AstraZeneca

**Amended Clinical Study Protocol**

| | |
|---|---|
| Drug Substance | Cediranib (RECENTIN, AZD2171) |
| Study Code | D8480C00013 |
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# A Randomised, Double-blind, Multicentre Phase II/III Study to Compare the Efficacy of Cediranib (RECENTIN™, AZD2171) in Combination with 5-fluorouracil, Leucovorin, and Oxaliplatin (FOLFOX), to the Efficacy of Bevacizumab in Combination with FOLFOX in Patients with Previously Untreated Metastatic Colorectal Cancer

**Sponsor: AstraZeneca AB, 151 85 Sodertalje, Sweden.**

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**AstraZeneca Research and Development site representative** [redacted]



**The following Amendment(s) and Administrative Changes are included in this amended protocol:**

| Amendment No. | Date of Amendment | Local Amendment No. | Date of local Amendment |
|---|---|---|---|
| 001 | 30 May 2006 | | |
| 002 | 10 September 2007 | | |
| **Administrative change No.** | **Date of Administrative Change** | **Local Administrative change No.** | **Date of local Administrative Change** |

# PROTOCOL SYNOPSIS



## A Randomised, Double-blind, Multicentre Phase II/III Study to Compare the Efficacy of Cediranib (RECENTIN™, AZD2171) in Combination with 5-fluorouracil, Leucovorin, and Oxaliplatin (FOLFOX), to the Efficacy of Bevacizumab in Combination with FOLFOX in Patients with Previously Untreated Metastatic Colorectal Cancer

**International Co-ordinating Investigator**

Phase II:

[redacted]

**Study centres and number of patients planned**

The study will comprise 2 parts. During the phase II part of the study, approximately 225 patients will be recruited from approximately 100 centres in Europe, North America and Australia. Patient recruitment will continue while patients are being followed for response and analysis of the phase II part is performed to decide whether to continue to the subsequent phase III part of the study and to select which dose of cediranib (RECENTIN™, AZD2171) should be used. Following completion of the phase II analysis, if the phase III part of the study proceeds, a further approximately 170 centres in Europe, North and South America, Australia and Asia will be initiated to enrol further patients. The total number of patients enrolled will be approximately 1600.

| Study period | | Phase of development |
|---|---|---|
| Estimated date of first patient enrolled | July 2006 | Phase II/III |
| Estimated date of last patient completed | January 2011 | |

The end of the study is defined as the date when 950 patients have died.

**Objectives**

The primary objective of the study is to determine:

- The efficacy of cediranib in combination with 5-fluorouracil (5-FU), leucovorin (or equivalent folinic acid preparation) and oxaliplatin (FOLFOX) compared to the efficacy of bevacizumab in combination with FOLFOX by assessment of progression free survival (PFS).

The secondary objectives of the study are to determine:

1. The efficacy of cediranib in combination with FOLFOX compared to the efficacy of bevacizumab in combination with FOLFOX by assessment of overall survival (OS), overall response rate (ORR; complete response [CR] + partial response [PR]) and duration of response.

2. The safety and tolerability of randomised study therapies in combination with FOLFOX.

3. The effects on quality of life (QoL) and disease-related symptoms of cediranib in combination with FOLFOX, compared with the effects of bevacizumab in combination with FOLFOX.

The exploratory objectives of the study are:

1. To obtain archival tumour samples for assessment of biomarkers of disease activity, angiogenesis or activity of cediranib and for optional DNA extraction and retrospective mutation analysis of genes as potential markers of the activity of cediranib, bevacizumab and FOLFOX.

2. To obtain blood samples for biomarkers of angiogenesis and optional DNA extraction for retrospective pharmacogenetic analysis of the activity of cediranib, bevacizumab and FOLFOX.

3. To investigate the effects on health status, as assessed by the EuroQol-5 Dimension Health status Measure (EQ-5D), of cediranib in combination with FOLFOX, compared with the effects of bevacizumab in combination with FOLFOX.

**Study design**

This is a randomised, double-blind, international multi-centre study to compare the efficacy of cediranib in combination with FOLFOX to the efficacy of bevacizumab in combination with FOLFOX, in patients with metastatic colorectal cancer (CRC).

The study will consist of 2 parts. In the phase II part of the study, patients will be randomised in a 1:1:1 ratio to receive cediranib 30 mg or cediranib 20 mg or bevacizumab. An analysis of the phase II data will be performed after 225 patients have had 3 months of follow up. The results of this analysis, in combination with the results from a second line study of cediranib (with the same treatment arms), will be used to decide whether to continue to the phase III part of the study and to confirm the selected dose of cediranib. If the results of these two analyses are equivocal, data from a third, placebo-controlled, cediranib study in first line CRC (D8480C00051) may be used in the decision to continue to the phase III part of the study. Recruitment to the original 3 treatment arms will continue during the analysis of the phase II data; however, once the phase III dose decision has been made, all subsequent patients will be randomised in a 1:1 ratio to receive the selected dose of cediranib or bevacizumab.

It is important that patients are assessed according to the study visit schedule and that patients continue to be assessed for progression until objective progression occurs, regardless of whether they continue study drug or start to receive other anti-cancer therapy.

First line chemotherapy and blinded study medication should be administered until progression (or other criteria for discontinuation are met), unless there is toxicity. If the toxicity is attributable to one component alone, then this component should be withdrawn and the other components continued until progression. Eg, if oxaliplatin must be discontinued due to toxicity, 5-FU and leucovorin (or equivalent folinic acid preparation) must be continued until progression along with the blinded study medication.

It is also proposed to collect an optional blood sample for genotyping. Provision of this blood sample for genetic analysis will be optional for patients entering the study and will involve a separate consent procedure. A patient's acceptance of this procedure will not be a requirement of their participation in the study.

**Target patient population**

Male and female patients aged ≥18 years with histologically- or cytologically-confirmed metastatic CRC who have received no prior oxaliplatin therapy for metastatic disease and completed any adjuvant/neoadjuvant therapy at least 12 months before study entry (5-FU adjuvant therapy can have been received at least 6 months prior to study therapy). Patients must have a World Health Organisation (WHO) performance status (PS) of <2 and must have measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.

Phase II

**Investigational product and dosage**

(see Section 3.2.1)

Patients in **Treatment Group A** will be given cediranib 30 mg/day, cediranib matched placebo 20 mg/day and bevacizumab placebo every 2 weeks.

Patients in **Treatment Group B** will be given cediranib 20 mg/day, cediranib matched placebo 30 mg /day and bevacizumab placebo every 2 weeks.

**Comparator and dosage**

Patients in **Treatment Group C** will be given cediranib matched placebo 20 mg and 30 mg daily, and bevacizumab 5 mg/kg every 2 weeks.

In addition to the investigational product, patients in Treatment Groups A, B and C will receive FOLFOX.

**Mode of administration of study drugs**

**Cediranib**

Cediranib 30 mg will be administered as a single 30 mg tablet together with a placebo tablet matching cediranib 20 mg, to be taken orally once daily.

Cediranib 20 mg will be administered as a 20 mg tablet together with a placebo tablet matching cediranib 30 mg, to be taken orally once daily.

**FOLFOX**

The FOLFOX regimen in this study will be a modified FOLFOX6 regimen, repeated every 2 weeks:

- Oxaliplatin 85 mg/m$^2$ with leucovorin (or equivalent folinic acid preparation) 400 mg/m$^2$ administered intravenously over 2 hours on Day 1.
- 5-FU 400 mg/m$^2$ bolus immediately after completion of the oxaliplatin infusion on Day 1, followed immediately by 5-FU 2400 mg/m$^2$ administered by a continuous iv infusion over 46 hours.

**Bevacizumab**

Bevacizumab should be stored, prepared and administered according to its labelling information and standard clinical practice. Bevacizumab vials must be refrigerated at 2–8°C (36–46°F) and protected from light.

It should be diluted for infusion by a healthcare professional using aseptic technique. The necessary amount of bevacizumab for a dose of 5 mg/kg should be withdrawn and diluted in a

total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Any unused portion left in a vial should be discarded as the product contains no preservatives.

The diluted bevacizumab solution should be inspected visually for particulate matter and discoloration prior to administration. Diluted bevacizumab solutions for infusion may be stored at 2–8°C (36–46°F) for up to 8 hours.

Bevacizumab infusions should not be administered or mixed with dextrose solutions and should not be administered as an iv push or bolus.

Bevacizumab should be administered as per standard clinical practice. The initial bevacizumab dose should be delivered over 90 minutes as an IV infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. Bevacizumab should be administered on Day 1 every 2 weeks.

**Placebo**

Patients randomised to the bevacizumab arm will receive cediranib placebo, administered as 2 placebo tablets daily, one matching cediranib 30 mg and one matching cediranib 20 mg.

Patients randomised to the cediranib arms will receive bevacizumab placebo (physiological saline), given as an infusion every 2 weeks, as described above.

Phase III

**Investigational product and dosage**

On completion of the phase II analysis, if it is decided that at least one dose of cediranib is tolerable and unless there is a reasonable probability of inferiority to bevacizumab, one dose of cediranib (30 or 20 mg) will be selected and the study will continue to the phase III part. In the event that both doses are declared non-inferior to bevacizumab, and there is no clear advantage of the 20 mg cediranib dose, the 30 mg dose will be selected to continue. All subsequent patients will be recruited into the treatment arm (A or B) that is selected. No further patients will be recruited to the dose of cediranib that is not selected.

For example, if the selected dose is 30 mg (Treatment Group A):

- New patients will receive cediranib 30 mg/day and bevacizumab placebo every 2 weeks in addition to FOLFOX.

If the selected dose is 20 mg (Treatment Group B):

- New patients will receive cediranib 20 mg/day and bevacizumab placebo every 2 weeks in addition to FOLFOX

**Comparator and dosage**

New patients in Treatment Group C will be given placebo to match the selected dose of cediranib daily and bevacizumab 5 mg/kg every 2 weeks in addition to FOLFOX.

For example if the 30 mg dose is chosen:

- New patients in Treatment group C will receive cediranib matched placebo 30 mg and bevacizumab 5 mg/kg every 2 weeks in addition to FOLFOX.

If the 20 mg dose is chosen:

- New patients in Treatment group C will receive cediranib matched placebo 20 mg and bevacizumab 5 mg/kg every 2 weeks in addition to FOLFOX.

**Mode of administration of study drugs**

**Cediranib/Placebo**

If the 30 mg dose is selected:

- Cediranib 30 mg will be administered as a single 30 mg tablet or placebo to match to be taken orally once daily.

If the 20 mg dose is selected:

- Cediranib 20 mg will be administered as a single 20 mg tablet or placebo to match to be taken orally once daily.

**FOLFOX**

FOLFOX will be administered as per phase II.

**Bevacizumab/placebo**

Bevacizumab will be administered as per phase II.

**Duration of treatment**

Randomised treatment will continue for an indefinite period even if chemotherapy agents have been discontinued, until a criterion for discontinuation is met (i.e. disease progression, toxicity or consent withdrawal). The precise duration of study treatment will be documented.

Patients in all groups may continue with blinded randomised treatment after progression following discussion with AstraZeneca, if, in the opinion of the investigator, the patient is receiving benefit. There will be no cross over to cediranib treatment for patients in the FOLFOX plus bevacizumab treatment group. Patients with disease progression who continue with randomised treatment should also be offered an effective second line therapy, such as an

irinotecan-containing chemotherapy unless this also includes a VEGF inhibitor. All subsequent cancer therapy must be recorded and the patient must be followed for survival.

**Outcome variables**

- **Efficacy**
  - **Primary outcome variable:**
    - PFS
  - **Secondary outcome variables:**
    - OS
    - ORR (CR + PR)
- **Patient reported outcomes (PROs)**
  - Time to worsening of QoL
  - Time to worsening of disease related symptoms
- **Exploratory outcome variables**
  - Levels and changes from baseline in biomarkers of disease activity, angiogenesis and activity of cediranib and bevacizumab in plasma and serum archived tumour samples, and optional tumour samples, if available during the course of the study. Retrospective analysis of host genes involved in the absorption, distribution, metabolism and excretion and response to cediranib, and drugs taken in addition to cediranib, as well as genes in the pathways targeted by cediranib, in DNA obtained from an additional blood sample.
  - Health status as measured by EQ-5D
- **Safety**
  - Adverse events (AEs)
  - Laboratory findings (clinical chemistry, haematology, urinalysis)
  - Vital signs
  - Physical examination including blood pressure (BP)
  - Electrocardiogram (ECG)

## Statistical methods

### Phase II part

The phase II analysis will be performed when a total of 225 patients (75 per group) have been followed for 3 months. The efficacy of each dose level will be assessed using response rate in conjunction with PFS data from a randomised phase II study in comparison with bevacizumab in second line CRC patients (D8480C00041). Data from a third, placebo-controlled, cediranib study in first line CRC (D8480C00051) may be used if the results from this study and the phase II study are equivocal. The study will continue if there is at least one dose that is tolerable, unless there is a reasonable probability of inferiority to bevacizumab (see Section 6.6). In the event that both doses are declared non-inferior to bevacizumab, and there is no clear advantage of the 20 mg cediranib dose, the 30 mg dose will be selected to continue.

### Phase III part

The primary objective of the study is to determine the efficacy of cediranib in combination with FOLFOX compared to the efficacy of bevacizumab in combination with FOLFOX. This objective will be assessed by the primary variable of PFS. Whilst the study has been powered on the basis of showing superiority, the statistical analysis will also describe the extent of non-inferiority.

