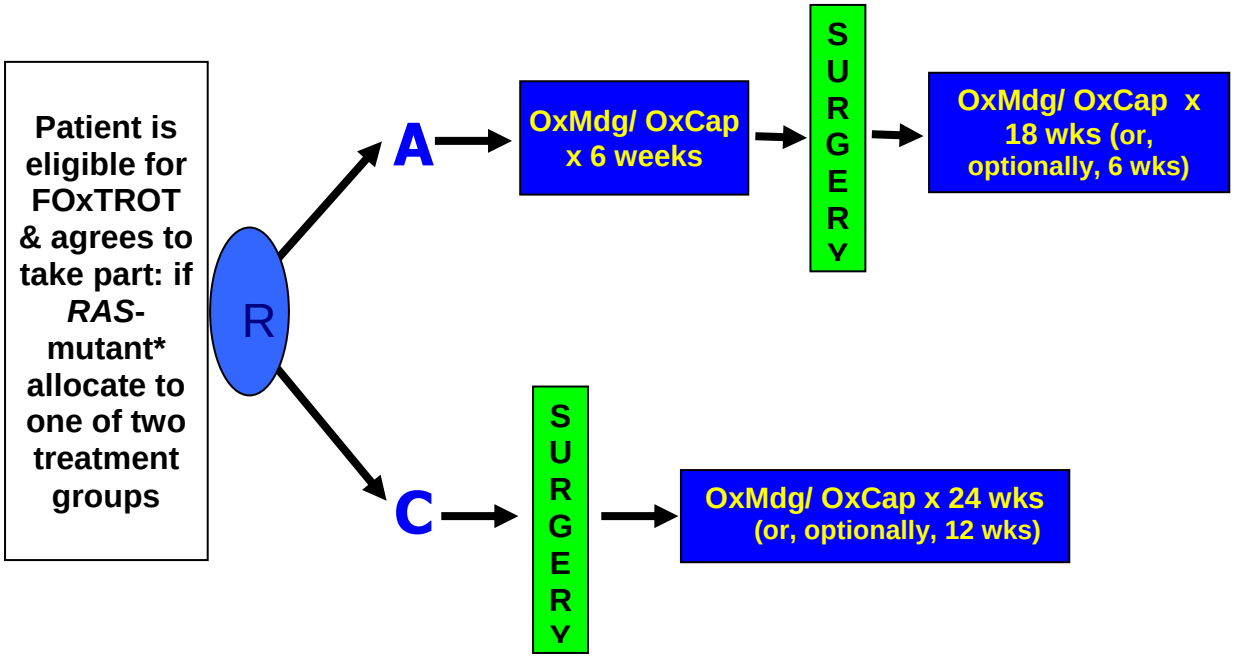
A) Six weeks of pre-operative oxaliplatin/fluoropyrimidine (OxFP) chemotherapy followed by surgery then 18 (or, optionally, 6) weeks of post-operative OxFP chemotherapy

B) The same chemotherapy regimen with concomitant panitumumab for the first 6 weeks

C) Surgery then 24 (or, optionally, 12) weeks of post-operative OxFP chemotherapy.



Patients with RAS-mutant tumours, and patients at centres not taking part in the panitumumab randomisation, are randomised just between arms A and C:



* or centre not taking part in panitumumab randomisation or patient opts out

Chemotherapy options – 24 or 12 weeks and OxMdG or OxCap

The recommended chemotherapy regimen is 24 weeks of oxaliplatin plus modified de Gramont infusional fluorouracil (OxMdG).[30] If allocated pre-operative chemotherapy, the first 6 weeks are given pre-operatively and the remaining 18 weeks post-operatively. There are, however, two additional chemotherapy options ("dealer's choices"):

Duration: Clinicians can opt to use a shorter 12-week course of chemotherapy ('**FOxTROT lite**') for patients for whom 24 weeks is considered excessive, eg elderly patients, or intermediate risk patients (rT3 with <5mm extramural extension). If 12-week rather than 24-week treatment is considered appropriate, then chemotherapy will consist of either 6 weeks pre-operatively followed by surgery and the remaining 6 weeks of chemotherapy post-operatively or, if allocated standard treatment, 12 weeks of post-operative chemotherapy. Patients with *RAS*-wildtype tumours who are allocated to receive preoperative CT plus panitumumab receive this with the first 6 weeks of chemotherapy.

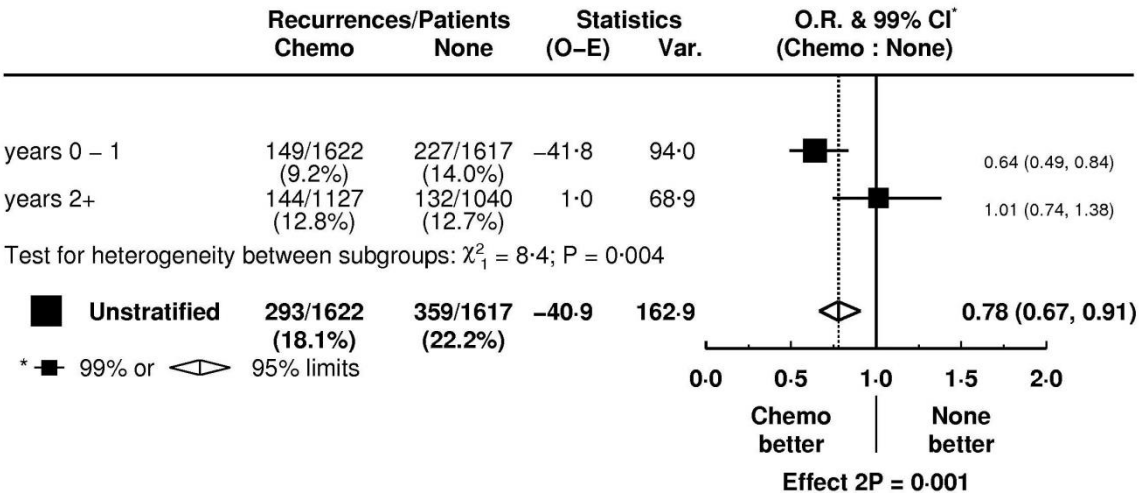
Regimen: The standard chemotherapy regimen is OxMdG. However, for patients who are NOT entered in the panitumumab randomisation (due to *RAS*-mutant tumour, non-consent or non-participating institution), OxCap may be substituted. Oxaliplatin plus capecitabine (OxCap) has similar efficacy to OxMdG but should not be used in patients randomised for panitumumab because of unacceptable toxicity when combining EGFR directed mAbs with OxCap.[13]

Please note that **if either of the "dealer's choice" options is to be used, this decision must be made before randomisation is carried out** in order to ensure that the randomisations are balanced for these factors. Also, please note that OxMdG must be used even for patients who are randomised to no panitumumab to ensure a clean comparison between panitumumab and no panitumumab.

Outcome measures

The primary outcome measure for the comparison of pre- plus post-operative versus post-operative chemotherapy alone is freedom from recurrent or persistent disease two years after randomisation. This includes failure of macroscopic disease clearance at primary surgery as well as colon cancer recurrence. The rationale for choosing this primary endpoint is to maximise statistical power as most of the effect of chemotherapy on recurrence is concentrated in this period. For example, in the QUASAR study adjuvant fluorouracil/ folinic acid chemotherapy reduced the risk of recurrence by 36% (99% CI 16%-51%) in the first two years after surgery with no further benefit or loss of benefit subsequently (see below).

QUASAR1 study: effect of chemotherapy on recurrence by year of follow-up



The primary outcome measure for the comparison of preoperative chemotherapy ±panitumumab is pathological down-staging, measured by depth of extramural spread. This continuous outcome measure is statistically efficient and will also allow early reporting, which will facilitate the design of the next generation of neoadjuvant trials.

Secondary outcome measures are:

- Death from colon cancer
- Overall survival
- Freedom from recurrence or persistent disease at 2 years (panitumumab comparison)
- Pathological assessment of downstaging (involvement of lymph nodes; serosa; resection margin, regression grading)
- Quality of resection specimen and distance to high-tie
- Radiological assessment of response to neoadjuvant treatment
- Quality of life (EORTC QLQ C-30, EuroQol EQ-5D)
- Length of hospital stay
- Surgical morbidity/mortality
- Chemotherapy toxicity
- Adverse events

3. PATIENT ENTRY

Recruitment through Multi-disciplinary Teams

Recruitment is co-ordinated through the Multi-Disciplinary Team. Colon cancer is most commonly diagnosed in surgical clinics, and initial staging investigations arranged, after which the case is discussed at the MDT. At that point, if the patient meets the radiological selection criteria (see below), and is considered potentially suitable for **FOxTROT**, they will be referred to the oncology clinic. The Nurse Specialist or Research Nurse, working with the Oncologist, has a key function in coordinating the provision of trial information, obtaining consent and transferring tissue for the *RAS* test, obtaining consent for the main **FOxTROT** study, and coordinating the smooth transition between chemotherapy and surgery phases of the patient's treatment pathway. Much of this process is already in place for the management of rectal cancer and will be used for colon cancer for the purposes of the trial.

Most patients will be recruited from the elective setting. However, patients who present urgently with obstruction are eligible for **FOxTROT** if obstruction is first relieved by a primary defunctioning stoma. Indeed, the potential for neoadjuvant therapy to down-stage such tumour makes the neoadjuvant concept particularly attractive in this setting and could have the additional benefit of improving emergency surgical management of obstructed colonic cancer by allowing definitive elective

treatment by specialist colorectal surgeons. Patients with signs of peritonitis or evidence of distant metastases are, however, excluded.

Eligibility Criteria

Inclusion Criteria

- Histologically proven adenocarcinoma of the colon or high grade dysplasia on histology plus unequivocal radiological evidence of invasive cancer.
- A candidate for adjuvant oxaliplatin/ fluoropyrimidine chemotherapy based on:
  - Either radiological high risk (rT4 or rT3 tumour with extramural extension ≥ 5mm)
  - Or radiological intermediate risk (rT3 tumour with <5mm extramural extension) and younger age/good general health
- Patients presenting with acute colonic obstruction may enter the trial only after obstruction is relieved by a successful defunctioning stoma, and when recovered to a fitness level consistent with the other eligibility criteria
- Adequate full blood count: WBC >3.0 $x10^9$/l; Plts >100 $x10^9$/l. Anaemia (Hb < 10.0 g/dl) is not an exclusion, but should be corrected by transfusion prior to surgery and chemotherapy. If Hb remains low despite transfusions, surgery and chemotherapy can be given at the decision of the surgical and oncology teams.
- Adequate renal biochemistry: GFR >50 ml/min calculated by the Wright or Cockroft formula or EDTA clearance >70 ml/min
- Adequate hepatobiliary function: bilirubin < 25 µmol/l (Patients with Gilbert's syndrome who have raised bilirubin but otherwise normal liver function tests are eligible for the study.)
- Aged 18 or over
- WHO performance status of 0, 1 or 2
- If female and of childbearing potential, must:
  - Have a negative pregnancy test ≤72hours prior to initiating study treatment
  - Agree to avoid pregnancy during and for 6 months after study treatment
- If male with a partner of childbearing potential, must:
  - Agree to use adequate, medically approved, contraceptive precautions during and for 90 days after the last dose of study treatment
- Patient able and willing to provide written informed consent for the study

Exclusion criteria

- Any patient for whom radiotherapy is advised by the MDT
- Strong evidence of distant metastases or peritoneal nodules (M_1)
- Peritonitis (secondary to perforated tumour)
- Colonic obstruction that has not been defunctioned
- Serious medical comorbidity, eg uncontrolled inflammatory bowel disease, uncontrolled angina or recent (<6 months) MI
- Another serious medical condition judged to compromise ability to tolerate neoadjuvant therapy and/or surgery
- Any other malignant disease within the preceding 5 years with the exception of non-melanomatous skin cancer, carcinoma in situ and early stage disease with a recurrence risk <5%

Additional exclusion criteria for panitumumab randomisation

- *RAS*-mutant or unknown *RAS* status tumours
- Allocated post-operative chemotherapy
- History of interstitial pneumonitis or pulmonary fibrosis
- History of severe or life-threatening hypersensitivity reactions
- Serum magnesium levels within the normal range at trial entry (which can include intravenous correction)

Radiological staging

All patients will require a spiral/ multidetector CT of abdomen and pelvis with IV contrast and ideally oral contrast (oral contrast not required in obstructed patients). The scan is used to select patients of poor or intermediate prognosis based principally on the depth of tumour extension beyond the muscularis propria. The scan is also important in excluding patients with inoperable disease, tumour perforation or established distant metastases. Examples are given in appendix B. To ensure accurate and consistent radiological staging, central radiological training for the site GI radiologist is a requirement.

FOxTROT includes on-going development and validation of the preoperative radiological staging criteria. Comparison of radiological vs. pathological staging throughout the trial will be used to further develop and validate the risk-scoring system, and it is likely that some adaptive "fine-tuning" of the radiological selection criteria will be made.

CT scan central review – To facilitate the ongoing development and validation of preoperative radiological staging criteria, **t**he baseline and interval CT scans will undergo central review by the FOxTROT lead radiologist. CT scans should be sent to:

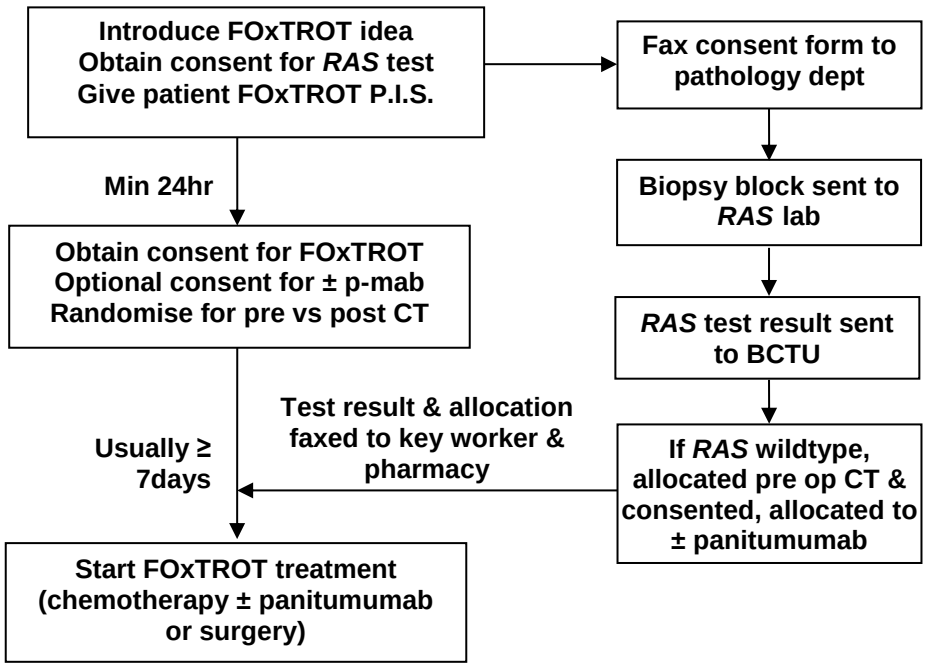
FOxTROT Study Office, Birmingham Clinical Trials Unit, School of Health & Population Sciences, Public Health Building, University of Birmingham, Birmingham, B15 2TT.

The scans will be logged and forwarded to the **FOxTROT** Lead Radiologist.

RAS screening prior to panitumumab randomisation

RAS testing* of the biopsy tissue is mandatory for patients in the **FOxTROT** panitumumab randomisation. Patients with *RAS*-wildtype tumours who have been allocated preoperative CT will then be randomised to receive panitumumab or not (i.e. arms A or B). Patients with *RAS*-mutant or undetermined tumours are not eligible for panitumumab.

A pre-randomisation *RAS* screening patient information sheet (P.I.S.) and consent form is provided (Appendices A & B). *RAS* testing can be initiated immediately the patient is introduced to the trial concept, and before they have been asked to give consent for trial participation. Consent for *RAS* testing may be obtained at the first visit when the **FOxTROT** trial concept is introduced. This helps to avoid delays if the patient subsequently decides to take part in **FOxTROT** and is allocated pre-operative therapy. *RAS* testing is provided free-of-charge and results are usually available within 1 week.



*both *KRAS* and *NRAS* genes are tested for detection of mutations in codons 12, 13, 61, and 146 for *KRAS* and codons 12, 13, and 61 for *NRAS*.

Informed consent

The conduct of the study will be in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004.

Participants who potentially fulfil the inclusion criteria for this trial must have their eligibility confirmed by medically qualified doctor with access to and a full understanding of the potential participant's medical history. If eligibility has been assessed and documented by medically qualified doctor, then the process of obtaining informed consent may be delegated as appropriate to another medically qualified doctor and documented on the FOxTROT Delegation and Signature Log.

The patient's written consent to participate in the trial must be obtained before randomisation and after a full explanation has been given of the treatment options, and the manner of treatment allocation. Patient information sheets are provided in the **FOxTROT** trial pack so that patients can find out more about **FOxTROT** before discussing whether or not to participate. Patients can consent immediately to *RAS* testing of their biopsy sample but should have sufficient time (usually 24 hours) to consider whether to take part in the **FOxTROT** randomisation. The original signed Consent forms should be kept in the **FOxTROT** study file, one copy for the patient, one kept with the patient's notes and one sent to the **FOxTROT** Study Office.

Randomisation by telephone or internet

Patients are entered in the trial by telephone call to the randomisation service (telephone number **0800 953 0274**, toll-free in the UK, or **+44 (0) 121 415 9137** from elsewhere) or by internet on the **FOxTROT** website https://www.trials.bham.ac.uk/FOxTROT. Telephone randomisation is available Monday-Friday 0900 – 1700 UK time. Randomisation out of hours is available at any time through the website. Each centre and each randomiser will be provided with a unique log-in and password to do this. Patients can be randomised between pre- plus post-operative and post-operative chemotherapy as soon as radiological staging is available and the patient has consented to participate in **FOxTROT**. The person randomising will need to answer **all** of the telephone questions, and completing the randomisation notepad before calling may help in preparing for them. According to local preference, patients may be randomised either by the surgeon or by the oncologist or the nurse.

Two-stage treatment allocation

To facilitate treatment planning, the **chemotherapy** treatment allocation (pre- plus post-operative or post-operative chemotherapy) is specified at the end of the telephone call. A date for surgery or start of chemotherapy may then be arranged – the allocated initial treatment should be undertaken as soon as possible, preferably within two weeks of randomisation.

The consent includes the optional question: **If RAS screening shows that I am eligible, I agree to receive panitumumab if allocated (yes / no).** If the patient has answered "yes", but is allocated surgery first (Arm C), they will not receive panitumumab regardless of *RAS* status. However, if they are allocated neoadjuvant therapy first, the treatment allocation is then made after confirmation of the *RAS* status: if *RAS*-wt it will be either Arm A or Arm B (1:1 ratio): if *RAS*-mut it will be Arm A (see pages 6-7). The Study Office will inform the oncology team and hospital pharmacy of the panitumumab allocation as soon as the *RAS* test result has been received (see randomisation flow chart above).

At time of trial entry, all patients should be given a laminated **FOxTROT** patient card. This card should be kept with them at all times. The patient's GP should be notified that they are in **FOxTROT** and a specimen "Letter to GP" is provided for this purpose.

4. TREATMENT

The chemotherapy regimens: "dealer's choice"

(Please see appendices P and Q for details of the drug regimens and management of toxicity)

Patients in **FOxTROT** receive oxaliplatin/fluoropyrimidine chemotherapy with a **choice** (not randomisation) between two alternative regimens, and between 24 and 12 weeks of treatment (see page 7). These are:

- 'OxMdG' (2-weekly oxaliplatin with folinic acid, bolus and infusional fluorouracil)[30]
- 'OxCap' (3-weekly oxaliplatin with capecitabine). **N.B. Only for patients not eligible for panitumumab randomisation**

MRC COIN trial centres are familiar with these regimens, and with the concept of "dealer's choice". OxMdG is given on a day-case basis using a PICC or Hickman line but, if insertion of a line will incur a delay, it is better to administer the first cycle as an in-patient. OxCap is given on a day-case basis and does not require indwelling venous access. The side-effect profiles of OxMdG and OxCap, as well as their practicalities, differ somewhat; clinicians may find it helpful to refer to the interim toxicity report of COIN.[13]

For patients allocated pre- plus post-operative chemotherapy (Arms A and B), the same chemotherapy regimen is used in the neoadjuvant and postoperative phases. It is not recommended to cross over regimens unless there is a compelling clinical reason (eg failure of venous access); in that case, be aware that if crossing from OxMdG to OxCap, capecitabine may cause increased toxicity when given after recent folinic acid (in OxMdG) and a dose-reduction is required. Please refer to notes in Appendix D.

The neoadjuvant therapy phase (Arms A and B)

Patients in **Arms A and B** receive neoadjuvant treatment for six weeks starting as soon as possible after randomisation. This comprises three 2-week cycles of OxMdG or, optionally for patients not randomised for panitumumab, two 3-week cycles of OxCap.

Patients in **Arm B** (who will have been established to have *RAS*-wildtype tumours) also receive panitumumab, 6mg/kg by IV infusion over 60 minutes on day 1 of each cycle of neoadjuvant OxMdG.

Every effort should be made to complete neoadjuvant treatment on time and as planned unless a clear contraindication develops, in which case the **FOxTROT** office should be notified. Examples would be:

- evidence of cancer progression (eg the development of complete bowel obstruction)
- persistent severe toxicity which, in the opinion of the treating oncologist, would require more than a 20% reduction in chemotherapy doses or delays of more than 2 weeks
- withdrawal of patient consent

The final day of chemotherapy is 31 days after the start of treatment for OxMdG and 37 days for OxCap. At the time of starting treatment, the patient should be booked for the resection surgery to take place 52 days after the start of treatment, or as soon as possible thereafter (and certainly before 70 days). If a delay occurs during chemotherapy, the timing of surgery should be put back by the appropriate number of days to preserve the chemotherapy-to-surgery interval.

Post-operative chemotherapy (all Arms)

Following surgery, patients should be scheduled to start postoperative chemotherapy no earlier than 4 weeks after surgery, and preferably in the interval 4-8 weeks as per normal practice. Patients with ongoing surgical complications requiring a longer recovery period may, however, start later at the discretion of the treating oncologist. Postoperative treatment is given according to the trial allocation as shown in Section 2 of this protocol:

Arms A and B

- **Standard** post-operative duration is 18 weeks
  - nine 2-week cycles of OxMdG
  - or six 3-week cycles of OxCap if receiving the OxCap "Dealer's Choice"
- **FOxTROT-lite** postoperative duration is 6 weeks
  - three 2-week cycles of OxMdG
  - or two 3-week cycles of OxCap if receiving the OxCap "Dealer's Choice"

Arm C

- **Standard** post-operative duration is 24 weeks

  - twelve 2-week cycles of OxMdG
  - or eight 3-week cycles of OxCap if receiving the OxCap "Dealer's Choice"
- **FOxTROT-lite** postoperative duration is 12 weeks
  - six 2-week cycles of OxMdG
  - or four 3-week cycles of OxCap if receiving the OxCap "Dealer's Choice"

A proportion of patients in **FOxTROT** will develop cumulative toxicity, such as peripheral sensory neuropathy, that will prevent completion of the full planned postoperative treatment course. Please refer to Appendices P and Q for guidance in adjusting or stopping treatment.

Panitumumab supply

At the time of site approval, an initial supply of panitumumab, and the FOxTROT Pharmacy Manual, will be shipped to the pharmacist at the Investigator's institution, who will check the amount and condition of the drug, enter these data into the Proof of Receipt form and fax this to Amgen (+00 44 1223 228 100).

Once a patient has been randomised to receive panitumumab, it is the responsibility of the site to ensure that there are adequate supplies of the drug for treatment. If quantities are not adequate, the site should contact Amgen to initiate additional supply. The procedure for resupply is detailed in the pharmacy manual. All details of panitumumab labelling, storage and preparation are as per the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004 and detailed in the FOxTROT Pharmacy Manual.

Surgical resection

There are no proscriptive criteria for surgical resection of the primary tumour in this trial. It is however expected that resection of the tumour will be undertaken in the elective setting by a colorectal specialist. The surgical team will be required to fill out an operative and a hospital discharge proforma to record whether there was macroscopic clearance of the tumour, surgical and/or post-operative complications and length of hospital stay.

Blood and tumour sample collection.

- **Blood samples** - A 20 ml EDTA blood sample, to be used in translational research, will be collected prior to treatment if the patient has consented for this at trial entry. The blood sample should be labelled with the **patient's initials, FOxTROT trial number and date of birth but not with their name**. The tube(s) should be sealed and sent in the prepaid safe box provided by the **FOxTROT** study office and posted to:

  Dr Susan Richman, **FOxTROT** Trial Laboratory, Leeds Institute of Molecular Medicine, Section of Pathology and Tumour Biology. Wellcome Trust Brenner Building, St James's University Hospital, Leeds, LS9 7TF.