The final analysis of PFS and the secondary endpoints ORR and duration of response will be performed after 850 progression events have occurred. This number of progression events is expected to have occurred approximately 37 months after the first patient has entered the study. If the true hazard ratio (HR) for cediranib:bevacizumab is equal to 0.8, this analysis will have 90% power to demonstrate a statistically significant difference at a 2-sided 5% level.

An interim analysis of the secondary endpoint, OS, will be performed at the time of the final PFS analysis, and it is anticipated that approximately 501 patients will have died at this time (assuming a 25 month median OS). This will enable calculation of a sufficiently precise estimate of the treatment effect in order to provide reassurance regarding the relative effect on OS. For example, if a HR of 1 were observed for OS, its 95% confidence interval (CI) would range from 0.84 to 1.19.

A final analysis of OS will be performed after a total of 950 deaths. This number of deaths is predicted to occur approximately 58 months after the first patient has entered the study. An O'Brien and Fleming spending function (O'Brien PC and Fleming TR 1979) will be used to control the family-wise type 1 error rate, between the interim and final analyses of OS.

It is intended that approximately 1400 patients will receive either bevacizumab or the cediranib dose selected for phase III expansion. Together with patients in the cediranib dose group dropped after the phase II analysis, it is expected that a total of approximately 1600 patients will be recruited into the study.

The primary statistical analysis of the efficacy of cediranib will include all randomised patients and will compare the treatment groups on the basis of randomised treatment,

regardless of treatment actually received. Therefore, all efficacy and QoL data will be summarised and analysed on an intention-to-treat (ITT) basis. When assessing tolerability, summaries will be produced based on study treatment actually received for all patients who received at least one dose of study medication (termed the evaluable for safety [EFS] population). The phase III analyses will include all data from patients recruited into the bevacizumab group and selected dose group in both the phase II and phase III parts of the study (data from the cediranib dose group discontinued at the end of the phase II part of the study will not be included). Since PFS data from patients recruited into the phase II part of the study will be used in the phase III analyses, and data from the phase II part will be used to select the phase III dose, the Todd and Stallard methodology (Todd S and Stallard N 2005) will be used to adjust the type 1 error for the primary analysis.

PFS and OS will be analysed using a log-rank test stratified by PS (0 or 1), baseline albumin and baseline alkaline phosphatase.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

| Abbreviation or special term | Explanation |
|---|---|
| 5-FU | 5-fluorouracil |
| ACTH | Adrenocorticotropic hormone |
| AE | Adverse event (see definition in Section 4.7.1.1) |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| Assessment | An observation made on a variable involving a subjective judgement (assessment) |
| APTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| BP | Blood Pressure |
| BUN | Blood urea nitrogen |
| CCS | Colorectal Cancer Subscale |
| CEA | Carcinoembryonic Antigen |
| CI | Confidence Interval |
| CK | Creatine kinase |
| CKMB | Creatine kinase MB |
| CKMM | Creatine kinase MM |
| $C_{max,ss}$ | Maximum concentration at steady-state |
| $C_{min,ss}$ | Minimum concentration at steady-state |
| CR | Complete Response |
| CRC | Colorectal cancer |
| CRA | Clinical Research Associate |
| CRO | Contract Research Organisation |
| CT | Computed tomography |
| CTCAE | Common Toxicity Criteria Adverse Event |
| DCE-MRI | Dynamic contrast enhanced magnetic resonance imaging |
| ECG | Electrocardiogram |
| eCRF | electronic Case Report Form |

| Abbreviation or special term | Explanation |
|---|---|
| EFS | Evaluable for Safety |
| EGFR | Epidermal growth factor receptor |
| EQ-5D | EuroQol 5 Dimension Health Status Measure |
| FACT-C | Functional Assessment of Cancer Therapy - Colorectal |
| FACT-G | Functional Assessment of Cancer Therapy - General |
| FCSI | FACT Colorectal Symptom Index |
| FDA | US Food and Drug Administration |
| Flt | fms-like tyrosine kinase |
| FOLFIRI | Irinotecan, Leucovorin, and 5-fluorouracil (bolus followed by continuous iv infusion over 46 hours) |
| FOLFOX | Oxaliplatin, Leucovorin, and 5-fluorouracil |
| GCP | Good Clinical Practice |
| HIF1α | Hypoxia-inducible factor 1α |
| HR | Hazard Ratio |
| HUVEC | Human Umbilical Vein Endothelial Cell |
| ICH | International Conference on Harmonisation |
| IDMC | International Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IFL | Irinotecan, 5-fluorouracil, and Leucovorin |
| IND | Investigational New Drug |
| INR | International Normalised Ratio |
| IRB | Institutional Review Board |
| ITT | Intention-to-Treat |
| iv | Intravenous |
| IVRS | Interactive Voice Response System |
| KDR | Kinase Insert Domain-containing Receptor |
| Measurement | An observation made on a variable using a measurement device. |
| MR | Minor Response |
| MTD | Maximum Tolerated Dose |
| MVD | Microvessel Density |
| NCI | National Cancer Institute |
| NCIC | National Cancer Institute of Canada |

| Abbreviation or special term | Explanation |
|---|---|
| NCR | No Carbon Required |
| OAE | Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment; see definition in Section 4.7.1.1). |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| Outcome variable | A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective. |
| Parameter | A quantity (usually unknown) that characterises the distribution of a variable in a population of patients. |
| PFS | Progression Free Survival |
| PR | Partial Response |
| Principal investigator | A person responsible for the conduct of a clinical study at an investigational study site. Every investigational study site has a principal investigator. |
| PRO | Patient Reported Outcomes |
| PS | Performance Status |
| QoL | Quality of Life |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| RPLS | Reversible posterior leucoencephalopathy syndrome |
| SAE | Serious Adverse Event (see definition in Section 4.7.1.1). |
| SAP | Statistical Analysis Plan |
| SDV | Source Data Verification |
| SmPC | Summary of Product Characteristics |
| sVEGF | Soluble Vascular Endothelial Growth Factor |
| TOI | Trial Outcomes Index |
| TSH | Thyroid Stimulating Hormone |
| ULRR | Upper Limit of Reference Range |
| VEGF | Vascular Endothelial Growth Factor |
| VEGFR | Vascular Endothelial Growth Factor Receptor |
| WHO | World Health Organisation |

# 1. INTRODUCTION

## 1.1 Background

### 1.1.1 Colorectal cancer

Colorectal cancer (CRC) is one of the most common malignancies. The worldwide incidence of CRC in 2000 was estimated as 944,700 cases (males: 498,800 cases; females: 446,000 cases; Parkin DM et al 2001). Of newly diagnosed patients, 40% have metastatic disease at diagnosis, and approximately 25% of patients with localised disease at diagnosis will ultimately develop metastatic disease. With the exception of patients with localised liver metastases that can be resected, the majority of patients with metastatic CRC ultimately die of their disease, with a median survival of less than 2 years.

The mainstay of first line treatment of metastatic disease is a chemotherapy regimen combining oxaliplatin or irinotecan with intravenous (iv) 5-fluorouracil (5-FU) and leucovorin (FOLFOX or FOLFIRI/IFL, respectively (Maindrault-Goebel F 2006). The best published median survival results, up to 20.6 months, have been seen with sequential FOLFOX and FOLFIRI in either order (Tournigand C et al 2004). The progression free survival (PFS) for FOLFOX alone in the first line setting is up to 9.0 months (De Gramont A et al 2000).

Bevacizumab (Avastin™) is a monoclonal antibody against vascular endothelial growth factor (VEGF) that was recently approved in the USA and Europe in combination with iv 5-FU/leucovorin or IFL based regimens. The PFS for patients treated with irinotecan, bolus 5-FU and leucovorin (IFL) plus bevacizumab was 10.6 months and overall survival (OS) was 20.3 months, which were statistically significantly better than the results for IFL alone; PFS of 6.2 months and OS of 15.6 months (Hurwitz et al 2004). As a result, the use of bevacizumab in combination with 5-FU-based chemotherapy is becoming the standard of care in the USA and is starting to be made available across Europe.

The combination of bevacizumab with FOLFOX has been investigated in two phase III studies. In 2005, it was demonstrated that patients with advanced CRC who had previously been treated with irinotecan and a fluoropyrimidine who received bevacizumab in combination with FOLFOX had a 26% reduction in the risk of death (hazard ratio [HR] of 0.74) and improved OS of 17% compared with patients treated with FOLFOX alone (Giantonio BJ et al 2005). More recently, the final results from the first line therapy study XELOX-1/NO16966 confirmed that bevacizumab + chemotherapy (XELOX or FOLFOX) was superior to chemotherapy alone in terms of PFS (HR 0.83; p=0.0023), although the OS data did not reach statistical significance (HR 0.89; p=0.0769; Saltz LB et al 2007).

It is hypothesised that bevacizumab, or other anti-angiogenic agents such as cediranib, may augment the effect of different chemotherapy regimens in CRC.

### 1.1.2 Cediranib (RECENTIN™, AZD2171)

Cediranib (RECENTIN™, AZD2171) has been developed as a potent inhibitor of the tyrosine kinase activity of VEGF receptor 2 (VEGFR-2; also called kinase insert domain-containing receptor [KDR]), VEGF receptor 1 (VEGFR-1 also called fms-like tyrosine kinase-1 [Flt-1]) and VEGF receptor 3 (VEGFR-3, also called fms-like tyrosine kinase-4 [Flt-4]), and of VEGF-driven human umbilical vein endothelial cell (HUVEC) proliferation. Cediranib is expected, at chronic oral dosing, to inhibit VEGF-driven angiogenesis and, as a consequence, constrain tumour growth. Since angiogenesis is necessary for the growth and metastasis of most tumours and VEGF is believed to have a pivotal role in this process, cediranib treatment may have broad-spectrum clinical utility.

#### 1.1.2.1 Pre-clinical experience with cediranib

For full details of the pre-clinical information, please refer to the latest version of the Investigator's Brochure (Investigator's Brochure).

#### 1.1.2.2 Clinical experience with cediranib

For full details of the clinical information, please refer to the latest version of the Investigator's Brochure (Investigator's Brochure).

At the time of writing this protocol, approximately 1063 patients have received cediranib. Phase I studies include five monotherapy studies in patients with: advanced solid tumours with liver metastases (D8480C00001), acute myeloid leukaemia (D8480C00002), prostate cancer (D8480C00003), non small cell lung cancer/head and neck cancer (D8480C00015), solid metastatic tumours (D8480C00019), and a maximum tolerated dose (MTD) study in Japanese patients with advanced solid tumours (D8480C00023).

There are also 5 studies of cediranib in combination with the following agents:

- gefitinib (D8480C00004)
- fulvestrant (D8480C0007)
- modified oxaliplatin, leucovorin and 5-FU (mFOLFOX6), pemetrexed, docetaxel, irinotecan with and without cetuximab (D8480C00008)
- carboplatin/paclitaxel and capecitabine (D8480C00009/NCIC IND 171, a collaboration with the National Cancer Institute of Canada [NCIC])
- cisplatin/gemcitabine and FOLFOX (D8480C00022/NCIC IND 175, a collaboration with the NCIC)

Data from studies D8480C00004, D8480C00008, D8480C00009 and D8480C000022 indicate that the adverse event (AE) profile of cediranib, when dosed in combination with gefitinib and

standard chemotherapy agents, is the same as that observed in monotherapy studies, although the identified MTD of cediranib has differed between protocols.

In the monotherapy study D8480C00001, cediranib was well tolerated at doses up to and including 45 mg in patients with advanced solid tumours. In study D8480C00009, the 45 mg dose was well tolerated in combination with standard dose carboplatin and paclitaxel as first/second line therapy in patients with metastatic NSCLC. However, in the subsequent phase II study D8480C00005, the 45 mg dose was found to be not well tolerated due to a higher incidence of diarrhoea than seen with carboplatin and paclitaxel alone, and the recommended dose was reduced to 30 mg. In studies D8480C00008, D8480C00009 and D8480C000022, the 30 mg dose was found to be well tolerated in combination with FOLFOX, capecitabine and other standard chemotherapy agents.

In addition, at the time of writing this protocol, the following later phase studies are ongoing:

- a signal search programme of approximately 26 studies in collaboration with the National Cancer Institute (NCI): carboplatin/paclitaxel versus carboplatin/paclitaxel alone as first line therapy in patients with advanced non small cell lung cancer (NSCLC; Study BR.24, a collaboration with the NCIC).
- a randomised phase II/III study of cediranib in combination with carboplatin/paclitaxel versus carboplatin/paclitaxel alone as first line therapy in patients with advanced NSCLC (Study D8480C0005 [BR.24] a collaboration with the NCIC).
- a randomised phase II/III study of cediranib in combination with FOLFOX versus bevacizumab in combination with FOLFOX as first line therapy in patients with metastatic CRC (study D8480C00013).
- a two-part open-label phase II study to determine the effect of food upon the pharmacokinetics of a single dose of cediranib (Part A) followed by a randomised assessment of safety, tolerability and efficacy of multiple doses of cediranib (Part B) in patients with advanced solid tumours (D8480C00021).
- a randomised phase II study of cediranib versus placebo in patients with metastatic or recurrent renal cell carcinoma with no previous anti-VEGF therapy (Study D8480C00030).
- a randomised phase II study of hypertension prophylaxis versus early treatment of emergent hypertension in patients treated with 30 mg and 45 mg cediranib (Study D848000038).
- a randomised phase II study of cediranib in combination with FOLFOX versus bevacizumab in combination with FOLFOX as second line therapy in patients with advanced metastatic CRC (Study D8480C00041).

- an open-label, phase II study to evaluate the biological activity of cediranib as measured by FDG-PET response, in patients with metastatic gastro-intestinal stromal tumours resistant or intolerant to imatinib mesylate (D8480C00046).