- **FFPE tumour blocks** - Provided the patient has not withheld consent for tissue removed at biopsy and surgery to be used for research, one block from the biopsy and three blocks from the resection (two blocks from tumour and one block from normal mucosa) will be obtained for the **FOxTROT** biomarker analyses. Local sites may prefer to take additional blocks of tumour/normal tissue from the resection for research as these blocks will be retained by the trial until after all biomarker analyses are complete. While blocks are preferred, it is possible to send 20 unstained tumour sections - 10 of 5 micron (5µm) thickness on charged slides and 10 of 10 micron (10µm) thickness on uncharged slides from both the biopsy and the resection. FFPE blocks (or unstained sections) plus the associated pathology report should be labelled with the **patient's initials, FOxTROT trial number and date of birth but not with their name** and sent to the **FOxTROT** study office. Place the sample in a sealed envelope and place in a Jiffy bag along with the pathology report and send to:

  FOxTROT Study Office, Birmingham Clinical Trials Unit, Institute of Applied Health Research, Public Health Building, University of Birmingham, Birmingham, B15 2TT.

The tissue blocks and pathology reports will be logged, anonymised and forwarded to the **FOxTROT** lab at St. James's University Hospital.

Histological evaluation of resection specimen

A primary outcome of the FOxTROT study is the effect of neo-adjuvant chemotherapy upon the tumour as assessed by histology and an important objective of the **FOxTROT** trial is to develop and apply rigorous criteria for the preparation and evaluation of the resected specimen (Appendix C). Standardised specimen handling and evaluation criteria have not been established for colon cancer, whereas many of the advances seen in rectal cancer have been enabled by this approach. Adapted versions of the MRC CLASICC and CR07 pathology forms are used to assess the quality of surgery, including measurements of the greatest length of mesentery removed. Mesocolon resection quality will be assessed using a good/ intermediate/ poor classification similar to that used in the CLASICC and CR07. To ensure consistency, the nominated study GI histopathologist will be asked to attend CME-accredited trial-specific training days. Photographs of the specimens will be collected for central review of the quality of surgery and sections of the histology. We will collect standard data on pathology, completeness of resection and, importantly, the response to neoadjuvant chemotherapy. The histology will be centrally reviewed and digitised to create a unique archive to quality control the study and to allow further research. Centres can either send the original H&E stained glass slides or a set of copies for scanning. These will then be returned to the local centre after scanning is complete.

Assessment schedule

Trial data will be recorded by hospital research staff on the Case Report Forms (CRFs) and submitted to the **FOxTROT** Study office at BCTU. Radiological assessment will be performed as per Appendix B. Surgical morbidity will be recorded intra-operatively. Post-operative complications should be recorded on the hospital discharge form. Toxicity of chemotherapy will be recorded following completion of the 6th and 12th week of chemotherapy and then, if on standard chemotherapy, after the 18th and 24th week of chemotherapy. Quality of life forms will be completed prior to surgery, prior to the first course of post-operative chemotherapy and at 1 year following randomisation. Annual follow-up forms should be completed at 12 months and annually thereafter. This information will be supplemented, where possible, by the use of national mortality records and hospitals episodes statistics to ensure long-term follow-up.

	Prior to patient entry	**After each 6-week treatment cycle (pre- or post)**	**Before surgery**	**After surgery**	**Before 1st post-op chemo-therapy**	**1 year post rand**	**2+ years post rand**
Informed Consent	**X**						
Radiological staging	**X**						
Surgical morbidity				**X** [a]			
Quality of Life			**X**		**X**	**X**	
Histopathology [b]				**X**			
Chemotherapy toxicity		**X**					
Annual follow-up						**X**	**X**
Adverse Events [c]	**Monitor throughout the course of the study**						

a. Intra-operatively and at hospital discharge.

b. Blood samples taken as routine haematology and tumour tissue from the resection specimen will be analysed for biomarkers. Resected specimen will be evaluated in line with standardised method (Appendix C)

c. See section 5, Safety Monitoring Procedures.

Clinical follow-up

Follow-up after surgery will include regular clinical follow-up as per usual practice. It is recommended that CEA should be assessed every 6 months and abdominal CT scans annually for the first 3 years, or as clinically indicated. The primary outcome of **FOxTROT** is the proportion disease-free at 2 years following randomisation and thus a full investigation for recurrent disease (including CEA and a pelvis/thorax/abdomen CT scan, colonoscopy for metachronous disease is optional as long as full bowel examination was performed prior to surgery) should be undertaken at this time point. The use of investigations after 3 years is left to clinical discretion. The information routinely recorded in normal clinical notes should be sufficient for completion of the annual follow-up forms.

	Prior to patient entry	Prior to 1st treatment cycle (pre- or post)	Prior to subsequent treatment cycles	Before surgery	After surgery	Clinical follow-up [a]	1 year post rand	2 yrs post rand
Medical history	X							
Clinical evaluations, physical examination [b]	X	X		X	X	X		X
Vital signs	X	X			X			
ECG [c]	X							
Concomitant medication		X	X		X	X		X
Pregnancy Test [d]		X						
Blood Test [e]	X	X	X	X		X		
Colonoscopy	X							X [f]
CT scan [g]	X					X		X [h]
CEA						X	X	X

a. Safety follow-up visits will be conducted regularly (6 month time-points).
b. Performance status (WHO criteria) will be assessed.
c. ECG should be completed within one month prior to trial entry.
d. In women of childbearing potential, urine or serum pregnancy test within 72 hrs before initiating treatment.
e. Routine blood test to include FBC, LFTs, U&Es, Mg and Ca.
f. 2 year colonoscopy is not mandatory if full bowel examination has been performed prior to surgery.
g. CT scans will be performed as per standard clinical practice annually for the first 3 years, or as clinically indicated. The pre-randomisation CT scan should ideally be completed a maximum of one month prior to trial entry.
h. At 2 years a pelvis/thorax/abdomen CT scan should be performed.

N.B. Female participants who become pregnant will be immediately withdrawn from trial treatment.

Pregnancy and Patient Withdrawal

Participants will be asked to inform members of their research team at site of any pregnancies (i.e. of female participants or female partners of male participants) which occur during the trial participation period. All pregnancies will be followed up for outcome, any outcome meeting the definition of an SAE will be reported to the **FOxTROT** Trial Office on the relevant CRF. Pregnancy is an exclusion criteria and female participants who become pregnant will be immediately withdrawn from the trial treatment.

Patient Withdrawal

Patients may withdraw at any time during the **FOxTROT** trial if they choose not to continue or if their clinical team feel that continued participation in the trial is inappropriate.

Within **FOxTROT** there are different types of withdrawal, if a patient decides to withdraw the details should be documented in the medical notes and the **FOxTROT** Trial Office informed.

The types of withdrawal in **FOxTROT** are:

- Withdrawal from trial-specific treatment:
  - The patient will not complete treatment as per the FOxTROT protocol. Follow-up according to the protocol would still be requested.

- Withdrawal from trial-specific follow-up:
  - The patient has had trial treatment but does not wish to be followed up according to the protocol. The patient will be followed up according to standard practice. It must be confirmed that the patient has agreed that follow-up data collected at standard clinic visits may be used in the final analysis.
  - Patients should be asked if data held by central registries at The Health and Social Care Information Centre can still be collected for the study.

- Complete withdrawal:
  - The patient is not willing to be followed up for trial purposes at any further visits, i.e. only data collected prior to the withdrawal of consent can be used in the final analysis.

5. SAFETY MONITORING PROCEDURES

General definitions

Investigational Medicinal Product (IMP)

Within the trial, the following are defined as IMPs: oxaliplatin, fluorouracil, Capecitabine, folinic acid and panitumumab.

Adverse event (AE)

An AE is:

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing disease or illness
- any clinically relevant deterioration in any laboratory assessments or clinical tests

The following are not AEs:

- A pre-existing condition (unless it worsens significantly during treatment)
- Diagnostic and therapeutic procedures, such as surgery (although the medical condition for which the procedure was performed must be reported if new)

Serious adverse event (SAE)

An SAE is an untoward event which:

- is fatal or immediately life threatening
- requires or prolongs hospitalisation
- is significantly or permanently disabling or incapacitating
- constitutes a congenital anomaly or a birth defect or
- may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

Events NOT considered to be SAEs are hospitalisations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study, and did not worsen
- admission to a hospital or other institution for general care, not associated with any deterioration in condition
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

Although death as a result of disease progression is also not an SAE, an SAE form should be completed and returned to BCTU to inform the Study Office of the event.

Expected SAEs for specific drugs/treatments

Expected SAEs are those listed in the current Investigator's Brochure (IB) and Summary of Product Characteristics (SPC) for the drugs used in the study. These events do not meet the criteria of SUSAR unless for reason of their unexpected severity. For convenience, the current expected events for panitumumab are listed in Appendix A but please always use the most recently updated IB or SPC. The BCTU will ensure that any IB updates are circulated to all investigators; in addition, up-to-date SPCs of the drugs used in **FOxTROT** are all available at http://emc.medicines.org.uk/.

Serious adverse reaction (SAR)

An SAE which is assessed as possibly, probably or definitely related to study treatment is classified as a Serious Adverse Reaction (SAR).

Suspected unexpected serious adverse reaction (SUSAR)

A SUSAR is an SAE suspected to be related to a product, which is of a **type or severity** which is NOT consistent with the up-to-date product information (i.e. IB for panitumumab).

Reporting AEs

From the first administration of trial treatment until 3 weeks after the last trial drug administration, all toxicities related to the underlying colorectal cancer or its treatment, whether observed directly or reported by the patient, will be collected and recorded on the Chemotherapy Form.

Reporting SAEs

SAEs will be collected for all patients in the study from the first trial treatment to 60 days after the last trial treatment. All SAEs must be recorded on the SAE Form and faxed to the BCTU on +44 (0) 121 415 9135 within 24 hours of the research staff becoming aware of the event. Please ensure that the local Principal Investigator has assigned causality to the SAE before reporting.

For each SAE, the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates; times, if applicable)
- action taken
- outcome
- causality, in the opinion of the investigator*

*Assessment of causality must be made by a doctor. If a doctor is unavailable, initial reports without causality and expectedness assessment should be submitted to the BCTU by a healthcare professional within 24 hours, but must be followed up by medical assessment as soon as possible thereafter.

The local investigator and others responsible for patient care should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors and provide further follow-up information as soon as available. If a patient dies, any post-mortem findings including histopathology must be provided to the BCTU. The BCTU will report all fatal SAEs to the DMEC for continuous safety review.

SAEs still present at the end of the study must be followed up at least until the final outcome is determined, even if it implies that the follow-up continues after the patient finishes the study treatment and, when appropriate, until the end of the planned period of follow-up.

The BCTU will inform the owner of panitumumab (Amgen Inc.) of all SAEs in patients receiving panitumumab, regardless of whether the event is suspected to be related to panitumumab. BCTU will inform Amgen of SAEs at 3-monthly intervals. The BCTU will report SAEs to the Trial Steering Committee and to the DMEC at their meetings, and to the main REC annually. Local Investigators are responsible for reporting SAEs to their host institution, according to local regulations, but they do not need to inform MHRA or main REC as this will be done by the BCTU as detailed below. All adverse drug reactions suspected to be related to other licensed drugs used in standard care should be reported by the local investigator using the yellow card system.

Reporting SUSARs

SAEs categorised by the local investigator as **both** suspected to be related to the trial drugs **and** unexpected are SUSARs, and are subject to expedited reporting. The Chief Investigator (CI) or

nominated individual will undertake urgent review of SUSARs within 24 hours of reporting and may request further information immediately from the patient's clinical team.

The BCTU will report all SUSARs to the MHRA, DMEC and the main REC. If the SUSAR resulted in death or was life-threatening this will be done within 7 days of the initial report being received, or within 15 days for any other SUSAR. BCTU will also notify all SUSARs related to panitumumab to the marketing authorisation holders.

If information is incomplete at the time of initial reporting, or the event is ongoing, the BCTU will request follow-up information, including information for categorisation of causality, from the local investigator and will send the follow-up information to the MHRA and main REC within an additional 8 days for fatal or life-threatening SUSARs and as soon as possible for any other events.

Pharmacovigilance responsibilities

Local Principal Investigator (or nominated individual in PI's absence):

- Medical judgement in assigning seriousness and causality to AEs
- To fax SAE forms to BCTU within 24 hours of becoming aware, and to provide further follow-up information as soon as available
- To report SAEs to local committees if required, in line with local arrangements.
- To sign an Investigator's Agreement accepting these responsibilities.

Chief Investigator (or nominated individual in CI's absence):

- To assign causality and expected nature of SAEs where it has not been possible to obtain local assessment
- To review all events assessed as SAEs in the opinion of the local investigator
- To review all events assessed as SUSARs in the opinion of the local investigator. In the event of disagreement between local assessment and Chief Investigator with regards to the causality, expectedness or seriousness assessment given by the local investigator, local assessment will not be over-ruled, but the Chief Investigator may comment on these prior to reporting to MHRA.

Birmingham Clinical Trials Unit:

- To report SUSARs to MHRA and main REC within required timelines as detailed above
- To prepare annual safety reports to MHRA, main REC
- To prepare SAE safety reports for the DMEC and TSC at their meetings
- To notify Investigators of SUSARs which compromise patient safety
- To notify Amgen of cases of abuse, misuse or overdose of panitumumab within 15 days of identification.

Trial Steering Committee:

- To provide independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies
- To review blinded data, including accuracy of radiological staging, patient compliance, completion rates, adverse events (during chemotherapy and post surgery) and overall response data
- To receive and consider any recommendations from the DMEC on protocol modifications.

Data Monitoring & Ethics Committee:

- To review (initially at approx 3-monthly intervals) unblinded overall safety data to identify safety issues which may not be apparent on an individual case basis
- To review interim analyses of unblinded safety and efficacy data at least annually
- To advise the TSC whether the DMEC's review of unblinded interim safety and response data provides any good reason why the TSC's review should also be of unblinded data
- To recommend to the TSC whether the trial should continue unchanged, continue with protocol modifications, or be halted following the pilot phase.

AMGEN INC:

- To report all SUSARs related to panitumumab to the Global Regulatory Authorities (except MHRA), within the required timelines.
- To report to BCTU any new data that might impinge on safety monitoring.

End of Trial

The end of the trial for regulatory purposes is defined as 12 months after the date of the last visit of the last patient undergoing the protocol based follow-up. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The Trials Office will notify the MHRA and REC that the trial has ended within 90 days of the end of trial. Where the trial has terminated early, the Trials Office will inform the MHRA and REC within 15 days of the end of trial. The Trials Office will provide them with a summary of the clinical trial report within 12 months of the end of trial.

Long-term follow-up, to at least 5 years after randomisation of the last patient, constitutes the non-interventional phase of the trial.

6. SIZE, STATISTICS & DATA MONITORING

Projected accrual

FOxTROT aims to randomise at least 1050 patients. As the first trial to investigate preoperative chemotherapy for colon cancer, it incorporated a pilot phase, which has demonstrated the feasibility and practicability of this novel approach and established the new clinical pathways necessary for recruitment. Recruitment to the pilot phase (~10 per month) was, however, slower than anticipated partly because the deliberately conservative entry criteria considerably reduced the numbers deemed eligible. The reassuring data from the pilot phase on the safety of preoperative therapy, and the confirmation of the accuracy of preoperative radiological staging in identifying high-risk patients for the trial, now indicate that the entry criteria can be safely widened to include 'intermediate risk' rT3 tumours with less than 5mm extramural extension on the CT scan. This should substantially increase the eligible patient number while still selecting locally advanced tumours with an event rate sufficient to enable a robust result from the trial. A further measure to boost recruitment is the introduction of an option for shorter, 12-week chemotherapy for patients for whom there are concerns that 6 months of oxaliplatin and fluoropyrimidine chemotherapy might be excessive. OxCap, which was not used in the pilot phase because GI toxicity is more frequent with OxCap than OxMdG,[13] will now be allowed but only for patients who are not randomised for panitumumab. Recruitment should be substantially increased with these protocol amendments and the target recruitment for the **FOxTROT** full study is at least 10 patients per centre per annum.

Statistical considerations

The primary endpoint for the main comparison of "pre-plus-postoperative" and "postoperative alone" chemotherapy will be recurrence, or persistent disease, in the two years following randomisation. 1050 randomised in a 2:1 ratio (i.e. 700 vs 350 patients) will provide over 80% power, at $p<0.05$, to detect a 25% proportional reduction (~8% absolute difference) in recurrence at 2 years (eg 32% reduced to 24%). The 2:1 allocation ratio increases the numbers of patients randomised for the important questions of whether the addition of the monoclonal antibody alters tumour response prior to surgery and whether tumour markers predict response to chemotherapy or anti-EGFR therapy. The 2:1 allocation ratio does not materially affect statistical power nor will any quantitative treatment interactions (e.g. greater treatment effect in the presence than absence of panitumumab).

The primary outcome measure for assessment of the effect of adding panitumumab to preoperative chemotherapy will be pathological down-staging as measured by depth of extramural spread among patients allocated pre-operative chemotherapy ± panitumumab. As tumour shrinkage is a continuous outcome measure, there will be higher statistical power to detect differences between treatments than for the dichotomous (recurrence yes/no) outcome variables. It is anticipated that about 60% (n=420) of the 700 patients randomised to pre-operative chemotherapy will have *RAS*-wildtype tumours and hence be eligible for the 1:1 panitumumab randomisation. With 420 patients with *RAS*-wildtype tumours randomised to pre-operative chemotherapy ± panitumumab, **FOxTROT** would have 90% statistical power to detect a small to moderate (0.38sd) difference in tumour shrinkage at $p<0.01$, and also good statistical power to detect any clinically useful predictive variables.

Randomisation will be obtained by telephone or internet from the **FOxTROT** Study office. A minimised randomisation procedure will be used to ensure balance of treatment allocation overall and by the following variables to be used in the pre-specified sub-group analyses:

- **a)** Age (<50, 50-59, 60-69, 70+ years)
- **b)** Radiological T-stage (rT3 <5mm invasion, rT3 ≥5mm, rT4)
- **c)** Radiological nodal status (Nx, N0, N1, N2)
- **d)** Site of primary tumour
- **e)** Defunctioning colostomy (Yes, No)
- **f)** Proposed chemotherapy (OxMdG, OxCap)
- **g)** Planned chemotherapy duration (24 weeks, 12 weeks)

The main analysis will be undertaken once all patients have reached 2 years from randomisation. The statistical analyses will use standard methods (e.g. t-tests for continuous variables and log-rank for time to event analyses). Subgroup analyses will be undertaken, appropriately cautiously, for variables for which the randomisation is stratified, and for biomarkers potentially predictive of treatment efficacy, using standard tests for interactions.

Data monitoring and ethics committee

During the period of intake of the study, interim analyses of safety, response, recurrence and mortality data (and of any other information on major endpoints that is available) will be supplied, in strict confidence, to an independent data monitoring and ethics committee (DMEC) along with any other analyses that the committee may request. The DMEC will advise the chair of the trial steering committee (TSC) if, in their view, the randomised comparison in **FOxTROT** has provided both (a) "proof beyond reasonable doubt"[a] that for all, or for some, types of patient one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in the main outcome measures, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can then decide whether to modify intake to the study. Unless this happens, however, the steering committee, the collaborators, funding bodies, study sponsor and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain ignorant of the interim results.

If the clinical coordinators are unable to resolve any concern satisfactorily, collaborators, and all others associated with the study, may write through the **FOxTROT** trial office to the chairman of the DMEC, drawing attention to any worries they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

Throughout the study, the **FOxTROT** TSC will also review data, including accuracy of radiological staging, patient compliance, completion rates, adverse events (during chemotherapy and post surgery) and overall response data and will recommend whether the **FOxTROT** treatment arms should continue unchanged (with regular DMEC scrutiny), continue with protocol modifications, or be halted. The TSC's evaluation of the safety of preoperative treatment will be blinded with respect to panitumumab allocation unless the DMEC advise the TSC that their review of unblinded interim safety and response data provides any good reason why the TSC's review should also be of unblinded data.

7. ORGANISATION

To ensure the smooth running of **FOxTROT** and to minimise the overall procedural workload, it is proposed that each oncology centre should designate individuals who would be chiefly responsible for local coordination of clinical, radiological, pathological and administrative aspects of **FOxTROT**. The **FOxTROT** Trial Office, working together with NCRN networks, will provide as much assistance as they can to local coordinators and investigators in obtaining Trust approval in each centre, and by providing lists of local surgeons and oncologists who have expressed interest, and helping resolve any local problems that may be encountered.

Principal Investigator at each centre

[a] Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

Each Centre should nominate one person to act as the Local Principal Investigator. Their responsibilities will include:

1. **Liaising with local surgeons, radiologists, oncologists, nurses and pathologists** The Principal Investigator will need to liaise with all surgeons who refer patients to the oncology centre to encourage them to consider suitable patients for **FOxTROT**. Local Operating Procedures will need to be developed to ensure prompt radiological staging, discussion of individual patient's suitability for **FOxTROT** at Multi-Disciplinary Team meetings, providing eligible patients with **FOxTROT** information sheets, arranging *RAS* testing and an appointment to discuss taking part in the study. Any member of the clinical team can obtain consent and randomise patients into **FOxTROT** although it is obviously essential that surgical and oncological teams liaise closely to agree who randomises, which patients are suitable for **FOxTROT**, and to ensure that surgical and chemotherapy slots are available if allocated.
2. **To ensure that all medical and nursing staff involved in the care of colon cancer are reasonably well informed about the study** This involves distributing the **FOxTROT** materials to all relevant staff, displaying the wall-chart where it is likely to be read, and distributing the **FOxTROT** newsletters. A regularly updated PowerPoint presentation will be provided for each hospital so that they can be shown from time to time, especially to new staff.
3. **To ensure compliance with research governance requirements** This involves obtaining management approval for **FOxTROT**, ensuring that all members of the clinical team are familiar with the protocol and trial procedures, in particular serious adverse event reporting, maintaining the Local Study Site File with copies of trial materials, approval documents, consent forms and any other required documents as advised by the **FOxTROT** Study office.

Chief Radiology Coordinator at each centre

High quality radiological staging is an essential component in **FOxTROT**. It is suggested that each Centre should designate one person as Local Radiology Coordinator. This person will be required to attend a CME-accredited trial training day, and will provide scans for centralised study evaluation. This person will be responsible for ensuring that potentially eligible patients are carefully staged prior to randomisation and that all suitable patients are considered for entry to **FOxTROT**. This person will be sent updates and newsletters, and will be invited to **FOxTROT** progress and training meetings.

Chief Pathology Coordinator at each centre

High quality pathology is another essential component in **FOxTROT**. It is suggested that each centre should also designate one person as Local Pathology Coordinator. This person will be required to attend a CME-accredited trial training day, and will provide tissue and pathological reports for centralised study evaluation. This person will be sent updates and newsletters, and will be invited to **FOxTROT** progress and training meetings.

Chief Nursing Coordinator at each centre

It is suggested that each Oncology Centre should designate one nurse as Local Nursing Coordinator. This person would be responsible for ensuring that all eligible patients are considered for **FOxTROT**, that patients are provided with **FOxTROT** information sheets, and have an opportunity to discuss the study as required, consent is obtained, a biopsy and resection tissue are sent for central testing, randomisation, and referral to oncological and surgical units as appropriate. The Nursing Coordinator will also ensure that **FOxTROT** trial forms, questionnaires and treatments are administered as scheduled (unless some contraindication develops). Again, this person would be sent updates and newsletters, and would be invited to **FOxTROT** progress meetings.

Central coordination, randomisation data collection and analysis

The **FOxTROT** Study Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing collaborating centres with the **FOxTROT** folders containing trial materials. The **FOxTROT** Study Office will assist the local Principal Investigators in obtaining Trust approval. Patient entry in a centre can start as soon as Trust approval is given. Additional supplies of any printed material can be obtained on request. The **FOxTROT** Study Office also provides the 24-hour randomisation service and is responsible for collection of data (including reports of serious adverse events thought to be due to trial treatment) and for data analyses.

Clinical Queries

During office hours, the clinical coordinators (see inside front cover for contact details) provide an on-call service for any **clinical** queries about the trial.

Finance

FOxTROT is funded by Cancer Research UK. Panitumumab is being provided free-of-charge by Amgen who have also provided funding for *RAS* testing, additional interim CT scans and support for meetings. The general structure of the study was, however, designed by the UK National Cancer Research Institute's colorectal cancer Clinical Studies Group, independently of any pharmaceutical companies, who will, like the Trial Steering Committee (which has no Amgen representation), remain blind to the results as they accumulate. This arrangement is intended to ensure that no suggestions of lack of objectivity of the findings can be justified.

Cost implications

The **FOxTROT** trial can offer no financial support to the collaborating hospitals for treatments, other than provision of *RAS* testing and free supplies of panitumumab. However, **FOxTROT** should not involve any extra research costs for participating hospitals. The OxMdG chemotherapy used in **FOxTROT** is that recommended in the recent NICE guidance for Dukes' C patients, and so does not involve any increase in costs. The alternative option, OxCap, is of similar duration and cost. The panitumumab is supplied free-of-charge and no additional follow-up visits or investigations are needed other than those that would normally be required for standard patient care.