- a randomised phase III study of cediranib in combination with FOLFOX or capecitabine and oxaliplatin (XELOX) versus placebo in combination with FOLFOX or XELOX as a first line therapy in patients with metastatic CRC (D8480C00051).

The Investigator's Brochure was updated in August 2007 (Investigator's Brochure). However, investigators are requested to refer to the latest version, in case of any changes.

### 1.1.2.3 Pharmacokinetic profile

The pharmacokinetic profile of cediranib is supportive of once-daily oral dosing. In study D8480C00001 the $C_{max}$ ranged from 1 to 8 hours following a single dose. Concentrations declined in an apparent bi-exponential manner thereafter with a $t_{1/2\lambda z}$ ranging from 12.4 to 35.7 hours with an overall arithmetic mean value of 22.0 hours. Steady-state plasma concentrations were predicted by the single dose pharmacokinetics, with the grand arithmetic mean TCP value being 0.988. This supports no time dependent changes in pharmacokinetics. Visual inspection of the trough plasma concentration values shows that steady-state plasma concentrations are attained after 7 days of repeated once daily dosing. Following multiple oral doses of cediranib 20 mg in Parts A and B, the unbound $C_{ss,min}$ was 4.86 times above the HUVEC proliferation $IC_{50}$. Dose proportionate increase in $C_{ss,max}$ and $AUC_{ss}$ were observed for cediranib doses ranging from 0.5 to 60 mg. However, further pharmacokinetic data are needed to make a definitive statement about linearity or dose proportionality.

In the mass-balance study D8480C00019, the amount of radioactivity recovered in the urine and faeces samples within 168-hours post dosing ranged from 84.8 to 93.0% with most of the radioactivity was recovered in the first 72 hours following dosing for 5 out of 6 patients. In one patient, the radioactivity recovered in urine and faeces was only 34.1% over the first 168 hours post dosing. In all 6 patients, majority of the radioactivity was excreted in the faeces (arithmetic mean of 58.8%) with an arithmetic mean of 20.8% being excreted in the urine. Examining the ratio of plasma radioactivity to cediranib plasma concentration revealed that cediranib plasma concentrations are a fraction of the drug related substance following administration of cediranib suggesting extensive metabolism.

Preliminary results from part A of study D8480C00021 to determine the effect of food on the pharmacokinetics of a single dose of cediranib have shown that the pharmacokinetics of cediranib are affected by food with a reduction in $AUC_{0-\infty}$ of 22% and $C_{max}$ of 33% in the presence of food (AZ Data on File). Therefore, cediranib should be administered at least 1 hour before or 2 hours after food.

Based on available preliminary data from study D8480C00008, cediranib does not appear to have a major effect on the pharmacokinetic profile of oxaliplatin, 5-FU, pemetrexed, irinotecan (SN38) and docetaxel. Steady-state pharmacokinetic parameters of cediranib in

combination with the chemotherapy agents are comparable with those seen previously with cediranib monotherapy.

#### 1.1.2.4 Pharmacodynamic profile and tumour response

**Tumour response and pharmacodynamic profile**

The phase I studies were designed primarily to investigate the safety, tolerability and pharmacokinetic profile of cediranib; however, encouraging pharmacodynamic effects and anti-tumour activity have been observed, as described below.

**Pharmacodynamic data**

In Study D8480C00001 (Drevs J et al 2007), serial assessments of blood flow and vascular permeability in liver metastases were carried out by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Across the dose range studied in Study D8480C00001 (0.5 to 60 mg), there was a strong negative association between cediranib exposure and percentage change from baseline in the DCE-MRI parameter, iAUC60 (a measure of both blood flow and vascular permeability). In the randomised cohort expansion part of the study, significant decreases from baseline were seen at 20, 30 and 45 mg. Within this range, the difference between the doses was not statistically significant.

Initial biomarker assessments from Study D8480C00001 show increases in VEGF-A have been detected at all doses, and time-dependent reductions in VEGFR-2 have been documented at doses of 10 mg and higher. Dose-dependent reductions in VEGFR-2 have also been seen at doses of up to and including 20 mg. Similar changes in VEGF and soluble VEGFR-2 (sVEGFR-2) have also been observed in Studies D8480C00002 and D8480C00004. Decreases in sVEGFR-2 levels may be a surrogate for decreased angiogenesis and changes in VEGF could potentially be indicative of acute vascular effects.

**Tumour responses in monotherapy studies**

In Study D8480C00001, 63 patients with advanced cancers were evaluable for tumour response according to Response Evaluation Criteria in Solid Tumours (RECIST):

- 2 confirmed partial responses (PR) in prostate cancer (45 mg) and renal cancer (60 mg).
- 23 patients with stable disease, including 2 unconfirmed PRs in hepatocellular cancer (30 mg and 45 mg), 1 unconfirmed PR in soft tissue carcinoma (60 mg) and 8 confirmed minor responses (MR) in soft tissue sarcoma (60 mg), head and neck and hepatocellular cancer (45 mg); lung, stomach and breast cancer (30 mg); CRC and breast cancer (20 mg).

In Study D8480C00038, 109 patients with advanced cancers were evaluable for tumour response according to RECIST:

- 9 PRs (4 at 30 mg and 5 at 45 mg) 3 in patients with breast cancer, 2 in melanoma 1 in renal cell carcinoma, prostate and cervical cancers.

- 52 patients with SD.

In an interim analysis of 16 patients enrolled in an NCI-sponsored study of patients with recurrent glioblastoma treated with cediranib 45 mg, 9 of 16 patients had a radiographic partial response, 5 patients reached 6 months without progression and the median PFS was 111 days. There was also evidence of reduction in vascular permeability, vasogenic oedema and steroid usage (Batchelor TT et al 2007).

In an NCI –sponsored study of patients with first-line, progressive, unresectable, advanced metastatic renal cell carcinoma treated with cediranib 45 mg, 24 patients were evaluable for response as of May 2007. There was a 33% ORR (8 PRs and 1 unconfirmed CR) (Sridhar SS et al 2007).

**Tumour response in combination studies**

In Study D8480C00004, in which cediranib was given in combination with gefitinib, 73 patients with advanced solid tumours were evaluable for RECIST tumour response:

- 8 PRs (1 at cediranib 20 mg, 1 at 25 mg, 4 at 30 mg, 1 at 37.5 mg, and 1 at 45 mg). 6 in primary renal tumours, 1 in mesothelioma, and 1 in osteosarcoma.

- 38 patients with stable disease.

In Study D8480C00022, cediranib was given in combination with oxaliplatin and infusional 5-FU (mFOLFOX6) in patients with advanced CRC (Chen E et al 2007). Of the 14 patients evaluable for response, there was 1 CR, 6 PRs, and 5 patients with SD. Liver metastatic disease became resectable in 2 patients after 20 and 16 cycles of treatment, respectively.

### 1.1.2.5 Safety profile

Cediranib appears to be well tolerated in patient studies at doses up to and including 45 mg/day as monotherapy, with no clinically significant abnormalities in laboratory or electrocardiogram (ECG) parameters. When cediranib is administered in combination with gefitinib 250 mg, the MTD appears to be 30 mg.

Hypertension is an expected AE with agents that inhibit VEGF signalling. In cediranib studies, increases in blood pressure have been observed and cases of hypertension have been reported, including CTC Grade 4 hypertension and end-organ damage related to hypertension, such as cerebrovascular events.

Left ventricular dysfunction, in some cases leading to cardiac failure, has been observed in patients receiving cediranib with risk factors for left ventricular dysfunction (including previous or concomitant anthracycline treatment). A number of events of bleeding and

haemorrhage have occurred. Some events of haemorrhage were fatal but causality to cediranib could not be unequivocally assigned.

Fatigue, diarrhoea, nausea and vomiting are commonly occurring AEs in cediranib studies. Dehydration has been observed in clinical studies as a consequence of cediranib or chemotherapy related diarrhoea; chemotherapy associated vomiting, anorexia or reduced oral intake may also be the cause. Hoarseness (dysphonia) has been reported as common and is dose-related. Muscle weakness, proteinuria, dry mouth and oral mucosal inflammation have also been observed in cediranib studies.

One case of MRI-confirmed reversible posterior leucoencephalopathy syndrome has been observed in a patient receiving cediranib in a clinical study. In addition, there is some evidence suggesting a dose-related trend of increases from baseline in thyroid stimulation hormone (TSH) levels, which may be associated with clinical hypothyroidism.

## 1.2 Rationale for this study

With the exception of patients with localised liver metastases that can be resected, the median survival time for patients with metastatic CRC is less than 2 years. There is, therefore, a need to develop novel treatment regimens to improve survival in these patients.

This study will demonstrate whether small molecule inhibition of VEGF receptor signalling is a superior anti-angiogenic approach to monoclonal antibody binding of VEGF by comparing the combination of cediranib plus FOLFOX to bevacizumab plus FOLFOX. Cediranib is a highly potent inhibitor of all three VEGF receptors, which may offer superior anti-angiogenic effect compared with bevacizumab based on complete blockade of signalling from the receptor that is expected to be more effective at blocking angiogenesis than a monoclonal antibody (Fan F et al 2005). In addition, emerging data suggest a role for VEGF receptors on CRC cells (Wedge SR et al 2005).

The efficacy of bevacizumab in metastatic CRC has been demonstrated in combination with IFL or 5-FU/leucovorin (AVF2107 study, Hurwitz H et al 2004) and FOLFOX/XELOX (XELOX-1/NO16966 study; Cassidy J et al 2006) in the first line treatment setting; and in combination with FOLFOX in the second line setting (Giantonio BJ et al 2005). The recently presented preliminary results of the phase III first line XELOX-1/NO16966 study confirmed that bevacizumab plus chemotherapy (XELOX or FOLFOX) was superior to chemotherapy alone in terms of PFS (HR 0.83; p=0.0023), although the magnitude of this effect was less than had been previously observed in the AVF2107 study, when bevacizumab was added to IFL (HR 0.58; p<0.001).

Results from a recent phase III study of FOLFOX4 in combination with another small molecule inhibitor of VEGF receptor signalling PTK787/ZK222584 showed an improvement in PFS by investigator assessment compared to FOLFOX4 plus placebo (7.7m vs 7.5m; HR 0.83, p=0.026), although this improvement did not reach statistical significance when analysed by independent central review (Hecht JR et al 2005, ASCO 2005). These data indicate that the small molecule approach is likely to improve efficacy of chemotherapy regimens, although

properties of small molecules such as their half-life, auto-induction of metabolism and minimum concentration at steady-state ($C_{min,ss}$) may affect their overall contribution. The ratio of maximum concentration at stead state ($C_{max,ss}$) to ($C_{min,ss}$) following once daily oral repeated doses of 1000 mg was 45.1 for PTK787/ZK222584 (Morgan B et al 2003), whereas the same ratio for cediranib following once daily oral repeated doses of 45 mg was approximately 3.

Depending on the exposure response relationship needed for this class of agents, the constancy in plasma exposure at steady-state of cediranib compared to PTK/787/ZK222584 may be of therapeutic relevance.

# 2. OBJECTIVES

## 2.1 Primary objective

The primary objective of the study is to determine:

The efficacy of cediranib in combination with FOLFOX compared to the efficacy of bevacizumab in combination with FOLFOX by assessment of progression free survival (PFS)

## 2.2 Secondary objectives

The secondary objectives of the study are to determine:

1. The efficacy of cediranib in combination with FOLFOX compared to the efficacy of bevacizumab in combination with FOLFOX by assessment of OS, overall response rate (ORR; complete response [CR] + partial response [PR]) and duration of response.

2. The safety and tolerability of randomised study therapies in combination with FOLFOX.

3. The effects on quality of life (QoL) and disease-related symptoms of cediranib in combination with FOLFOX, compared with the effects of bevacizumab in combination with FOLFOX.

The exploratory objectives of the study are:

1. To obtain archival tumour samples for assessment of biomarkers of disease activity, angiogenesis or activity of cediranib and for optional DNA extraction and retrospective mutation analysis of genes as potential markers of the activity of cediranib, bevacizumab and FOLFOX.

2. To obtain blood samples for biomarkers of angiogenesis and optional DNA extraction for retrospective pharmacogenetic analysis of the activity of cediranib, bevacizumab and FOLFOX.

3. To investigate the effects on health status, as assessed by the EuroQol-5 Dimension Health status Measure (EQ-5D), of cediranib in combination with FOLFOX, compared with the effects of bevacizumab in combination with FOLFOX.

# 3. STUDY PLAN AND PROCEDURES

## 3.1 Overall study design and flow chart

This Clinical Study Protocol has been subjected to a peer review according to AstraZeneca standard procedures.

This will be a randomised, double-blind, international multi-centre study to compare the efficacy of cediranib in combination with FOLFOX to the efficacy of bevacizumab in combination with FOLFOX, in patients with metastatic CRC.

A total of approximately 1600 patients with histologically- or cytologically-confirmed metastatic CRC will be recruited from approximately 270 centres in Europe, North and South America, Australia and Asia.

Patients have to have received no prior oxaliplatin therapy for metastatic disease and completed any adjuvant therapy at least 12 months before study entry (5-FU adjuvant therapy can have been received at least 6 months prior to study therapy).

It is important that patients are assessed according to the study visit schedule (see Table 1) and that patients continue to be assessed for progression until objective progression occurs, regardless of whether they continue to receive treatment with study drug or start to receive other anti-cancer therapy.

Following the Screening visit, patients will attend study visits at Day 1, and then after 1, 2, 4, and 8 weeks and then every 4 weeks until he or she is withdrawn from all randomised therapy due to one of the other reasons specified in Section 3.3.5. Patients who have not objectively progressed should continue to visit for tumour assessment (RECIST) as per protocol (i.e. Weeks 8, 16, 24 and then every 12 weeks) until progression. A visit will be performed following discontinuation of treatment to record any new AEs occurring within 30 days of the last dose of randomised therapy.