Indemnity

FOxTROT was developed by the NCRI colorectal cancer Clinical Studies Group independently of any pharmaceutical companies. It is funded by Cancer Research UK and the University of Birmingham is the trial 'Sponsor'. As it is not an industry-sponsored trial, ABPI guidelines on indemnity do not apply and there are no special arrangements for compensation for any non-negligent harm suffered by patients as a result of participating in the study. The normal NHS indemnity liability arrangements for clinician initiated research will, therefore, operate – see NHS Executive Health Service Guidelines HSG (96) 48, 8th November 1996. It should be noted, however, that negligent liability remains the responsibility of the hospital, whether or not a patient is part of a clinical trial, because of the duty of care that the hospital has for their patients.

Publication and ancillary studies

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators **prior** to publication. The success of **FOxTROT** depends entirely on the wholehearted collaboration of a large number of surgeons, oncologists, radiologists, pathologists and nurses. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. It is requested that any proposals for formal additional studies of the effects of the trial treatments on some **FOxTROT** patients (e.g. special investigations in selected hospitals) be referred to the steering committee for consideration. In general, it would be preferable for the trial to be kept as simple as possible, with very few add-on studies.

Appendix A: Panitumumab – Expected toxicities

Toxicities/side-effects that have previously occurred and are listed in the current panitumumab Investigator's Brochure (IB) and Summary of Product Characteristics (SPC) do not have to be reported to the MHRA. If the outcome of the side-effect is serious, the SAE form should be completed. Any SAE not described below (or in the most recent IB or SPC), i.e. a serious toxicity that is unexpected, and believed to be related to study treatment, will be reported as a SUSAR (see pages 14-15).

Based on an analysis of all patients receiving panitumumab monotherapy (N = 920), the most commonly reported adverse reactions are skin reactions occurring in approximately 90% of patients. These reactions are related to the pharmacologic effects of panitumumab, and the majority are mild to moderate in nature with approximately 10% severe (grade 3 or higher, NCI-CTC).

Except where indicated, the data describe adverse reactions reported from clinical studies in patients with metastatic colorectal carcinoma who received panitumumab as a single agent:

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

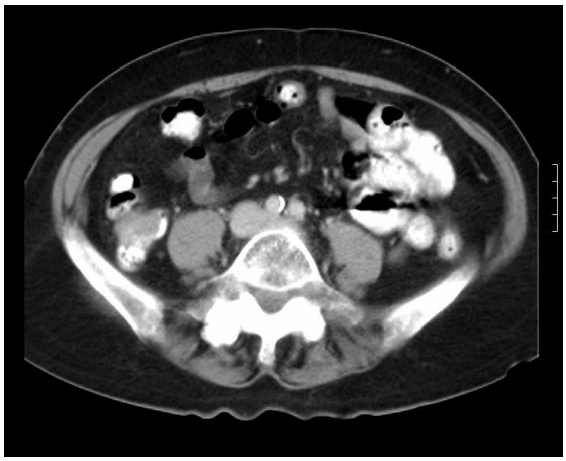
MedDRA Organ System	Frequency	Undesirable Effect
Skin and subcutaneous tissue disorders	Very common (≥ 1/10)	Rash Erythema Skin exfoliation Pruritus Dry skin Skin fissures Paronychia
Gastrointestinal disorders		Diarrhoea
General disorders and administrative site conditions		Fatigue
General disorders and administrative site conditions	Common (≥ 1/100 to < 1/10)	Infusion reactions (pyrexia, chills)
Metabolism and nutrition disorders		Hypomagnesaemia Hypocalcaemia Hypokalaemia Dehydration
Gastrointestinal disorders		Nausea Vomiting
Respiratory, thoracic and mediastinal disorders		Dyspnoea Cough
Nervous system disorders		Headache
Eye disorders		Conjunctivitis Growth of eyelashes Increased lacrimation Ocular hyperaemia Dry eye Eye pruritus
Skin and subcutaneous tissue disorders		Stomatitis Mucosal inflammation Onycholysis Hypertrichosis Alopecia Nasal dryness Dry mouth

Appendix B: Pre operative radiological staging for colon cancer

In colon cancer, T4 stage, N2 stage and extramural vascular invasion, along with emergency presentation, are independent predictors of disease recurrence. These risk factors should be identifiable through radiological evaluation, enabling tumours with a poor prognosis to be identified prior to resection and targeted for neoadjuvant chemotherapy. All patients will require a spiral/ multidetector CT of abdomen and pelvis with IV contrast and ideally oral contrast (oral contrast not required in obstructed patients). All participating centres must agree to undertake central specific radiological training for the site GI radiologist.

Patients with rT4 or 'rT3 bad' (extramural depth of ≥5mm) were eligible for the **FOxTROT** pilot study, in which we assessed the accuracy of radiological staging in identifying patients with high risk tumours that would require adjuvant chemotherapy. This review indicates that these CT eligibility criteria (rT4 or rT3 and ≥5mm extramural extension) are selecting a very high-risk population (93% T3 and above), and successfully excluding patients with low-risk cancers unsuitable for chemotherapy. Comparisons of radiological and pathological staging in a parallel audit also found that 93% of patients with rT3 tumours and a radiologically estimated depth of invasion of less than 5mm ('intermediate risk' patients) were suitable for chemotherapy. The entry criteria for the **FOxTROT** main study have accordingly been widened to include all radiological T3 tumours not just those with ≥5mm extramural invasion.

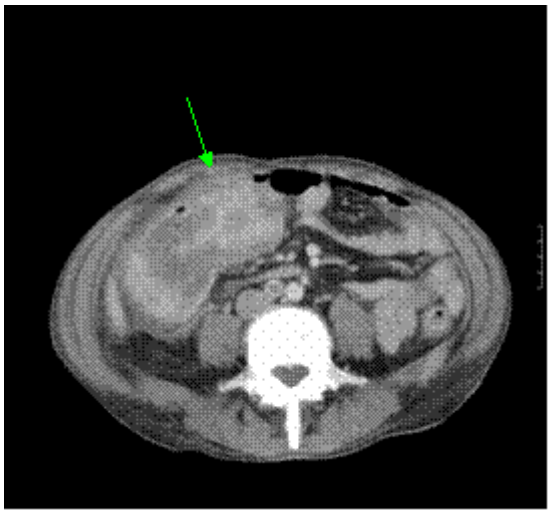
CT demonstration of an early stage good prognosis tumour

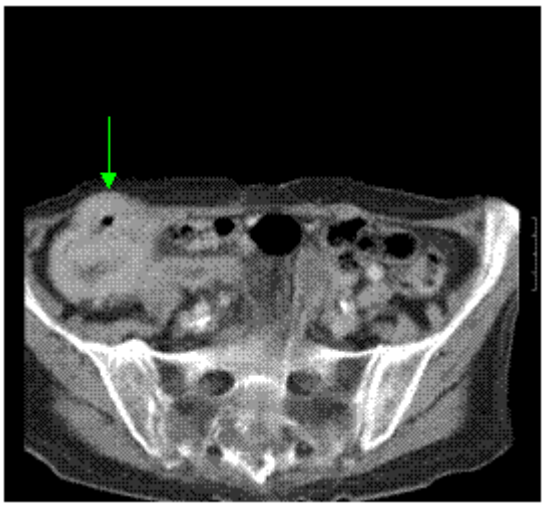


There is a polypoidal tumour with no evidence of bowel wall disturbance and no evidence of spread beyond the contour of the bowel wall. This corresponded to a pT2 tumour on histology and would not have been selected as a high risk patient for preoperative neoadjuvant therapy.

CT identified poor prognosis tumours.

Loss of plane anteriorly suggesting T4 peritoneal involvement in two different caecal tumours. This was confirmed on histology.





Appendix C: Histological Assessment

The pathological reporting and audit of surgery – colonic cancer

Bryan Warren and Phil Quirke, Oxford and Leeds

Introduction

The overall survival of colonic cancer is now lower than that of rectal cancer both in the Yorkshire and national UK cancer registry data and in Swedish and Danish data. Following observations in the MRC CLASICC study and courses on colonic surgery that PQ has taught on at the Karolinska Hospital, Sweden it is apparent that, as is the case in rectal cancer, there is marked variation in the quality of surgery of colonic cancers. This variation takes the form of incomplete removal of the mesocolon and its lymphatic supply, different lengths of resection to the high tie lymph node and different clearances of the surgically created mesocolic resection margin, e.g. caecum and ascending colon (Bateman et al). A primary outcome of the **FOxTROT** study is the effect of neo-adjuvant chemotherapy upon the tumour as assessed by histology. It also provides a unique opportunity to prospectively evaluate resectional quality and its influence on outcome for colon cancer. The trial management committee contains the necessary surgical, histological and radiological expertise to complete this important aspect of the study. Future trials of adjuvant and neoadjuvant chemotherapy will gain considerable benefit if this study can establish criteria for grading resectional quality.

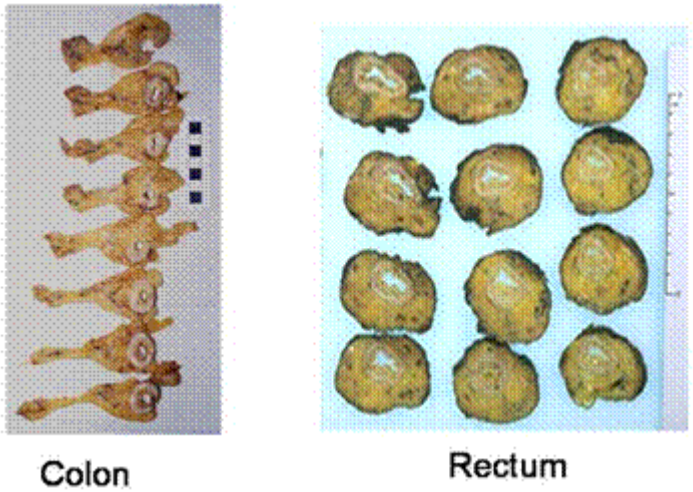


Figure 1 Mesocolon vs mesorectum showing good resections of both structures

Preparation of specimen and photography

Dissection should be by protocol using the method described here which is consistent with the MRC CLASICC trial, the Royal College guidelines and the UKCCCR booklet (1997).

The intact whole specimen should have the front and back surfaces digitally photographed alongside a metric scale (preferably while fresh and prior to inking of any non-peritonealised surfaces) to allow audit of the quality of surgery. If the specimen is not received in the fresh state then whole fixed specimen photographs are acceptable but ideally these should be taken before opening the specimen. The specimen should then be opened along the anterior aspect down to just above the tumour (but not through the tumour). The anterior surface in the area of the tumour should be preserved to allow assessment of this surface for direct and peritoneal spread. All non-peritonealised surfaces should be painted with ink e.g. india ink (figure 2). It should be remembered that the circumferential margin only applies to the surgically incised mesocolic planes and not to the peritonealised surfaces (e.g. the retroperitoneal margin in right-sided specimens and the upper mesorectal margin in left-sided specimens)

Specimen dissection, cross-sectional slicing and photography.

After the non-peritonealised surfaces have been inked, and the specimen fixed in formalin for a minimum of 2 days, it should then be described in detail and as assessment of the quality of surgery should be undertaken (see below). A second assessment will be made centrally to identify and the tumour thinly (3-5mm) sliced transversely from 2 cm below to 2 cm above. **The slices should also be photographed as a valuable demonstration of the quality of the surgery and copies of the slides forwarded to the trials office. Three views are required: front, back and cross sectional slices with a metric scale e.g. ruler (figure 2). An assessment of the quality of surgery should be made by the reporting pathologist.** A second assessment will be made centrally to identify inter-observer agreement. This will be done on the digital photographs, which will be uploaded to a central data base.

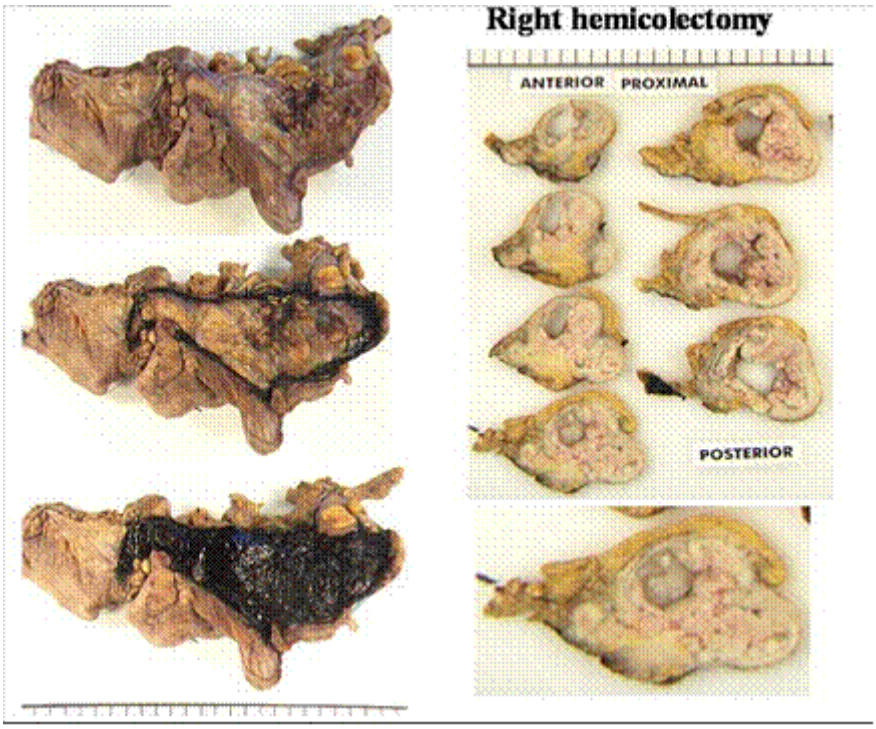


Figure 2 Dissection method showing inking of the retroperitoneal margin and cross sectioning to assess tumour spread. Note the metric scale in the images.

Not opening the specimen facilitates comparison of the cross sectional slices with MRI/CR imaging. The slices should be carefully inspected and the position of the tumour recorded according to the quadrants of involvement. The distance of direct spread outside the muscularis propria and the distance from the tumour to the nearest non-peritonealised margin should be recorded along with the tumour thickness. These measurements should be made initially from the slices and confirmed histologically e.g. by using the Vernier scale. Large blocks should be taken from the area closest to the circumferential margin wherever possible and also from any area where the tumour extends to within 3 mm of the non-peritonealised margin. Any area identified as interesting by the radiologist should also be embedded in large blocks. Other blocks should be taken to allow at least 5 blocks of tumour to confirm presence or absence of extramural venous invasion. The number of any large blocks containing tumour can be subtracted from these 5. Likewise the peritoneal surface should be sampled by a minimum of 2 blocks if the tumour impinges on it.

Figure 3 Peritoneal/serosal involvement by tumour

The local lymph nodes around the tumour should be identified and embedded as should all of the lymph nodes above and below the tumour. The tumour should be staged by both Dukes' and TNM 5 methods. **FOxTROT** will use TNM 5 not TNM 6 or 7 criteria as the latter are not recommended by the Royal College of Pathologists. An added advantage is that MRC CLASICC and MRC CR07 used TNM5 criteria and inter-trial analysis will therefore be possible. Dukes' staging allows easy communication between surgeons and the clinical team whereas TNM 5 gives more prognostic information, especially with respect to early tumours and local spread, e.g. peritoneal and direct spread (figure 3).

Histological reporting

The circumferential margin is considered involved (i.e. an an incomplete excision) if the tumour extends to within 1 mm of the non-peritonealised resection margin. Measurement is best made by using a sheet of graph paper that is photocopied onto a sheet of acetate and cut to size. This can be provided. This is more easily used than the Vernier scale. This is shown in Figure 4 and can also be used for measuring the EMVI to see if it is greater than 3mm. No distinction is currently made between the various modes of involvement, e.g. direct spread, lymph node spread, vascular, etc. Although all are associated with an increased local recurrence rate, this is lower in the case of involvement by tumour within a lymph node.

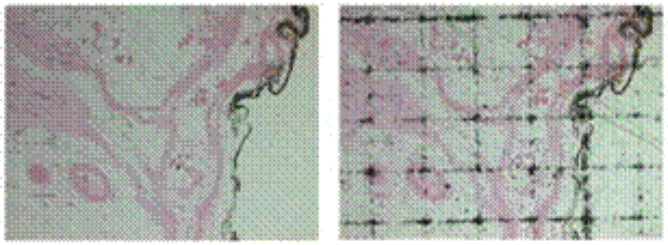
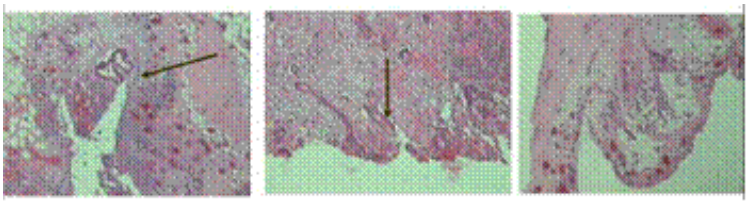


Figure 4 Easy measurement of distance of tumour to non-peritonealised resection margin by overlaying a simple grid

Peritoneal involvement (pT4) should be diagnosed if tumour cells penetrate the peritoneal surface (figure 5).

Tumour must penetrate the peritoneal surface



Yes **Yes** **No**

Figure 5 Peritoneal involvement should be assessed by the method of Shepherd et al 1995

Regression grading and sampling cases with complete pathological response

Regression grading should be performed by the Dworak modification of Mandard grading thus 5 grades could be assigned. Subsequently these will be collapsed into the Wheeler method (Wheeler et al 2002) as well as the Rodel modification of Mandard grading. These different methods will be compared. Assessment of complete pathological response will be undertaken using the CORE trial method (CORE protocol) where 5 blocks of tumours are taken initially. If no tumour is found, the entire area of scanning is blocked and if tumour is still absent all of these blocks should undergo examination of three deeper levels. If no tumour is seen at this point then the tumour has undergone a complete response. No further sections should be taken to ensure consistency.

Grading the quality of mesocolic resection

The quality of the mesocolic resection can be easily assessed. We recommend a 4 grade classification, first used in the MRC CLASICC trial but modified to include an extra grade. These systems have been demonstrated to be usable in the context of phase III clinical trials and were shown to predict a higher risk of local recurrence in the Dutch rectal cancer trial (Nagtegaal et al, JCO 2002). The frequency of mesocolic non-peritonealised resection margin involvement can also be determined and it is likely that this is a good early determinant of the

quality of colonic cancer surgery and subsequent risk of local recurrence, as has been shown in rectum (Birbeck et al, Ann Surg 2005). The 4 grades are:

1. **Mesocolic plane –** Mesocolic tissue removed intact with no lacerations of the mesocolic surface (figure 6). The height of the vascular tie is low.

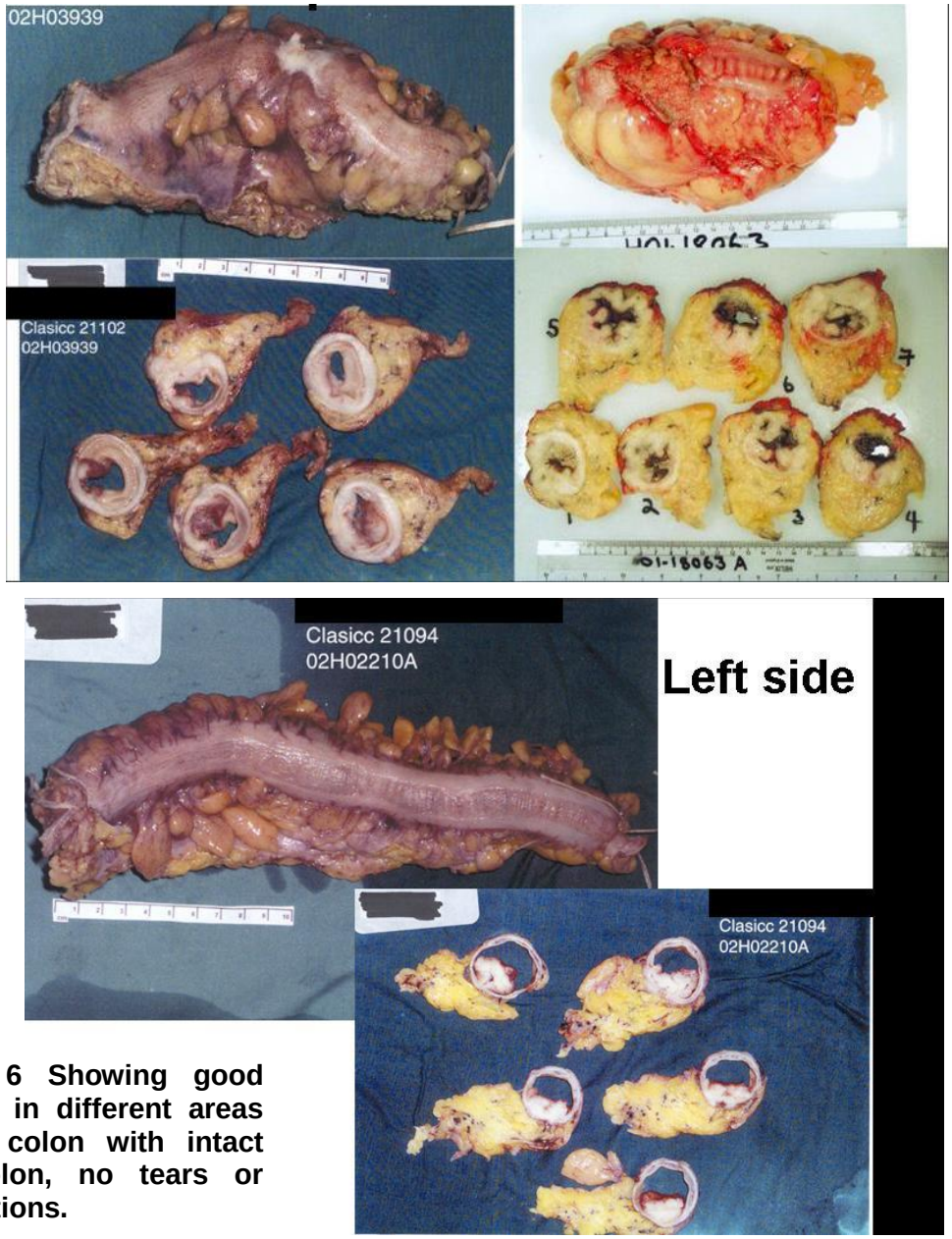


Figure 6 Showing good surgery in different areas of the colon with intact mesocolon, no tears or perforations.

2. Intramesocolic plane – Mesocolic tissue largely intact but the mesocolon shows irregularity/laceration/defects that do not reach down to the muscularis propria (figure 7)

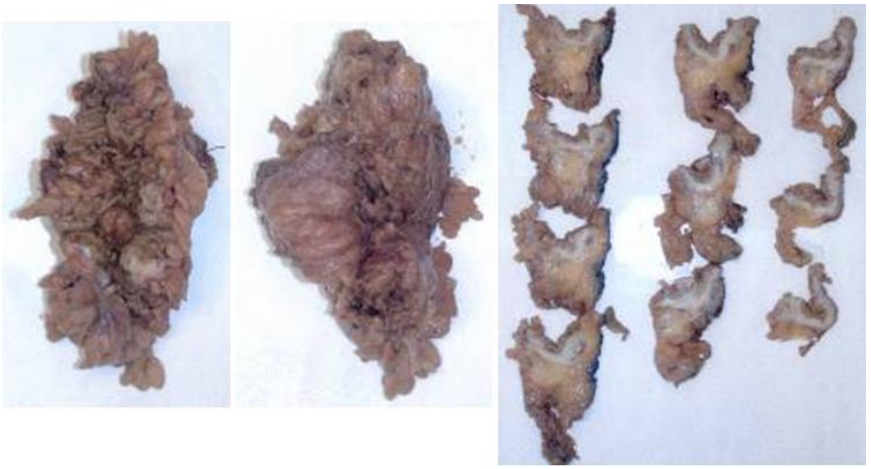


Figure 7 Showing intermediate surgery where there are superficial incursions, areas of mesocolon missing but, most importantly, in no area is the muscularis propria exposed in an area covered by mesocolon.

3. Muscularis propria plane – Mesocolic tissue is extensively disrupted with marked irregularity of the mesocolon (figure 8). The surgical margin will extend down onto the muscularis propria in mesocolic areas. Please note that this feature should only be assessed on the areas covered in mesocolon and not in the areas where peritoneum is closely adherent to the muscularis propria.