All patients must be followed for survival post objective progression every 12 weeks.

The study will consist of 2 phases, as follows:

Phase II part of the study

The phase II part of the study will be conducted in approximately 100 centres randomising 225 eligible patients in a ratio of 1:1:1 to one of the following treatment groups (see Section 3.2.1):

- Treatment A: cediranib 30 mg/day + cediranib matched placebo 20 mg + bevacizumab placebo (75 patients)
- Treatment B: cediranib 20 mg/day + cediranib matched placebo 30 mg + bevacizumab placebo (75 patients)
- Treatment C: bevacizumab + cediranib matched placebo 20 mg and 30 mg (75 patients)

In addition to the investigational product, patients in treatment groups A, B and C, receive FOLFOX.

**Dose decision procedure:** After 225 patients have received 3 months of follow-up (75 patients per group), the phase II analysis will be performed. The efficacy of each dose level will be assessed using response rate in conjunction with PFS data from a randomised phase II study in comparison with bevacizumab in second line CRC patients (D8480C00041). Data from a third, placebo-controlled cediranib study in first line CRC (D8480C00051) may be used if the results from this study and the phase II study are equivocal. The study will continue if there is at least one dose that is tolerable, unless there is a reasonable probability of inferiority to bevacizumab.

Subsequent data collection; validation and analysis will take 2 to 3 months. Patient recruitment will continue during the analysis period.

Phase III part of the study

If the study continues to phase III, a further approximately 170 centres will be initiated and further eligible patients will be randomised to receive the selected dose of cediranib or bevacizumab in a ratio of 1:1 as follows:

- Treatment A or B: cediranib 30 or 20 mg/day + bevacizumab placebo
- Treatment C: bevacizumab + cediranib placebo

In addition to the investigational product, patients in both treatment groups will receive FOLFOX.

Upon expansion of the study, further patients will be randomised to the bevacizumab group and the selected cediranib group until the total number of patients randomised to these two groups during the phase II and III parts of the study is approximately 1400 patients.

Up to 200 patients may have been randomised to the discontinued dose of cediranib during the phase II part of the study. On completion of the phase II part of the study and following review by an Independent Data Monitoring Committee (IDMC), if there is a clear difference between the two doses then the patients from the discontinued dose will be unblinded and may be automatically switched or may be given the option to continue treatment on their current

dose of cediranib or to switch to the dose of cediranib selected for the phase III study. If there is no clear difference between the doses then patients will be allowed to continue but will remain blinded. These patients will be followed up for PFS and OS. Data from the cediranib dose discontinued at the end of phase II will not be included in the final analysis but may be analysed separately.

First line chemotherapy and blinded study medication will be administered until progression (or other criteria for discontinuation are met), unless there is toxicity. If the toxicity is attributable to one component alone, then this component should be withdrawn and the other components continued until progression. Eg, if oxaliplatin must be discontinued due to toxicity, 5-FU and leucovorin (or equivalent folinic acid preparation) must be continued until progression along with the blinded study medication.

Patients in all groups may continue with blinded randomised treatment after progression following discussion with AstraZeneca, if, in the opinion of the investigator, the patient is receiving benefit. There will be no cross over to cediranib treatment for patients in the FOLFOX plus bevacizumab treatment group. Patients with disease progression who continue with randomised treatment should also be offered an effective second line therapy, such as an irinotecan-containing chemotherapy unless this also includes a VEGF inhibitor. All subsequent cancer therapy must be recorded and the patient must be followed for survival..

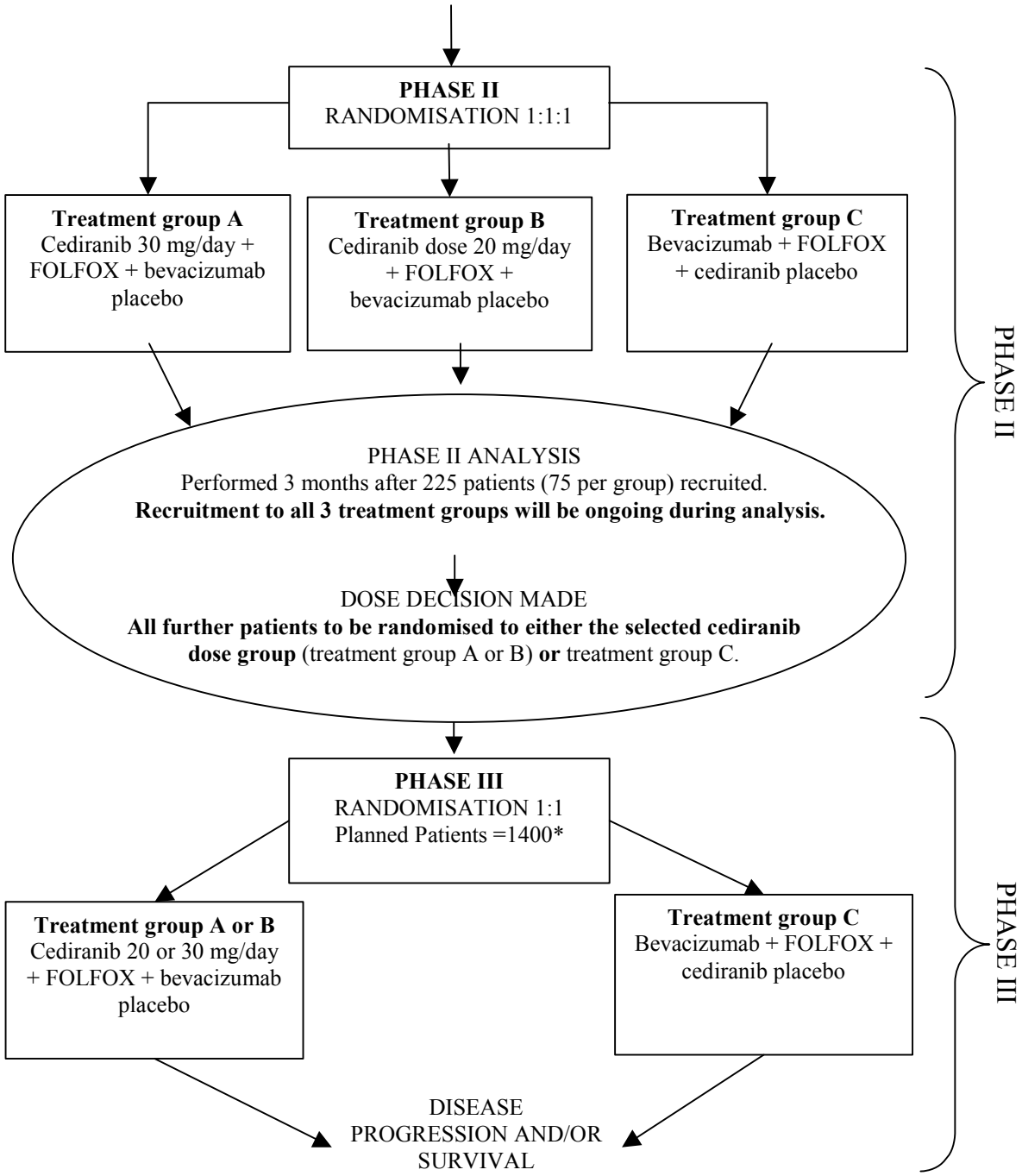
All additional or subsequent cancer therapy used post-randomisation should be recorded and the patient followed up for survival and progression (if the patient has not already progressed).

If toxicity is encountered, the dose of cediranib may be reduced or treatment with cediranib and bevacizumab stopped until resolution of symptoms according to the details provided in Section 3.4.4. At the discretion of the investigator, treatment may then be restarted.

There will be an external, Independent Data Monitoring Committee (IDMC) responsible for the review of safety data. The IDMC will provide advice on the study, including consideration of the interim results, ongoing safety data and external information. Full details will be prospectively defined in an IDMC charter document.

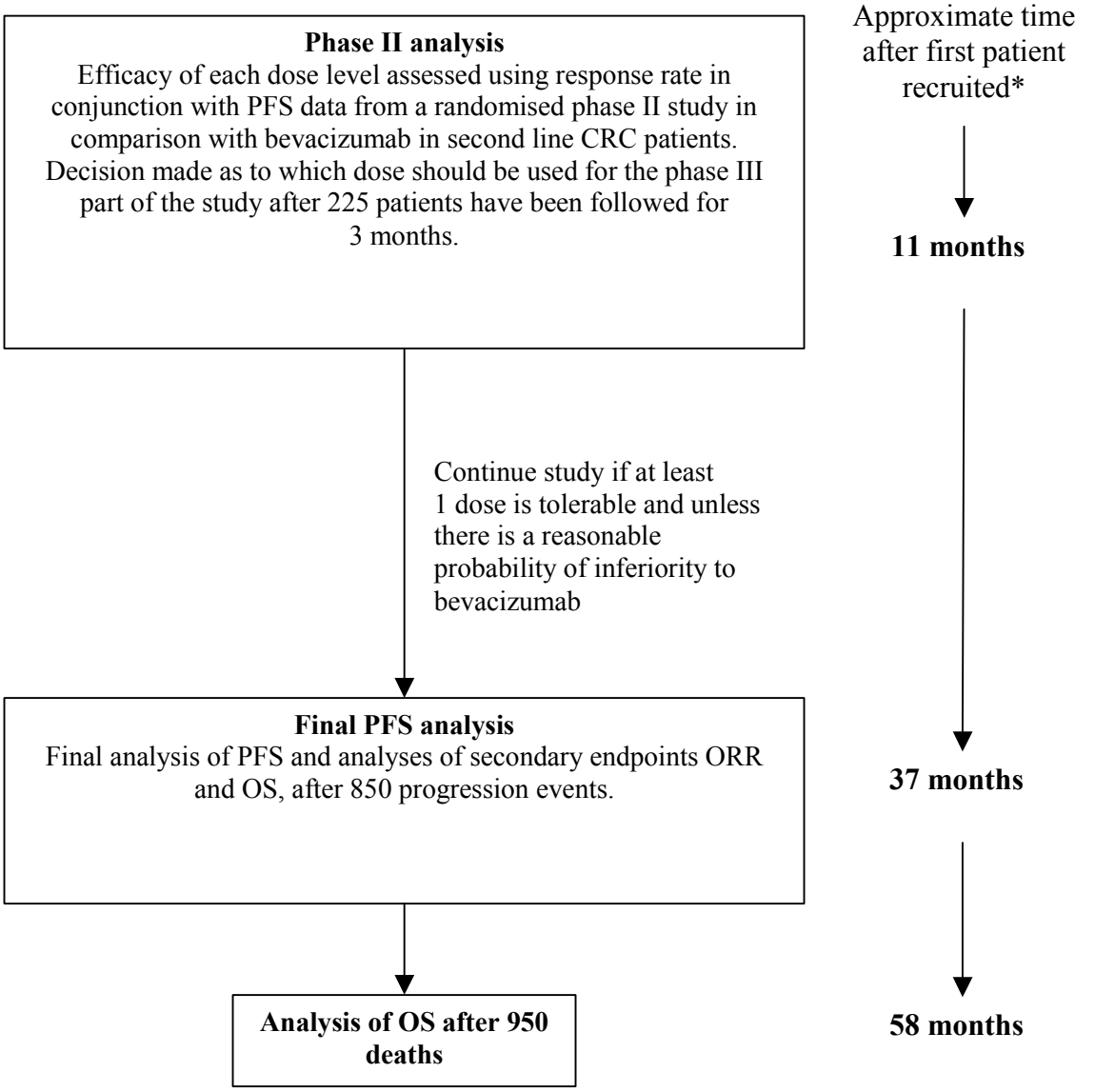
The final comparison of PFS between the cediranib plus FOLFOX and bevacizumab plus FOLFOX treatment groups will occur when 850 PFS have occurred; this analysis is expected to occur approximately 37 months after the first patient has entered the study. The OS update analysis will occur when 950 deaths have occurred, which is expected to be approximately 58 months after the first patient has entered the study. The study flow chart is presented in Figure 1. A flow chart of PFS and OS analyses is presented in Figure 2.

**Figure 1 Study flow chart**



*Note: A total number of approximately 1600 patients will be recruited, which includes both the phase II and phase III parts of the study.

**Figure 2 Flow chart of progression free survival and overall survival analyses**




*Timings are approximate and the analyses will be triggered by the number of events, not the time after the first patient is recruited.

Note: Investigators must assess PFS strictly in accordance with the visit schedule. Assessment for PFS must continue until the patient progresses objectively, regardless of whether the patient stops or reduces the dose of all

or part of their randomised therapy, and regardless of whether the patient starts taking other anti-cancer therapy prior to progression.