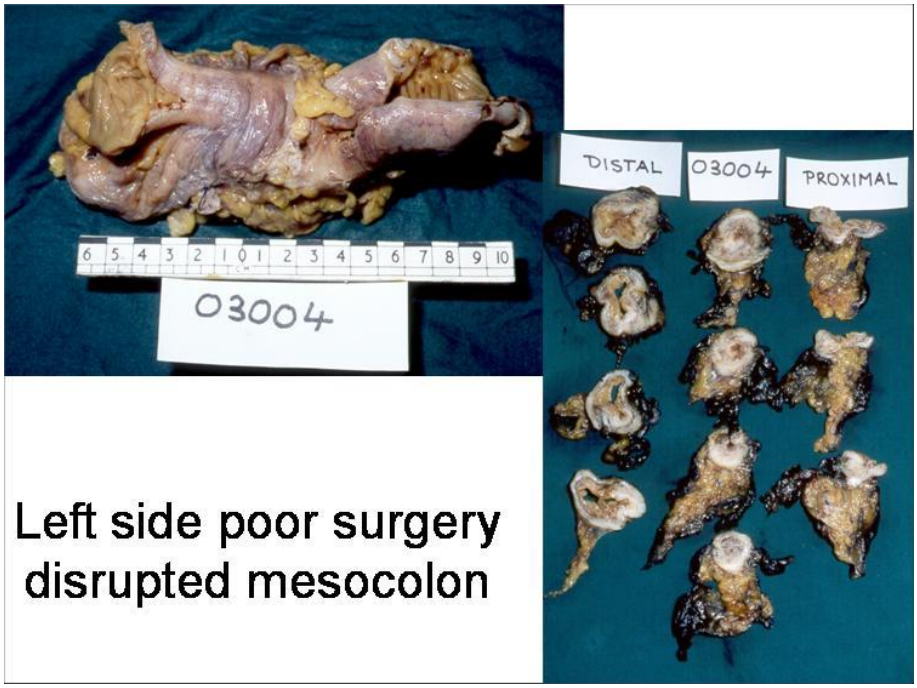


Figure 8 Showing poor/incomplete resection specimen with many areas of substantial loss of mesocolic tissue, area(s) of the muscularis propria are seen, and deep cuts and tears down onto the muscularis propria may also be present.

4. Mesocolic plane plus high ties – Mesocolic tissue removed intact with no lacerations of the mesocolic surface AND a central vascular ligation i.e. at the origin of the supplying vessels.

Pathology material to be forwarded to the FOxTROT trials office

It is mandatory to fill out the trial pathology proforma and return it to the trial office along with a copy of the anonymised pathology report. Digital copies of all photographs should be forwarded to the trials office (a minimum of three photographs are required: front of whole specimen, back of whole specimen and cross sectional slices).

Between 10 and 20 plus blocks will need to be taken to report the specimen to **FOxTROT** and RCPath standards. The original H&E stained sections mounted on glass slides must be forwarded to the trials office for scanning or alternatively, a duplicate set of sections can be cut. These will be returned to the local centre after scanning. Three tissue blocks (two tumour and one normal mucosa) from the resection specimen should also be sent to the trials office to facilitate translational research provided that the patient consented to this. As these will be retained by the **FOxTROT** researchers, local centres may wish to take additional research blocks if there is sufficient tumour material to do this. Providing that the patient has consented for translational research, the original diagnostic tissue biopsy block used for *RAS* analysis will be retained. These can be requested by local centres if required for further clinical testing but they should then be returned to the trials office.

Pathology references

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Appendix D: The OxMdG regimen

Treatment is given in two-weekly schedules as follows:

Day 1 of treatment schedule (14 day cycle):

0:00	IV bolus granisetron 3 mg (or equivalent); IV bolus dexamethasone 8 mg
	flush line with 5% dextrose
0:00 – 2:00	l-folinic acid 175mg (or d,l-folinic acid 350 mg) not adjusted for surface area. IV infusion over 2 hrs in 250 ml 5% dextrose concurrently with:
0.00 – 2:00	oxaliplatin 85 mg/m^2 IV infusion, 2 hrs, 250 ml 5% dextrose
2:00	flush line with 5% dextrose
2:00 - 2:05	5-fluorouracil 400 mg/m^2 IV bolus injection over 5 minutes
2:05 - 48:00	5-fluorouracil 2400 mg/m^2 IV infusion over 46 hours
48:00	Disconnect pump and flush line (5 ml heparinised saline).
Days 3-14:	No treatment

Notes:

- Bolus 5FU must be given as a 5 minute injection and not as a short 15 or 30 minute infusion
- Because of a potential *in vitro* chemical reaction between oxaliplatin and chloride ions, care is taken to avoid contact with normal saline in the drip-tubing etc.
- The OxMdG regimen is designed to be given via an indwelling central venous catheter. If given through a peripheral vein, appropriate dilutions of drugs are essential. Peripherally-administered oxaliplatin may cause vein pain, which is helped by applying an electric heat pad over the vein throughout the 2-hour infusion. Suitable therapeutic heat pads are available from Winterwarm® (38x30cm, model HP5/LT) or Dimplex® (38x28cm) each costing under £20. If this fails, extending the infusion time to 4-6 hours may be helpful.
- It is not recommended to cross over from the OxMdG to OxCap regimens unless there is a compelling clinical reason (eg failure of venous access); if so, be aware that capecitabine may cause increased toxicity when given after recent folinic acid (in OxMdG) and a capecitabine dose-reduction is required (50% in 1st, 75% in 2nd and 3rd OxCap cycles).
- Do not use injection equipment containing aluminium
- Local dose-banding may be applied by pharmacies, as long as the delivered dose falls within ± 5% of the calculated dose as per protocol. If wider dose bands are local practice, please contact the **FOxTROT** study office.
- Where local practice is to use sodium folinate, this may be used at the equivalent dose.

Oral antiemetics (starting day 2):

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

Note on the use of dexamethasone: For patients at high risk of steroid side effects (e.g. diabetics) or for those who develop toxicity attributable to steroids (e.g. dyspepsia; dysphoria; etc), the oral steroid should be omitted and “p.r.n.” oral 5HT3 inhibitor given.

Scheduled tests

- FBC and clinical assessment (NCI toxicity scores) should be performed on the day of starting each drug therapy cycle (or within 3 working days before) and the results available before starting.
- Biochemistry (including creatinine, bilirubin, and either AST or ALT) is done at the same time as FBC.
- If patient is clinically jaundiced bilirubin level must be reviewed prior to administration of oxaliplatin.
- On day 1 of each cycle or within 3 days prior, LFTs, U&Es, magnesium and calcium should be tested. Only patients allocated to panitumumab need to be tested for magnesium.

Toxicity and dose adjustments for OxMdG

The following are suggestions for dose reductions/delays and management of toxicity during chemotherapy. The final decision on dose adjustments and delays is however, the responsibility of the treating consultant, taking into account the full clinical situation.

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 < 75 x 10^9/l. Only treat when neutrophils and platelets are above these limits.
- If >1 delay, or 1 delay of ≥ 2 weeks occurs, reduce doses of oxaliplatin and both bolus and infusional 5FU by 20% for subsequent doses.
- If a further delay(s) for myelotoxicity occurs despite dose reduction, further dose adjustments may be made at the treating consultant's discretion (eg a further 20% reduction).

Neurotoxicity

- Oxaliplatin commonly causes transient paraesthesia of hands, feet and sometimes throat, precipitated by cold and lasting up to a few days after each dose. This does not require treatment or dose reduction.
- With cumulative dosing, some patients develop more severe neurotoxicity, requiring omission of oxaliplatin. For example:
  - persistent paraesthesia occurring in warm as well as cold conditions with significant discomfort
  - Numbness with loss of function (eg dropping objects) or pain

If one or more of these occur and persist through the cycle until the next dose is due, omit oxaliplatin from the regimen for the remainder of the **FOxTROT** therapy course.

If OxMdG has been well tolerated apart from neurosensory toxicity, the 5-FU dose should be increased from 2400 to 2800 mg/m^2 over 46 hours. Bolus 5-FU and folinate remain the same. This should occur from the start of the oxaliplatin-free cycles. If there is significant non-neurological toxicity in addition to neurosensory toxicity, 5-FU should remain at 2400 mg/m^2. It can be escalated to 2800 mg/m^2 if the first two oxaliplatin-free cycles are well tolerated.

Renal function

In **FOxTROT**, renal function needs to be above a threshold for safe administration of the chemotherapy schedules. Centres can use either the Wright or the Cockroft formula to estimate GFR (eGFR). The most commonly used is the Cockroft but is has low precision and low accuracy as it systematically underestimates clearance. This can result in systematic under-dosing when GFR is used as part of the dose calculation (eg. For carboplatin in the Calvert AUC formula). However, the purpose of the eGFR calculation in **FOxTROT** is simply to identify patients in whom EDTA clearance needs to be measured and Cockroft eGFR is a safe way of screening patients for renal function measurements, since very few patients have a Cockroft eGFR which is higher than the actual GFR.

The Wright formula is not more precise than Cockroft, but it is more accurate, therefore Wright is better for calculating carboplatin dose but possibly not as good as a screen for poor renal function; in approximately 50% of patients Wright eGFR will be higher than the actual GFR.

Clinicians should arrange EDTA clearance measurement for patients with a low eGFR (<50 ml/min), or in any patient in whom renal impairment is suspected.

- Before starting, ensure patient fulfils eligibility for renal function, i.e. GFR >50ml/min.
- Thereafter, if serum creatinine rises above normal limit, and >25% from baseline, check EDTA clearance. A significant deterioration in renal function should be investigated to exclude a postoperative complication or disease progression/relapse.
- If, after investigation, treatment is to continue despite the reduced renal function, the following adjustments should be made:
  - GFR 30-50 ml/min: full dose FU; reduce oxaliplatin by 25%
  - GFR <30 ml/min: reduce FU by 25%; omit oxaliplatin

Hepatobiliary function

- Bilirubin ≤ 1.25 x ULN and transaminase (either AST or ALT) ≤ 3 x ULN is required for study entry.
- Thereafter, any significant deterioration in hepatic function should be investigated to exclude a postoperative complication or disease progression/relapse.
- If, after investigation, treatment is to continue despite the altered hepatic function, the dose of both FU and oxaliplatin should be reduced by 50% if bilirubin is over 3x ULN.

Stomatitis

- Routine mouthcare (e.g. Corsadyl, 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) and oxaliplatin doses by a further 20%.

Diarrhoea

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

Hand-foot syndrome (HFS)

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

DPD deficiency; cardiotoxicity

- With any 5FU regimen, the occasional patient is encountered (approx. 1-3%) who has markedly exaggerated toxicity due to reduced catabolism. If this occurs, await full recovery. Further treatment at much reduced 5FU dose (e.g. 50%) or with single agent oxaliplatin may be considered. Please discuss with one of the clinical coordinators.
- Rarely, 5FU may provoke angina attacks or even MI in patients with ischaemic heart disease. In this event, the risk of continuing adjuvant therapy is likely to outweigh its benefits, and discontinuation is recommended.

Hypomagnesaemia management

- Patients should be evaluated and, if hypomagnesaemia is present, replacement should be managed as per local medical practice. A patient's serum magnesium level should be at or above 0.41 mmol/L throughout the study. It is important to assess and manage serum potassium and ionized calcium (corrected for albumin) in patients who have hypocalcaemia.

Allergic reactions to oxaliplatin

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

Appendix E: The 3-weekly OxCap (XelOx) regimen

Treatment schedule (21 day cycle)

Day 1, 0:00	IV bolus granisetron 3 mg (or equivalent); IV bolus dexamethasone 8 mg flush line with 5% dextrose
0.00 – 2:00	oxaliplatin 130 mg/m^2 IV infusion, 2 hrs, 250 ml 5% dextrose
2:00	flush line with 5% dextrose
Day 1, evening	capecitabine 1000 mg/m^2 p.o.
Day 2-14	capecitabine 1000 mg/m^2 p.o. twice daily
Day 15, morning	capecitabine 1000 mg/m^2 p.o.
Day 16-21	no treatment

Notes:

- The treatment cycle includes 28 capecitabine doses taken 12-hourly. This starts with the evening dose on day 1 and ends with the morning dose on day 15.
- The capecitabine dose is rounded to the nearest achievable dose.
- Patients are instructed to take capecitabine within 30 minutes after food, approximately 12 hourly (e.g. 8 am and 8pm).
- Because of a potential *in vitro* chemical reaction between oxaliplatin and chloride ions, care is taken to avoid contact with normal saline in the drip tubing etc.
- Peripherally-administered oxaliplatin may cause vein pain, which is helped by applying an electric heat pad over the vein throughout the 2-hour infusion. Suitable therapeutic heat pads are available from Winterwarm® (38x30cm, model HP5/LT) or Dimplex® (38x28cm) each costing under £20. If this fails extending the infusion time to 4-6 hours may be helpful, or consider fitting an indwelling central venous catheter.
- It is not recommended to cross over from OxMdG to OxCap unless there is a compelling clinical reason (eg failure of venous access); in that case, be aware that capecitabine may cause increased toxicity when given after recent folinic acid (in OxMdG) and a capecitabine dose-reduction is required (50% in first, 75% in 2nd and 3rd OxCap cycles).
- Do not use injection equipment containing aluminium
- Local dose-banding may be applied by pharmacies, as long as the delivered dose falls within ± 5% of the calculated dose as per protocol. If wider dose bands are local practice, please contact the **FOxTROT** study office.