## Table 1 Study plan

| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9 etc[a]** | **Disc'n of Study Treatment** | **Survival Visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit description** | **Screen** | **Day 1** | **Week 1** | **Week 2** | **Week 4** | **Week 6** | **Week 8** | **Week 12** | **Week 16 etc** | | |
| **Visit Window** (number of weeks [w] + number of days [d]) | **Within 2 w of Day 1** | | **1 w ±3 d after Day 1** | **2 w ±3 d after Day 1** | **4 w ±3 d after Day 1** | **6 w ±3 d after Day 1** | **8 w ±3 d after Day 1** | **12 w ±3 d after Day 1** | **4 w ±3 d after last visit** | **99** | |
| Informed consent | X | | | | | | | | | | |
| Demographic details | X | | | | | | | | | | |
| Medical/surgical history (including histological subtype of tumour and duration of response to first treatment) | X | | | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | | | |
| Randomisation | X | | | | | | | | | | |
| Obtain archived tumour specimen for biomarker assays (including epidermal growth factor receptor [EGFR] status) and genetic analysis (if separate consent given) | X | | | | | | | | | | |
| Pharmacogenetic sample (if separate consent given) | | X | | | | | | | | | |
| Physical examination including BP (monitored every 2 w prior to commencing iv infusions) | X | X | X | X | X | X | X | X | X | X | |
| Vital signs | X | X | X | X | X | X | X | X | X | X | |
| ECG (should be performed in triplicate. ECGs should also be performed when clinically indicated). | X | X | | X | | | | | | | |
| Haematology and clinical chemistry[b] (every 2 w) | X | X | X | X | X | X | X | X | X | X | |
| Urinalysis[b] | X | X | X | X | X | | X | X | X | X | |
| Creatinine clearance (Cockcroft-Gault equation) | X | X | X | X | X | | X | X | X | X | |

## Table 1 Study plan

| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9 etc[a]** | **Disc'n of Study Treatment** | **Survival Visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit description** | **Screen** | **Day 1** | **Week 1** | **Week 2** | **Week 4** | **Week 6** | **Week 8** | **Week 12** | **Week 16 etc** | | |
| **Visit Window** (number of weeks [w] + number of days [d]) | **Within 2 w of Day 1** | | **1 w ±3 d after Day 1** | **2 w ±3 d after Day 1** | **4 w ±3 d after Day 1** | **6 w ±3 d after Day 1** | **8 w ±3 d after Day 1** | **12 w ±3 d after Day 1** | **4 w ±3 d after last visit** | **99** | |
| Pregnancy test (as clinically indicated; within 3 d of Day 1) | X | | | | | | | | | | |
| Blood sample for biomarkers | X | | | | X | | X | X | X[f] | X[e] | |
| WHO Performance Status | X | X | X | X | X | | X | X | X | X | |
| FACT-C (to be completed before RECIST scans)[c] | X | | | | X | | X | | X[c] | X | |
| EuroQol 5 Dimension Health Status Measure ([EQ-5D]; to be completed before RECIST scans)[c] | X | | | | X | | X | | X[c] | X | |
| Radiological and clinical tumour assessment (RECIST)[d] | X | | | | | | X | | X[d] | X | |
| Cediranib/placebo dispensing | | X | | | X | | X | X | X | | |
| Bevacizumab/placebo dosing (every 2 w for iv infusions) | | X | | X | X | X | X | X | X | | |
| FOLFOX dosing (every 2 w for iv infusions) | | X | | X | X | X | X | X | X | | |
| Tolerability/AE reporting | X | X | X | X | X | | X | X | X | X | |
| Concurrent medication | X | X | X | X | X | | X | X | X | X | |
| All subsequent therapy | | | | | | | | | | X | |
| Survival (patients must be followed for survival unless they withdraw consent) | | | | | | | | | | X | X[g] |

Notes: Assessments are to be performed prior to dosing, unless otherwise stated. BP monitoring, routine haematology and clinical chemistry, bevacizumab/placebo dosing and FOLFOX dosing will be performed every 2 weeks throughout the study, however, not every 2-weekly visit is shown in the above Study Plan.

[a] Patient visits will occur every 4 weeks following Week 8 until discontinuation of randomised therapy (30 day follow-up for AEs required at next visit). Following objective progression, patients will be followed for survival every 12 weeks (visit 101, etc) if on randomised therapy assessments as per Week 20

etc, except FACT-C and EuroQol –5 not required. If randomised treatment discontinued, then any subsequent cancer therapy should be recorded along with the survival status.

[b] Haematology and clinical chemistry are not required on Day 1 if screening tests were done within the previous 3 days. Haematology and clinical chemistry are every 2 weeks except, TSH, T3 and T4, which should be assessed every 8 weeks for the first 24 weeks and then every 12 weeks (if abnormalities are noted, these tests should be performed monthly). CEA and LDH should be assessed every 8 weeks for the first 24 weeks and then every 12 weeks, at the same visit as RECIST scans. A further sample for TSH, CEA and LDH is required at the first follow-up visit after withdrawal from all randomised therapy. At Screening, if a patient has two consecutive urine protein measurements of greater than one plus (+) taken no less than 1 week apart, then a 24 hour urine collection should be performed to ensure urinary protein is <1.5 g for entry to the study. During treatment, if a patient has two consecutive two plus (++) urine proteinuria dipstick measurements, or one three plus (+++) or greater measurement, a 24 hour urine sample should be collected and the guidance in Section 3.4.4.3 (Management of Proteinuria) should be followed.

[c] FACT-C and EQ-5D questionnaires will be administered at Screening, Weeks 4, 8,16 and 24 and then every 12 weeks until objective progression whether the patient is receiving randomised therapy or not.

[d] RECIST to be assessed at Screening, Weeks 8, 16, 24 and then every 12 weeks. Patients must be followed until progression regardless of whether study treatment is discontinued or delayed. If scans are outside of a +/-2-week window and the patient has not progressed, every attempt should be made to perform the subsequent scans at the scheduled time points. RECIST measurements must be made using computed tomography (CT) or MRI scans covering the chest, abdomen and pelvis.

[e] A further sample for biomarkers is required at the first follow-up visit after withdrawal from all randomised therapy.

[f] Only required at Week 16, then discontinuation visit

[g] When disease progression has been documented or the patient has withdrawn from study treatment, the long-term follow-up information for survival should be collected at least every 12 weeks by telephone contact with the patient, patient's family, or by contact with the patient's current physician. If a patient stops study treatment prior to progression, they must continue to have RECIST assessments according to the protocol schedule until progression and then the above procedure continued for survival.

## 3.2 Rationale and risk/benefit assessment

### 3.2.1 Rationale for study design, doses and control groups

This is a phase II/III study to compare the efficacy of cediranib in combination with FOLFOX to the efficacy of FOLFOX in combination with bevacizumab. The study design meets the criteria set by the International Conference on Harmonisation (ICH ) for a therapeutic confirmatory study design (ie, large, randomised, double-blind with an appropriate active comparator).

The design of this study takes into account the patient population, the emerging toxicity profile of cediranib, the pharmacology of the selected anticancer drugs and the potential for drug-drug interactions that may impart treatment-related toxicities.

It is recognised there are no efficacy data of cediranib in combination with FOLFOX, therefore, a phase II step has been incorporated into the design. The objective of this phase is to assess the tolerability of each dose of cediranib in combination with FOLFOX and to obtain an initial assessment of the relative efficacy of cediranib and bevacizumab when given in combination with FOLFOX. The study will continue unless there is a reasonable probability that cediranib is inferior to bevacizumab. In the event that both doses are declared non-inferior to bevacizumab, and there is no clear advantage of the 20 mg cediranib dose, the 30 mg dose will be selected to continue.. These criteria consider tolerability and response rate data from this study in conjunction with tolerability and PFS data from a second line CRC, phase II study that contains the same 3 treatment groups. The incorporation of data from the second line CRC study enables the relative efficacy of the agents to also be assessed using a PFS endpoint instead of solely relying on response rate data. If the phase II decision were to be based solely on PFS data from this study, many more patients would be exposed before being able to assess the likelihood that the study might achieve its primary objective. If the results of these two analyses are equivocal, data from a third, placebo-controlled, cediranib study in first line CRC may be used in the decision to continue to the phase III part of the study

The FOLFOX regimen used in study D8480C00013 will be a modified FOLFOX6 regimen as follows:

- Oxaliplatin 85 mg/m$^2$ with leucovorin 400 mg/m$^2$ (or equivalent folinic acid preparation) administered intravenously over 2 hours on Day 1.
- 5-FU 400 mg/m$^2$ bolus immediately after the completion of the oxaliplatin infusion on Day 1, followed immediately by 5-FU 2400 mg/m$^2$ administered by a continuous infusion over 46 hours.

The regimen will be repeated every 2 weeks.

A number of different FOLFOX regimens have been evaluated in recent years, and many studies have investigated FOLFOX4, which contains oxaliplatin 85 mg/m$^2$, and infusional

5-FU combined with 2 bolus 5-FU doses (Goldberg RM 2004; De Gramont A et al 2000). In an attempt to reduce the incidence of haematologic toxicity associated with bolus 5-FU, the FOLFOX6 regimen includes only one 5-FU bolus. The modified FOLFOX6 regimen has been the most recent standard for clinical studies in both the first line metastatic and adjuvant settings, as shown by the use of this regimen in large, phase III cooperative group studies conducted in the United States (SWOG 0303, NSABP C-08, and CALGB 80203). This regimen includes an oxaliplatin dose of 85 mg/m$^2$, compared to a 100 mg/m$^2$ dose in FOLFOX6, in order to reduce the incidence of chronic neurotoxicity associated with higher doses of oxaliplatin.

The combination of cediranib plus FOLFOX is expected to produce greater benefit than FOLFOX plus bevacizumab due to improved delivery of the chemotherapy, or other synergistic effects, to the tumour.

It is intended that the daily doses of cediranib for this study will be 30 mg or 20 mg/day.

Cediranib is biologically active at doses of 20 mg and above in terms of reductions in tumour blood flow and permeability, blood pressure increases, and reductions in sVEGFR-2 and tumour size. Data from Study D8480C00001 also suggest that improvements in efficacy may be achieved with higher doses of cediranib.

Data from studies D8480C00004, D8480C00005, D8480C00008 and D8480C00009 indicate that the AE profile of cediranib when dosed in combination with gefitinib or standard chemotherapy agents is the same as that observed in monotherapy studies, although the identified MTD of cediranib has differed between protocols.

The combination of cediranib with FOLFOX has been studied in heavily pretreated patients with advanced CRC (study D8480C00008). In this situation the AE profile is also consistent with the known profile for FOLFOX (diarrhoea 67%, 11% Grade 3/4; fatigue 68%, 7% Grade 3/4). After reviewing the emerging safety data, it was determined that 30 mg was a safe dose to begin the expansion portion of the study, with a plan to review the dose after an initial 12 patients had been enrolled. Study D8480C00008 is ongoing.

The NCIC has carried out a further study (study D8480C00022) to evaluate the safety and tolerability of the combination of cediranib and FOLFOX as first or second line therapy in patients with metastatic CRC, the patient population to be included in this study. Data from this study have indicated that patients receiving the 45 mg dose have a high frequency of dose interruptions and discontinuations during the second and third treatment cycles, and the 30 mg dose is, therefore, the recommended MTD of cediranib in combination with FOLFOX.

The dose of bevacizumab used in this study will be 5 mg/kg/day, which is the dose that has been investigated in all previous studies of bevacizumab in the first line treatment of CRC (Hurwitz H et al 2004, Kabbinavar F et al 2003, Saltz LB et al 2007). In the only study to compare the 5 mg/kg/day dose with the 10 mg/kg/day dose in CRC, no difference was observed between the doses in terms of efficacy (Kabbinavar F et al 2003).

In this study, first line chemotherapy and blinded study medication should be administered until progression (or other criteria for discontinuation are met), unless there is toxicity. If the toxicity is attributable to one component alone, then this component should be withdrawn and the other components continued until progression. Eg, if oxaliplatin must be discontinued due to toxicity, 5-FU and folinic acid must be continued until progression along with the blinded study medication. The rationale for continuing the 5-FU chemotherapy when oxaliplatin has been discontinued is that the recently reported OPTIMOX 2 study showed a worse outcome for patients receiving a fixed number of cycles of FOLFOX followed by a treatment holiday compared to patients who continued on maintenance 5-FU/folinic acid (Maindrault-Goebel F 2006).

The rationale for continuing the chemotherapy and blinded study medication to progression is that in the XELOX-1/NO16966 study, the magnitude of the improvement in PFS when bevacizumab was added to FOLFOX4 (HR 0.83; p=0.0023) was less than had been previously observed when bevacizumab was added to IFL in the AVF2107 study (HR 0.58; p<0.001; Hurwitz H et al 2004). In study XELOX-1/NO16966, there was a greater incidence of early discontinuation of all treatment in the bevacizumab plus chemotherapy group than in study AVF2107. Only 46% of the patients in this study received bevacizumab treatment within 4 weeks of PD or death compared with 77% of patients in study AVF2107. In study XELOX-1/NO16966, it appeared that when oxaliplatin was discontinued (median 6 months) the investigators tended to also discontinue 5-FU and bevacizumab. A retrospective analysis showed an improved outcome in patients who continued bevacizumab to within 28 days of progression (HR 0.63; p=<0.001; Saltz LB et al 2007), which was more in keeping with the AVF2107 data. These data suggest that the poorer results for bevacizumab in study XELOX-1/NO16966 compared to study AVF2107 may have been largely attributable to differences between these two studies in the standard practices of administering chemotherapy, and that following discontinuation of oxaliplatin it may be beneficial to continue with VEGF inhibitors together with 5-FU/folinic acid until disease progression.

This study (D8480C00013) has been designed to include frequent monitoring of BP and renal function (blood urea nitrogen [BUN], creatinine, urinary protein) because hypertension is an expected AE with agents that inhibit VEGF signalling.

Liver function abnormalities have been observed in a phase I study in patients with advanced cancer with liver metastases, therefore, bilirubin and transaminases will be monitored during the study. Increased TSH levels have also been reported in patients receiving 60 mg doses of cediranib, therefore, thyroid hormones ($T_3$, $T_4$ and TSH) will be monitored.

PFS has been chosen as the primary efficacy variable because a delay in progression is considered to represent a clinical benefit. In addition, assessment of PFS provides a purer assessment of relative efficacy as it is free from the confounding effects of active second line therapy.

Patients with progressive disease will be given the option to remain on the randomised blinded study medication while receiving second line irinotecan-containing chemotherapy. The

rationale for this option is that patients are considered more likely to have developed resistance to oxaliplatin, due to clonal evolution within the tumour, than to the VEGF inhibitors, which primarily target the host vasculature. Recently reported data of 1953 patients included in the BRiTE registry database of patients who had received bevacizumab in combination with first line chemotherapy support this hypothesis: the median OS for all patients was 25.1 months, and those who continued bevacizumab with their second line treatment had an improved median OS (31.8 months) compared to those who received chemotherapy alone (19.9 months) or no treatment post progression (12.6 months) (Grothey A et al 2007).

### 3.2.2 Rationale for pharmacogenetics

Pharmacogenetic testing will be performed of patients who give consent in order to investigate the relationship between blood and tumour biomarkers and clinical efficacy and tolerability. It is proposed that initial analysis should focus on variants of genes in the pathway targeted by cediranib but the scope of the informed consent will allow the analysis of additional genes on a study specific basis. In addition to *kdr*/*flk-1*, the target of cediranib, genes in this pathway encode proteins that are either biomarkers themselves (VEGF-A) or regulate the expression of biomarkers (HIF1α microvessel density). Knowledge of variation in these genes will assist in the interpretation of biomarker data. Genes regulated by this pathway also include candidates for genetic factors predisposing to the development of hypertension in response to anti-angiogenic therapy.

Hypoxia inducible factor (HIF1α/ARNT) is a key regulator of cellular response to hypoxia and is thought to play an important role in tumour progression and metastasis through activation of genes that are involved in the regulation of angiogenesis, energy metabolism and other functions (reviewed by Semenza GL 2002). Tanimoto K et al 2003 have demonstrated a correlation between two polymorphic variants of HIFα and microvessel density in head and neck cancer.

Although no decrease in circulating VEGF was detected in a study with bevacizumab in rectal cancer (Willett CG et al 2004), VEGF-A levels may be modulated by cediranib. Polymorphisms in the VEGF-A gene have been shown to affect expression levels both *in vitro* and *in vivo* (Watson CJ et al 2000; Renner W et al 2000; Stevens A et al 2003).

Two common (>10% allele frequency) variants of the *kdr*/*flk-1* gene have been discovered. Both of the polymorphic amino acid residues are located in the external domain of the receptor. Single nucleotide polymorphisms have also been described in the promoter region of the *kdr*/*flk-1* gene and may correlate with expression levels of the receptor.

The development of hypertension has been reported in 23% of patients treated with bevacizumab plus IFL, 34% of patients treated with bevacizumab plus 5-FU and leucovorin compared to 14% of patients treated with IFL plus placebo. Grade 3-4 hypertension was reported in 12% of patients treated with bevacizumab plus IFL and 2% of patients treated with IFL plus placebo. These results indicate that some patients on anti-angiogenic therapy may be susceptible to the development of hypertension. If hypertension is observed in patients treated

with cediranib, analysis of candidate genes, such as endothelial nitric oxide synthase gene (*eNOS*), could be undertaken. Variants of *eNOS* have been associated with essential hypertension and renal disease (reviewed by Wattanapitayakul SK et al 2001) and may correlate with the development of hypertension in patients treated with anti-angiogenic therapy. Nitric oxide release is mediated via the activation of *kdr/flk-1* through downstream signalling mechanisms and components of these pathways could provide additional candidates (Drevs J et al 2007, Duval M et al 2003). Somatic mutations in the *kdr/flk-1* gene have been described in colorectal tumours (Bardelli A et al 2003). There are no data on the functional consequences of these mutations and there are no reports of mutations in the *kdr/flk-1* gene in other tumour types.

Retrospective analysis of p53 mutation status may assist in the classification of tumours likely to respond to anti-angiogenic therapy. The frequency of p53 mutations varies with tumour type and mutations leading to inactivation of the wild type p53 tumour suppressor gene can render cells less susceptible to apoptosis induced by hypoxic stress (Graeber TG et al 1996). Resistance to hypoxia may reduce the efficacy of anti-angiogenic therapy. Yu JL et al 2002 have shown that mice bearing mutant p53 tumours are less responsive to combination therapy with an anti-kdr/flk-1 antibody and vinblastine than mice bearing wild type p53 tumours. There are currently no data available regarding the p53 status of tumours responding to bevacizumab.

AstraZeneca intends to apply retrospective pharmacogenetic analyses across the whole cediranib clinical development programme. Genes that may be investigated include the VEGF and VEGFR-2 genes, other genes in pathways relevant to the activity of cediranib, and drugs taken in combination with cediranib. It is believed that genetic variations in such genes may influence the clinical therapeutic response to cediranib or drugs taken in combination with cediranib. It is likely that additional information on other genes important for the response to cediranib will become available in the future. It is, therefore, important to be able to store samples in order to retain the possibility of investigating additional genes in the context of cediranib and other drugs taken in combination with cediranib in the future.

### 3.2.3 Rationale for collection of blood samples and archival tumour samples for biomarker analysis

There are currently no known markers that are predictive of response or resistance to VEGF signalling inhibitors, including cediranib. By collecting and storing serial samples of plasma and serum for the first months of treatment with cediranib, it will be possible to explore the relationship between changes in biomarkers and tumour response as measured by changes in tumour size and RECIST responses, and the mechanisms underlying the biological response and resistance to VEGF signalling inhibitors. In addition, analysis of biomarkers isolated from archival tumour material may add to our knowledge of factors affecting the response to inhibition of VEGF signalling. It is likely that additional information and assays for biomarkers that are important for the response to cediranib will become available in the future. It is, therefore, important to be able to store samples in order to retain the possibility of investigating biomarker changes in the context of cediranib treatment in the future.

### 3.2.4 Risk/benefit and ethical assessment

Please refer to the latest version of the Investigator's Brochure for an overall risk/benefit assessment of cediranib.

Cediranib is a potent inhibitor of receptor tyrosine kinases, which influence the effects of VEGF, a key angiogenic factor. VEGF is implicated in tumour blood vessel formation and in disease progression in a range of solid tumour malignancies. Upon chronic oral dosing, cediranib is expected to inhibit VEGF-driven angiogenesis and, as a consequence, constrain solid tumour growth. Since angiogenesis is necessary for the growth and metastasis of all solid tumours and VEGF is believed to have a pivotal role in this process, cediranib treatment may have broad-spectrum clinical utility.

Regarding risk factors, hypertensive changes, thought to be mechanistically related, (ie, attributable to the inhibition of VEGF-signalling) have been observed in both pre-clinical and clinical studies. Secondly, vascular (myocarditis, choroid plexus, vasculitis) and renal (glomerulosclerosis and tubular degeneration) pathology has been seen in rat, dog and primate dosed with cediranib. AstraZeneca believes that these significant pathological findings are secondary to the hypertensive changes induced by potent VEGF signal inhibition, although the management of hypertension did not fully prevent choroid plexus effects in animal studies. Therefore, AstraZeneca believes that rigorous monitoring of individual patients' BP, combined with proactive medical management of any emergent hypertension should ameliorate these effects.

Currently available clinical data suggest there is increased tumour control with increasing doses of cediranib. In the phase I study D8480C0001, cediranib was biologically active at doses of 20 mg and above in terms of reductions in tumour blood flow and permeability, BP increases, and reductions in sVEGFR-2 and tumour size.

As of 31 July 2007, the AstraZeneca global safety database contained a total of 86 unvalidated serious adverse event (SAE) reports of hypertension from 83 patients across all studies. For 78 of the 83 patients, the investigator assessed the event(s) as possibly related to cediranib treatment. In addition to these patients, 6 patients reported 8 SAEs of hypertensive crisis that were all considered by the investigator to be related to cediranib treatment. Analysis of blood pressure data from Study D8480C00038 suggests that the development of hypertension is generally an early event, occurring in the first 4-6 weeks of treatment, although it can occur late in some patients, and that patients on prior anti-hypertensive therapy may be particularly at risk of developing moderate or severe hypertension.

A number of events of minor bleeding and haemorrhage have occurred in phase 1 studies. Two episodes of fatal haemorrhage have been observed, neither of which were unequivocally caused by cediranib. Fatigue and diarrhoea are commonly occurring AEs in cediranib studies. Hoarseness (dysphonia) has been reported as common and dose-related. Muscle weakness, dry mouth and oral mucosal inflammation have been observed in cediranib studies. In addition, there is some evidence suggesting a dose-related trend of increases from baseline in TSH levels.

RPLS is a rare syndrome effecting vascular endothelial cells in the brain that may lead to capillary leak and oedema. The syndrome has been associated with a number of conditions including renal failure, hypertension, fluid retention and the use of cytotoxic or immunosuppressive drugs. It has also been reported in association with the use of VEGF inhibitors including bevacizumab and sunitinib, with an incidence of <0.1%. At the time of writing this protocol, one MRI-confirmed case of RPLS has been reported in a patient receiving cediranib. The syndrome can present in a variety of non-specific ways, including headache, seizures, lethargy, confusion, blindness and other visual and neurological disturbances. Hypertension may be present, but is not necessary for the diagnosis of RPLS. Magnetic Resonance Imaging (MRI) is the most sensitive imaging modality to detect RPLS and is recommended in suspected cases to confirm the diagnosis. RPLS is reversible upon removal of any possible precipitating factors and control of hypertension.

## 3.3 Selection of study population

### 3.3.1 Study selection record

Investigator(s) must keep a record of patients who were considered for enrolment but were never enrolled (eg, patient screening log). This information is necessary to establish that the patient population was selected without bias.

### 3.3.2 Inclusion criteria

For inclusion in the study, patients must fulfil all of the following criteria:

1. Provision of written informed consent.

2. Males or females aged 18 years and older.

3. Histological or cytological confirmation of carcinoma of the colon or rectum.

4. Stage IV (metastatic) disease with one or more measurable lesions at least 10 mm in the longest diameter by spiral CT scan or 20 mm with conventional techniques (RECIST criteria). Patients who have previously been disease free following a neoadjuvant chemotherapy regimen and resection of all primary tumours and metastatic disease are eligible, provided they have measurable disease, as above.

5. Patients must have received no prior systemic therapy for metastatic disease. Any adjuvant/neoadjuvant oxaliplatin therapy must have been received >12 months prior to study entry and adjuvant/neoadjuvant 5-FU must have been received >6 months prior to study entry.

6. World Health Organisation (WHO) Performance score <2.

7. Life expectancy of ≥12 weeks.

#### 3.3.2.1 Genetic research

For inclusion in the genetic research component of the study, patients must fulfil the following criterion:

1. Provision of informed consent for genetic research.

If a patient declines to participate in the genetic research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they consent.

### 3.3.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Termination of adjuvant oxaliplatin therapy within 12 months of study entry or termination of adjuvant 5-FU therapy within 6 months of study entry.

2. Any unresolved toxicity >CTC Grade 1 from previous anticancer therapy (including radiotherapy), except haematological toxicity (see exclusion criterion 5) and alopecia.

3. Prior therapy with monoclonal antibodies or small molecule inhibitors against VEGF or VEGF receptors, including bevacizumab and cediranib.

4. Untreated brain or meningeal metastases. Patients with radiological evidence of stable brain metastases providing that they are asymptomatic and either do not require corticosteroids or have been treated with corticosteroids, with clinical and radiological evidence of stabilisation at least 10 days after discontinuation of steroids.

5. Inadequate bone marrow reserve as demonstrated by an absolute neutrophil count $\leq 1.5 \times 10^9$/L or platelet count $\leq 100 \times 10^9$/L or requiring regular blood transfusions to maintain haemoglobin >9 g/dL.

6. Serum bilirubin ≥1.5 x upper limit of reference range (ULRR), except in the case of known Gilbert's Syndrome.

7. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 x ULRR. If liver metastases are present, ALT or AST >5 x ULRR.

8. Serum creatinine >1.5 x ULRR or a creatinine clearance of ≤50 mL/min calculated by Cockroft-Gault formula (see Section 4.7.2.2).

9. Greater than +1 proteinuria on 2 consecutive dipsticks taken no less than 1 week apart unless urinary protein <1.5 g in a 24-hour urine collection.

10. Patients with a history of poorly controlled hypertension or with resting BP >150/100 mmHg in the presence or absence of a stable regimen of anti-hypertensive therapy. Measurements will be made after the patient has been resting supine for a minimum of 5 minutes. Two or more readings should be taken at 2 minute intervals and averaged. If the first 2 diastolic readings differ by more than 5 mmHg, then an additional reading should be obtained, and averaged.

11. Any evidence of severe or uncontrolled systemic diseases (eg, unstable or uncompensated respiratory, cardiac including arrhythmias, hepatic or renal disease).

12. Mean QTc with Bazett's correction >470 msec in screening ECG or history of familial long QT syndrome (as per ICH guideline E14).

13. Recent (<28 days) major abdominal or thoracic surgery prior to entry into the study, or a procedure considered to have a significant risk of internal bleeding. Presence of a surgical wound that is not fully healed.

14. Significant haemorrhage (>30 mL/bleeding episode in previous 3 months), or haemoptysis (>5 mL fresh blood in previous 4 weeks).

15. Pregnant or breast-feeding women or women of childbearing potential with a positive pregnancy test prior to receiving study medication.

16. Known severe hypersensitivity to cediranib, bevacizumab, oxaliplatin, 5-FU, or leucovorin, or any of the excipients of these products.

17. Other concomitant anti-cancer therapy (including luteinising hormone releasing hormone agonists) except steroids.

18. History of other malignancies (except for adequately treated basal or squamous cell carcinoma or carcinoma *in situ*) within 5 years, unless the patient has been disease free for 2 years and there is a tissue diagnosis of the primary cancer of interest from a target lesion.