Oral antiemetics (starting day 2):

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

Note on the use of dexamethasone: For patients at high risk of steroid side effects (e.g. diabetics) or for those who develop toxicity attributable to steroids (e.g. dyspepsia; dysphoria; etc), the oral steroid should be omitted and "p.r.n." oral 5HT3 inhibitor given.

Scheduled tests

- FBC and clinical assessment (NCI toxicity scores) should be done on the day of starting each cycle, (or within 3 working days before) and the results available before starting.
- Biochemistry (including creatinine, bilirubin, and either AST or ALT) is done at the same time as FBC; these results should either be available before starting the cycle or, if not, should be reviewed within 24 hours after starting the cycle (so that capecitabine can be interrupted if dictated by an elevated bilirubin level).
- If patient is clinically jaundiced, bilirubin level must be reviewed prior to administration of oxaliplatin.
- On day 1 of each drug therapy cycle, or within 3 days prior, patients should be tested for LFTs, U&Es, magnesium and calcium.

Toxicity and dose adjustments for OxCap

The following are suggestions for dose reductions/delays and management of toxicity during chemotherapy. The final decision on dose adjustments and delays is however the responsibility of the treating consultant, taking into account the full clinical situation.

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 < 75 x 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 capecitabine and oxaliplatin 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% reduction, a further dose reduction may be made, at the discretion of the treating investigator.

Neurotoxicity

- Oxaliplatin commonly causes transient paraesthesia of hands, feet and sometimes throat, precipitated by cold and lasting up to a few days after each dose. This does not require treatment or dose reduction.
- With cumulative dosing, some patients develop more severe neurotoxicity, requiring omission of oxaliplatin. For example:
    - persistent paraesthesia occurring in warm as well as cold conditions with significant discomfort
    - Numbness with loss of function (eg dropping objects) or pain

  If one or more of these occur and persist through the cycle until the next dose is due, omit oxaliplatin from the regimen for the remainder of the **FOxTROT** therapy course.

Renal function

- Before starting, ensure patient fulfils eligibility for renal function, i.e. GFR >50ml/min.
- Thereafter, if serum creatinine rises above normal limit, and >25% from baseline, check EDTA clearance. A significant deterioration in renal function should be investigated to exclude a postoperative complication or disease progression/relapse.
- If, after investigation, treatment is to continue despite the reduced renal function, the following adjustments should be made:
    - GFR 30-50 ml/min: reduce both drugs by 25%
    - GFR <30 ml/min: discontinue OxCap. Any further alternative treatment is at investigator's discretion.

Hepatobiliary function

- Bilirubin ≤ 1.25 x ULN and transaminase (either AST or ALT) ≤ 3 x ULN is required for study entry.
- Patients on capecitabine may have temporary treatment-related elevation of transaminases, which require interruption of treatment. Other alterations in hepatic function should be investigated to exclude a postoperative complication or disease progression/relapse.
- If, after investigation, treatment is to continue, the following adjustments should be made:
    - AST/ALT >5x ULN: withhold chemotherapy until recovered below this limit
    - Bilirubin >3x ULN: reduce both capecitabine and oxaliplatin by 50%

Stomatitis and Diarrhoea

- Patients should be provided with routine mouthcare. Loperamide should be provided for symptomatic treatment of diarrhoea.
- Grade 1 toxicity is managed symptomatically and does not usually require dose reduction or interruption
- For any toxicity of grade 2 or higher, **stop capecitabine** and treat symptomatically until the toxicity has resolved to grade 0 or 1.
    - NB: when capecitabine is stopped for toxicity the **doses are omitted, not delayed**. If resolution to grade 0–1 occurs before day 14, capecitabine is resumed for the remainder of the planned cycle; otherwise wait until the next cycle.

- When resuming after a pause for toxicity, use the following dose reduction scheme:

- Grade 2 toxicity: resume at the same dose after first pause, but reduce both capecitabine and oxaliplatin to 80% of the previous doses if a second pause is required.
- Grade 3 toxicity: resume at 80% of original doses (both capecitabine and oxaliplatin)
- Grade 4 toxicity: discontinue permanently.

- If further toxicity of grade ≥2 occurs after a dose-reduction, the doses should be reduced by a further 20%.

Hand-foot syndrome (HFS)

- Treat symptomatically. Pyridoxine 50 mg tds by mouth or topical corticosteroid may help.
- If HFS is still a problem, interrupt capecitabine and treat symptomatically until the toxicity has resolved to grade 0 or 1, then resume with a 20% dose reduction.

DPD deficiency; cardiotoxicity

- With any fluoropyrimidine regimen, the occasional patient is encountered (approx 1-3%) who has markedly exaggerated toxicity due to reduced catabolism. If this occurs, await full recovery. Further treatment at much reduced capecitabine dose (e.g. 50%) or with single agent oxaliplatin may be considered. Please discuss with the CI or one of the clinical co-investigators.
- Capecitabine may provoke angina attacks or even MI in patients with ischaemic heart disease. In this event the risks of continuing adjuvant treatment are likely to out-weigh the benefits, and discontinuation is recommended.

Hypomagnesaemia Management

- **Patients should be evaluated and managed as per local medical practice. If hypomagnesaemia is present, replacement should be managed as per local medical practice. A patient's serum magnesium level should be at or above 0.41 mmol/L throughout the study. It is important to assess and manage serum potassium and ionized calcium (corrected** for albumin) in patients who have hypocalcaemia.

Allergic reactions to oxaliplatin

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

Appendix F: Administration of Panitumumab

Patients who have been established to have *RAS* wild-type tumours, who are allocated neoadjuvant chemotherapy, and are then randomised to the panitumumab (Vectibix) arm (Arm B), should receive panitumumab at 6 mg/kg by IV infusion over 60 minutes, immediately prior to the start of each of the three 2-week cycles of OxMdG chemotherapy, i.e. for the full duration of the 6 weeks of neoadjuvant therapy. **Panitumumab should not be given with OxCap or with postoperative chemotherapy.**

The dose in mg/kg is calculated using body weight at baseline and is diluted in a minimum of 100 mL of pyrogen-free 0.9% sodium chloride solution.

Panitumumab will be packaged by Amgen and delivered to the hospital pharmacy. Each vial of panitumumab contains a nominal 10ml of a sterile solution containing 20 mg/ml of panitumumab.

Panitumumab is administered IV by an infusion pump through a peripheral line or indwelling catheter **using a 0.22-micron in-line filter infusion set-up** over approximately 60 minutes. Strict adherence to aseptic technique is used during preparation and administration. The bag should be labelled per site pharmacy Standard Operating Procedures (SOPs) and promptly forwarded to the chemotherapy unit for infusion.

Panitumumab hypersensitivity reactions

About 3% of patients treated with panitumumab have experienced infusion-related reactions, including chills, dyspnoea, flushing, hypertension, hypotension, pyrexia, tachycardia and vomiting, with most infusion reactions being mild to moderate (NCI-CTC grade ≤2) in severity. Severe infusion reactions (anaphylaxis, angioedema, bronchospasm, cardiorespiratory arrest and hypotension), occur in less than 1% of patients treated and, very rarely (<1 in 10,000), can be fatal. As of January 2012, three of over 75,000 patients with mCRC treated with panitumumab have died following hypersensitivity reactions. A fatal case of angioedema occurred 2 days after exposure, following a prior episode of angioedema that occurred 6 days after exposure. There have been two further post-marketing reports of hypersensitivity reactions with fatal outcomes during and immediately following an infusion of panitumumab. Both patients had previously experienced hypersensitivity reactions to cetuximab and oxaliplatin, respectively.

- **Panitumumab is, therefore, contraindicated in patients with a history of severe or life threatening hypersensitivity reactions**.
- Serious infusion-related reactions are unpredictable and can occur suddenly. Panitumumab should be permanently discontinued if a severe or life threatening reaction occurs.
- In patients experiencing a mild or moderate infusion-related reaction, the infusion rate should be reduced for the duration of that infusion. It is recommended to maintain this lower infusion rate in all subsequent infusions.
- Hypersensitivity reactions occurring more than 24 hours after infusion have also been reported. Patients should be warned of the possibility of a late onset reaction, made aware of possible symptoms and instructed to contact their physician if symptoms of a hypersensitivity reaction occur.
- An SAE form should be completed and sent to the **FOxTROT** Study office for any serious adverse events suspected to be associated with the use of panitumumab

Panitumumab dermatological toxicity

- Over 90% of patients treated with panitumumab in previous trials developed skin or nail side-effects, usually a mild-to-moderate acneiform rash, similar to that seen during cetuximab therapy. This reached NCI CTC Grade 3 in 4% and resulted in discontinuation of the drug in 1% of patients.
- All patients allocated to receive panitumumab should be forewarned that they are very likely to develop a rash. At the first development of a rash we recommend:
  - start an oral tetracyline, e.g lymecycline 408 mg b.d.
  - start topical emollients (e.g. E45®) and bath additives (e.g. Hydromol®)
- Skin toxicities will be recorded as adverse events on the Treatment Case Report Form and will be graded using the modified NCI CTC version 3.0.

Panitumumab non-dermatological toxicity

- In single-agent panitumumab studies, grade 1-2 diarrhoea, nausea, vomiting, abdominal pain and fatigue have been reported.
- In ongoing trials of combination chemotherapy + anti-EGFR therapy, including COIN, the addition of antibody increases the incidence of nausea, vomiting and diarrhoea. In the PACCE trial of combination chemotherapy + bevacizumab ± panitumumab, patients on the 4-drug combination arm had increased rates of severe diarrhoea and infections.
- It is therefore possible that panitumumab may contribute to a range of toxicities when given in combination with OxMdG or OxCap
- Toxicities will be recorded as adverse events on the AE Case Report Form

Panitumumab dose omissions and reductions

Toxicity should be assessed before giving the second and third dose of panitumumab. The brief treatment duration with panitumumab in **FOxTROT** - just 3 doses at 2-weekly intervals - means that few dose adjustments are anticipated. The following guidelines should be used for adjusting panitumumab in the event of toxicity.

- All patients should receive their first panitumumab treatment at the full protocol dose of 6 mg/kg. If this is tolerated with mild or moderate toxicity, the subsequent treatment(s) should be administered at the same dose.
- If the first panitumumab treatment produces severe skin or nail toxicity, which remains severe at the time the second or third chemotherapy dose is due, panitumumab should be withheld from that cycle. Examples of reasons for withholding panitumumab are:
  - Symptomatic skin- or nail-related toxicity of a severity requiring strong analgesia, systemic steroids, intravenous antimicrobial therapy or surgical debridement
  - Symptoms felt to be intolerable by the patient
  - If the second dose of panitumumab has been withheld for toxicity, panitumumab may be reintroduced at the third cycle at 50% dose (3mg/kg), provided the adverse event has improved to ≤ Grade 2, and systemic steroids, IV antibiotic or IV antifungal treatment are no longer required.
- Non-dermatological symptoms should be managed as advised in the chemotherapy regimen sections above, including dose reduction of OxMdG as appropriate. If the patient has severe non-dermatological toxicity to which, in the opinion of the investigator, panitumumab has contributed significantly, panitumumab should be withheld for the next cycle.
  - In this event, panitumumab may be re-introduced in the third cycle at 50% dose (3mg/kg), by IV infusion over 60 minutes prior to OxMdG, provided that the adverse event has improved to ≤ Grade 2

Panitumumab delays

- Panitumumab may only be given in combination with OxMdG (not OxCap), and only during the preoperative chemotherapy cycles.

- If a chemotherapy cycle is delayed for chemotherapy-related reasons (e.g. neutropenia), panitumumab is also delayed, and given on d1 of the next chemotherapy cycle when that is administered.

- If a patient is interested in participating in the panitumumab randomisation, but their RAS test result is delayed beyond the time when neoadjuvant chemotherapy is due to start, the cycle #1 OxMdG should be started without panitumumab. If a RAS-wild type result then becomes available during the 14 days from the start of cycle #1 OxMdG, the patient may be consented and randomised immediately. If allocated panitumumab, it is introduced as follows, depending on how many days have elapsed:

  a) 1-5 days into cycle #1 OxMdG: give panitumumab at the standard dose (6 mg/kg). Continue as usual from d1 cycle #2.

  b) 6-10 days into cycle #1 OxMdG: give panitumumab at half-dose (3 mg/kg). Continue at full dose as usual from d1 cycle #2.

  c) 11 days or later into cycle #1 OxMdG: do not give panitumumab during cycle #1, but start as usual from d1 cycle #2.

- If the RAS test is still not available when cycle 2 OxMdG is due to start, the patient may not participate in the panitumumab randomisation.

- In the event that a patient is allocated to receive panitumumab but it is not available because of an interruption to drug supply, please do not delay chemotherapy, but give the panitumumab when available using the same schema as given above.

- Missed cycles of Panitumumab should not be given post-operatively.

Appendix G: REFERENCES

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