19. History of central nervous disorders or uncontrolled seizures.

20. History of significant gastrointestinal impairment, as judged by the investigator that would significantly affect the absorption of cediranib.

21. Peripheral neuropathy ≥CTC Grade 2.

22. Known dihydropyrimidine dehydrogenase deficiency.

23. Hypersensitivity to Chinese hamster ovary cell products or other recombinant or humanised antibodies.

24. Previous enrolment or randomisation in the present study.

25. Treatment with an investigational (non-registered) drug during the last 30 days.

26. Known risk of the patient transmitting HIV or hepatitis B or C via infected blood.

### 3.3.4 Restrictions

The following restrictions are associated with participation in the study:

1. Caution in the concomitant use of any medication that may markedly affect renal function. Such medications may, however, be used with caution if deemed essential for treatment of a particular infection or continued if patients are using them prior to commencing the study with no effect on renal function demonstrable on blood or urine testing.

2. Caution in the concomitant use of any medication that may markedly affect hepatic P450 drug metabolising activity by way of enzyme induction (eg, phenytoin) or inhibition (eg, ketoconazole, ritonavir, erythromycin) within 2 weeks of the first dose of randomised therapy, and throughout the study period.

3. Patients who require oral anticoagulants (coumadin, warfarin) are eligible, provided there is increased vigilance with respect to monitoring international normalised ratio (INR). If medically appropriate and treatment available, consider switching to low molecular weight heparin.

4. Female patients must be post-menopausal, surgically sterile, sexually abstinent or use 2 reliable forms of contraception from the first day of dosing until 3 months after the last dose of randomised treatment. Postmenopausal females are defined as:

- Natural menopause with menses >1 year ago.
- Radiation-induced oophorectomy with last menses >1 year ago.
- Chemotherapy-induced menopause with 1 year interval since last menses.
- Serum follicle stimulating hormone, luteinising hormone, and plasma oestradiol levels in the postmenopausal range for the institution.
- Bilateral oophorectomy or hysterectomy.

5. Male patients must be surgically sterile or use a barrier method of contraception from the first day of dosing until 3 months after the last dose of randomised treatment.

6. For elective surgery during the study it is recommended that the dosing of tablets (cediranib or placebo) be stopped for 2 consecutive weeks prior to the surgical

procedure. The interval between termination of the bevacizumab infusion and subsequent elective surgery should take into consideration the calculated half-life of bevacizumab (approximately 20 days). Tablets and iv infusion can be restarted when the surgical wound has healed. If emergency surgery is performed, precautions should be taken to minimise the potential risk of bleeding and thrombosis associated with this class of agents, tablets and infusion should be stopped and close monitoring for bleeding, wound healing and thromboembolic complications should be initiated.

7. Patients who are blood donors should not donate blood during the study and for 3 months following their last dose of study treatment.

8. Caution in the concomitant or prophylactic use of calcium or magnesium due to the possibility of reduced response rate to FOLFOX treatment.

### 3.3.5 Discontinuation of patients from treatment or assessment

Patients may be discontinued from study treatment and assessments at any time.

#### 3.3.5.1 Criteria for discontinuation from study treatment

Specific reasons for discontinuing a patient from study treatment but continuing ongoing assessments are:

- Safety reasons as judged by the investigator and/or AstraZeneca.
- Incorrect enrolment (ie, the patient does not meet the required inclusion/exclusion criteria) of the patient if there are safety reasons as judged by the investigator and/or AstraZeneca.

Bevacizumab (or placebo) and cediranib (or placebo) should be permanently discontinued in the patients with the following conditions:

- Gastrointestinal perforation or wound dehiscence requiring medical intervention
- Serious haemorrhage, ie, requiring medical intervention
- Severe hypertension (see hypertension management protocol, Section 3.4.4.2)
- Nephrotic syndrome
- Severe arterial thromboembolic event

Bevacizumab (or placebo) infusion should be interrupted in patients with severe infusion reactions (see Section 3.4.4.1).

#### 3.3.5.2 Criteria for discontinuation from study treatment and assessments

Reasons for discontinuing from study treatment and assessments are:

- Voluntary discontinuation by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment.
- Patient lost to follow-up.

Specific reasons for discontinuing a patient from the genetic research are:

- Withdrawal of consent for genetics research. A patient may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study described in this protocol. Voluntary discontinuation by the patient will not prejudice further treatment.

#### 3.3.5.3 Procedures for discontinuation

All patients should attend a study discontinuation visit on discontinuation of randomised treatment. Patients will be followed up for progression regardless of whether study treatment is discontinued. All patients will be followed up for survival unless they withdraw consent.

Patients who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any AEs. If possible, they should be seen and assessed by an investigator(s). AEs should be followed up; questionnaires completed (eg, for patient reported outcomes) and investigational products should be returned by the patient.

**Discontinuing the blinded randomised study treatment at progression: considerations for second line treatment**

If a patient discontinues chemotherapy and the blinded randomised study treatment at disease progression, an effective second line treatment (such as irinotecan-based chemotherapy) should be offered. The treatment blind should not be broken unless it is essential for subsequent patient management.

If another VEGF inhibitor is available for inclusion in the proposed second line therapy, a subsequent VEGF inhibitor should not be given within 2 weeks of discontinuing the blinded tablets or within 6 weeks of discontinuing the blinded infusion, whichever is the longer (because of the long half-life of bevacizumab).

**Follow up post disease progression**

**Unblinding**

Following disease progression, all patients should be followed for survival. Unblinding should not occur unless essential for subsequent patient management. Eg, unblinding to determine suitability of patients for entry into second line clinical studies following Horizon III would only be necessary if prior treatment with named agents were not permitted.

If second line clinical studies specifically exclude patients with prior treatment with VEGF inhibitors, then all patients participating in Horizon III would be ineligible for such a study.

To avoid unnecessary un-blinding, the blind should only be broken AFTER:

- Objective progression has been observed and documented.
- The randomised study treatment has been permanently discontinued for the required length of time to allow introduction of a subsequent VEGF inhibitor.
- Confirmation that all other entry criteria for the subsequent clinical study have been met.

When disease progression has been documented or the patient has withdrawn from study treatment, the long-term follow-up information for survival should be collected at least every 12 weeks by telephone contact with the patient, patient's family, or by contact with the patient's current physician. If a patient stops study treatment prior to progression, they must continue to have RECIST assessments according to the protocol schedule until progression and then the above procedure continued for survival.

#### 3.3.5.4 Procedures for discontinuation from genetic aspects of the study

Patients who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their consent for this genetic research. It must be established whether the patient:

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic research in the future.
- Withdraws consent for the sample to be kept for genetic research in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The principal investigator is responsible for providing written notification to AstraZeneca of any patient who has withdrawn consent for the use of the sample taken for genetic research. AstraZeneca will provide written confirmation to the investigator of the actions taken with the sample, which must be filed in the investigator study file.

#### 3.3.5.5 Procedures for handling incorrectly enrolled patients

Patients not meeting the eligibility criteria for this study should not be enrolled into the study under any circumstances. There can be no exceptions to this rule. If it is identified after randomisation that a patient did not meet the criteria for the study, and so has been randomised in error, the Investigator must contact the AstraZeneca physician to discuss

whether the patient must be discontinued. The final decision must take into account ethical and safety factors and be clearly documented. Irrespective of whether or not a patient continues on randomised therapy, all patients who are randomised in an AstraZeneca clinical study should continue to be followed under the protocol for key clinical outcomes in line with the well-accepted principles of intention-to-treat (ITT).

### 3.3.6 Study discontinuation

The study may be prematurely discontinued by AstraZeneca in case of the following events:

- Medical or ethical reasons affecting the continued performance of the study.
- Difficulties in patient recruitment.
- Cancellation of drug development or decision not to proceed to the phase III part of the study.

## 3.4 Treatments

### 3.4.1 Identity of investigational product and comparators

#### 3.4.1.1 Bevacizumab

Bevacizumab is manufactured by Genentech Inc., San Francisco, California, USA and will be supplied as a sterile solution in single-use glass vials.

Bevacizumab placebo (physiological saline) will be supplied by local pharmacies.

#### 3.4.1.2 Cediranib

Cediranib will be manufactured by AstraZeneca. Cediranib placebo will be supplied as matching tablets. For details of the investigational product, see Table 2.

**Table 2 Identity of investigational product**

| Investigational product | Dosage form and strength | Manufacturer | Formulation number[a] |
|---|---|---|---|
| Cediranib | 30 mg tablet | AstraZeneca | F013345 |
| Cediranib | 20 mg tablet | AstraZeneca | F013343 |
| Cediranib | 15 mg tablet | AstraZeneca | F013341 |
| Placebo | Tablet matching cediranib 30 mg | AstraZeneca | F013367 |
| Placebo | Tablet matching cediranib 20 mg | AstraZeneca | F013366 |
| Placebo | Tablet matching cediranib 15 mg | AstraZeneca | F013365 |

[a] Batch numbers are not currently available and will be detailed in the clinical study report

### 3.4.2 Identity of Standard Treatment

#### 3.4.2.1 FOLFOX

Oxaliplatin (Eloxatin®) is manufactured by Sanofi Aventis (formerly Sanofi-Synthelabo), Guildford, UK and will be supplied as an aqueous solution for iv injection.

Oxaliplatin, 5-FU and leucovorin (or equivalent folinic acid preparation) will be supplied by local pharmacies.

### 3.4.3 Doses and treatment regimens

#### 3.4.3.1 FOLFOX

The FOLFOX regimen in this study will be a modified FOLFOX6 regimen, repeated every 2 weeks:

- Oxaliplatin 85 mg/m$^2$ with leucovorin 400 mg/m$^2$ (or equivalent folinic acid preparation) administered intravenously over 2 hours on Day 1.
- 5-FU 400 mg/m$^2$ bolus immediately after completion of the oxaliplatin infusion on Day 1, followed immediately by 5-FU 2400 mg/m$^2$ administered by a continuous iv infusion over 46 hours.

Oxaliplatin 85 mg/m$^2$ is administered intravenously over 2 hours in 250-500 mL 5% dextrose simultaneously with a separate bag of leucovorin 400 mg/m$^2$ (or equivalent dose of alternative folinic acid preparation) in 250-500 mL 5% dextrose, using a Y line, on Day 1, prior to the bolus and infusion of 5-FU.

Reconstitution or final dilution must never be performed with a chloride-containing solution. Oxaliplatin is incompatible in solution with alkaline medications, including basic solutions of 5-FU, and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with 5% dextrose prior to administration of any concomitant medication.

No pre-hydration is required. Pre-medication with antiemetics, including 5-hydroxytryptamine 3 blockers with or without dexamethasone is recommended.

First line chemotherapy and blinded study medication will be administered until progression (or other criteria for discontinuation are met), unless there is toxicity. If the toxicity is attributable to one component alone, then this component should be withdrawn and the other components continued until progression. Eg, if oxaliplatin must be discontinued due to toxicity, 5-FU and leucovorin (or equivalent folinic acid preparation) must be continued until progression along with the blinded study medication.

### 3.4.3.2 Bevacizumab

Bevacizumab should be stored, prepared and administered according to its labelling information and standard clinical practice. Bevacizumab vials must be refrigerated at 2–8°C (36–46°F) and protected from light.

It should be diluted for infusion by a healthcare professional using aseptic technique. The necessary amount of bevacizumab for a dose of 5 mg/kg should be withdrawn and diluted in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Any unused portion left in a vial should be discarded as the product contains no preservatives.

The diluted bevacizumab solution should be inspected visually for particulate matter and discoloration prior to administration. Diluted bevacizumab solutions for infusion may be stored at 2–8°C (36–46°F) for up to 8 hours.

Bevacizumab infusions should not be administered or mixed with dextrose solutions and should not be administered as an iv push or bolus.

Bevacizumab should be administered as per standard clinical practice. The initial bevacizumab dose should be delivered over 90 minutes as an iv infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. Bevacizumab should be administered on Day 1 every 2 weeks.

### 3.4.3.3 Cediranib

Phase II: The two doses of cediranib will be cediranib 30 mg and cediranib 20 mg to be taken orally once daily. To maintain the blind, patients will receive either one 20 mg tablet plus placebo matching cediranib 30 mg, or one 30 mg tablet plus placebo matching cediranib 20 mg.

Phase III: The chosen dose of cediranib (30 mg or 20 mg) will be taken orally once daily. To maintain the blind, patients will receive either one active tablet or a placebo matching the chosen dose of cediranib.

Cediranib or matching placebo should be taken no less than 1 hour prior to the consumption of a meal or more than 2 hours after a meal has been ingested. Patients will be instructed to take cediranib at approximately the same time each morning. Cediranib should be taken before chemotherapy is administered.

Patients may continue to receive study treatment indefinitely until toxicity or withdrawal of consent, even if chemotherapy agents have been discontinued. Patients with disease progression who continue with study treatment should also be offered second line therapy. After withdrawal, all subsequent therapy must be recorded, and the patient must be followed for survival.

Patients' genotype will not be used to stratify treatment.

If a patient forgets to take a tablet, and remembers within 6 hours of the scheduled time, the patient should be advised to take the study medication as soon as possible. If it is more than 6 hours after the scheduled time, then study medication should not be taken for that day. Study medication should continue as scheduled previously on the subsequent day. A patient should not take more than a single day's dose of tablets, within a day. In the event that the patient cannot hold the tablet(s) down (if the patient vomits) within 30 minutes after taking the tablet(s) or if the patient can identify the tablet(s) in the vomit content, the patient can re-take the tablet(s).

### 3.4.4 Management of toxicity

The following general guidance should be followed for management of toxicities and dose de-escalation. Specific guidance for management of hypertension and other toxicities attributable to cediranib/bevacizumab is provided in Sections 3.4.4.1, 3.4.4.2 and 3.4.4.3, and specific guidance for toxicities attributable to FOLFOX components is provided in Section 3.4.4.4.

1. Treat each of the toxicities with maximum supportive care (including holding the experimental therapy where required).

2. If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of study medications along with appropriate continuing supportive care. If medically appropriate, dose reductions are permitted for cediranib, 5-FU and oxaliplatin but not for bevacizumab since 5 mg/kg is the lowest recommended dose for this agent.

3. All dose changes should be documented with clear reasoning and documentation of the approach taken.

#### 3.4.4.1 Management of toxicity attributable to randomised study medication (cediranib or bevacizumab)

The AE profile of cediranib is described in Section 1.1.2.5.

The AE profile of bevacizumab is similar to that of cediranib, as most adverse effects are attributable to the class of VEGF inhibitors. Specific warnings in the bevacizumab labelling instructions are given below. Investigators are expected to be familiar with AEs related to bevacizumab and are advised to read the National Summary of Product Characteristics (SmPC) for further information. The latest version of the SmPC available at the time of writing this protocol is presented in Appendix G; however, investigators are requested to refer the manufacturer's website for the latest version.

The most common AEs in patients receiving bevacizumab are asthenia, pain, abdominal pain, headache, hypertension, diarrhoea, nausea, vomiting, anorexia, stomatitis, constipation, upper respiratory infection, epistaxis, dyspnoea, exfoliative dermatitis, proteinuria and hand foot syndrome. The most severe AEs are:

- Gastrointestinal perforations
- Wound healing complications
- Haemorrhage
- Arterial thromboembolic events
- Hypertensive crises
- Reversible posterior leucoencephalopathy syndrome (RPLS)
- Neutropenia and infection
- Nephrotic syndrome
- Congestive heart failure

With the EXCEPTION of hypertension, RPLS, hypothyroidism, proteinuria and diarrhoea, the following management plan should be followed for management of toxicity attributable to cediranib/bevacizumab (see Sections 3.4.4.2 and 3.4.4.3 for specific guidance on the management of hypertension, RPLS, hypothyroidism, proteinuria and diarrhoea).

- Dose interruptions should be used as the first approach to managing toxicity. For CTC Grade 3 or more, dosing with cediranib/bevacizumab should be interrupted. Dosing with cediranib/bevacizumab may be withheld for up to 14 days for management of toxicity. If a longer interruption is required due to unresolved toxicity, cediranib/bevacizumab should be discontinued.
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of cediranib/bevacizumab along with appropriate continuing supportive care.
- If the symptoms of the toxicity are considered related to cediranib/bevacizumab and do not promptly resolve to Grade 1 or below with maximum supportive care, the next dose level of cediranib below that being dosed should be instituted. No dose reductions are possible for bevacizumab.
- If symptoms do not resolve following the dose reduction, and it is considered medically appropriate, investigators may choose to permanently discontinue cediranib.
- In patients who experience wound healing complications or in whom an interventional procedure is required, cediranib/bevacizumab should be withheld until the wound is fully healed or patient considered sufficiently recovered (this

may be longer than 14 days). The half-life of bevacizumab is 20 days and this should be taken into account when considering when to restart therapy.

- Two dose reductions for cediranib will be permitted during the study. No dose re-escalation is permitted.
- In addition, there are certain circumstances in which study medication should be permanently discontinued (see Section 3.3.5).

The management of CTC Grade 3 or 4 toxicities attributable to cediranib/bevacizumab, with the EXCEPTION of hypertension is summarised below (see Table 3).

**Table 3 Dose reduction steps for study medication**

| Event | Tablets Cediranib/placebo | Infusion Bevacizumab/placebo |
|---|---|---|
| First episode of Grade 3 or 4 adverse drug reaction related to study medication (unless it meets a criterion for permanent discontinuation). | Hold dose until resolution (max 14 days). Restart at resolution. | Hold dose until resolution (max 14 days). Restart at next cycle as per protocol. |
| Recurrence of Grade 3 or 4 adverse drug reaction related to study medication. | Hold until resolution (max 14 days). Restart tablets one dose lower. Maximum of 2 dose reductions possible. | Hold until resolution (max 14 days). Consider continuation at next cycle or stopping – investigator discretion. |

Where dose reductions are indicated, patients receiving placebo cediranib tablets will also have matching reductions to ensure maintenance of the blind. Similarly, patients receiving placebo bevacizumab will have the physiological saline infusion delayed or stopped.

In patients who experience wound healing complications during therapy, study medication should be withheld until the wound is fully healed.

#### 3.4.4.2 Management of increases in BP with study medication

Increases in BP and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation.

In patients with severe hypertension requiring medical therapy, temporary interruption of bevacizumab/placebo and cediranib/placebo is recommended until adequate control is achieved. If hypertension cannot be controlled with the measures identified, treatment should be permanently discontinued. Therapy should be permanently discontinued in patients who develop malignant hypertension or hypertensive crisis.

**The following management plan for hypertension should be followed (Table 4):**

**Table 4 Hypertension management protocol for study medication[1]-induced hypertension**

| Hypertension severity | Actions | |
|---|---|---|
| **Mild to moderate hypertension:**<br><br>Blood pressure 140/90 mmHg on 2 consecutive occasions >24 hours apart<br><br>OR<br><br>Increase in diastolic pressure by ≥20 mmHg or to ≥100 mmHg or increase in systolic pressure to ≥150 mmHg | 1. | Repeat reading at least 1 hour later. If isolated increase, increase BP monitoring to twice weekly by health professional or daily home monitoring. **Continue all study medication at the same dose.** |
| | 2. | If confirmed by second reading, **continue all study medication at the same dose** and initiate monotherapy with a long acting dihydropyridine calcium-channel blocker (eg, nifedipine, amlodipine, felodipine) at low dose. |
| | • | If calcium-channel antagonist is contraindicated, use selective β blocker first line. |
| | • | Monitor BP daily by health professional until it stabilises. |
| | 3. | If BP >140/90 mmHg after 24 hours INCREASE the first agent to the full dose and consider adding an additional agent in combination (eg, selective beta-blocker, low dose combined alpha- and beta-blocker thiazide diuretic [angiotensin converting enzyme inhibitors or angiotensin receptor blockers if specific indication]). **Do not give study infusion (if due on that day) if BP >150/100 mmHg.** |
| | 4. | If BP >140/90 mmHg after a further 24 hours, add an additional agent if the patient is only on one new agent or increase to full doses of the 2-drug combination. **Do not give study infusion (if due on that day) if BP >150/100 mmHg.** |
| | 5. | If BP >160/95 mmHg and is increasing after 48 hours, **temporarily stop tablets** and continue anti-hypertensive therapy under close supervision. **Withhold study infusion.** |
| | 6. | Restart all study medication at the same dose (with maintenance antihypertensive therapy) when BP ≤140/90 mmHg. Monitor BP at least every 2 days by health professional until steady-state is reached (7 days) and BP |

[1] Study medication is defined as bevacizumab/placebo and cediranib/placebo

**Table 4 Hypertension management protocol for study medication[1]-induced hypertension**

| Hypertension severity | Actions | |
|---|---|---|
| | | stabilised. |
| | 7. | If BP increases to >160/95 mmHg follow step 5 and **restart all study medication but with the tablets at 1 dose lower than the starting dose** when BP<140/90 mmHg. |
| | 8. | If BP increases to >160/95 mmHg follow step 5 and **restart all study medication but with the tablet at 2 doses lower than the starting dose** when BP<140/90 mmHg. |
| | 9. | If BP increases to >160/95 mmHg after 2 dose reductions despite antihypertensive therapy, **permanently stop all study medication.** |

**Table 4 Hypertension management protocol for study medication[1]-induced hypertension**

| Hypertension severity | Actions | |
|---|---|---|
| **Severe hypertension:**<br><br>Increase in diastolic pressure to ≥110 mmHg or increase in systolic pressure to ≥180 mmHg on 2 readings >1 hour apart | 1. | **Temporarily stop all study medication** and consider if hospitalisation is necessary. |
| | 2. | Initiate treatment with a 2-drug combination including a calcium channel antagonist licensed for use in severe hypertension, tailored to the patient's underlying conditions and previous anti-hypertension treatment. |
| | 3. | If there is evidence of target-organ damage iv therapy should be considered while continuing oral therapy. |
| | 4. | Nitrates may adversely affect the therapeutic mechanism of action of cediranib but should be used if clinically indicated. |
| | 5. | Restart all study medication **but with the tablets at 1 dose lower than the starting dose** (with maintenance antihypertensive therapy) when BP ≤140/90 mmHg. Monitor BP at least every 2 days by health professional until steady-state is reached (7 days) and BP stabilised. |
| | 6. | If BP >160/95 mmHg and is increasing after 48 hours, temporarily stop cediranib/bevacizumab and continue anti-hypertensive therapy under close supervision. **Withhold study infusion.** |
| | 7. | Restart all study medication **but with the tablets at 2 doses lower than starting dose** (with maintenance antihypertensive therapy) when BP ≤140/90 mmHg. Monitor BP at least every 2 days by health professional until steady-state is reached (7 days) and BP stabilised. |
| | 8. | If BP increases to >160/95 mmHg after 2 dose reductions despite antihypertensive therapy, **permanently stop all study medication.** |

For all BP thresholds described in this protocol, a trigger level is considered to be met if either the systolic and/or the diastolic pressure reach the threshold. If the threshold is recorded at home, it must be confirmed by a healthcare professional as defined above before commencing any treatment.

CLEAR reasons for progressing to the next step in the management protocol must be documented.

When managing mild to moderate hypertension, the following principles should be noted:

- Patients on prior anti-hypertensive therapy may be particularly at risk of developing hypertension on cediranib. Patients with pre-existing hypertension are likely to benefit from having their blood pressure management optimised before starting cediranib therapy.
- The rigorous monitoring of blood pressure especially during the early phases of treatment is likely to be helpful in optimising hypertension management for all patients.
- Cediranib may cause rapid increases in BP in some patients.
- Calcium channel antagonists are the first line agents of choice
- If calcium channel antagonists are contraindicated, β blockers are second choice agents
- Increase anti-hypertensives to maximum doses and add additional agents as required.
- It is recommended that no more than 2 drugs are added in a 48-hour period before temporarily stopping cediranib.

The following cautions and contraindications should be noted:

- Calcium channel blockers: use with caution in patients with tachyarrhythmias, aortic stenosis, unstable angina or congestive cardiac failure and may cause headache.
- Short-acting dihydropyridines (such as diltiazem, verapamil) should be avoided since they may precipitate abrupt fall in BP and increase risk of myocardial ischaemia, infarction or stroke.
- Beta blockers: contraindicated in patients with asthma, chronic obstructive pulmonary disease and A-V block; they should be used with caution in patients with peripheral vascular disease, glucose intolerance and may cause fatigue.
- If diuretics are to be used, thiazides rather than loop diuretics are recommended.

CTC Grade 3 should NOT be assigned to hypertension AEs on the basis of the number of drugs used according to this protocol to treat mild-moderate hypertension since this is a

proactive treatment approach. CTC Grade 3 should be assigned **if hypertension is not controlled after 48 hours of per-protocol anti-hypertensive therapy.**

The definitions provided in Table 5 should be used to record the severity of increases in BP:

**Table 5 Severity of increases in BP - Modified CTCAE grading of hypertension AEs**

| CTC Grade | Definition |
|---|---|
| 1 | Asymptomatic, transient (<24 hr) increase by >20 mmHg (diastolic) or to >150/100 mmHg if previously within normal limits; intervention not indicated |
| 2 | Recurrent or persistent (>24 hr) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 mmHg if previously within normal limits; monotherapy may be indicated |
| 3 | CTC Grade 3 should not be assigned to hypertension AEs on the basis of the number of drugs used according to this protocol to treat mild-moderate hypertension, since this is a pro-active treatment approach. CTC Grade 3 should be assigned **if Grade 2 hypertension is not controlled after 48 hours of per-protocol anti-hypertensive treatment** |
| 4 | Life threatening consequences (eg, hypertensive crisis) |
| 5 | Death |

A record of the management of hypertension will be maintained.

#### 3.4.4.3 Management of RPLS, proteinuria, hypothyroidism and diarrhoea

**RPLS**

RPLS is a rare syndrome effecting vascular endothelial cells in the brain that may lead to capillary leak and oedema. The syndrome has been associated with a number of conditions including renal failure, hypertension, fluid retention and the use of cytotoxic or immunosuppressive drugs. It has also been reported in association with the use of VEGF inhibitors including bevacizumab and sunitinib, with an incidence of <0.1%. At the time of writing this protocol, one MRI-confirmed case of RPLS has been reported in a patient receiving cediranib. The syndrome can present in a variety of non-specific ways, including headache, seizures, lethargy, confusion, blindness and other visual and neurological disturbances. Hypertension may be present, but is not necessary for the diagnosis of RPLS. Magnetic Resonance Imaging (MRI) is the most sensitive imaging modality to detect RPLS and is recommended in suspected cases to confirm the diagnosis. RPLS is reversible upon removal of any possible precipitating factors and control of hypertension.

Active management of hypertension according to the hypertension management guidelines presented above may be expected to reduce the incidence of RPLS. However, if any case of

RPLS occurs that is confirmed by imaging (computed tomography or MRI), cediranib and bevacizumab should be immediately discontinued, in addition to any other measures to alleviate symptoms and control BP.

**Management of proteinuria**

If a patient has two consecutive two plus (++) urine proteinuria measurements during treatment, or one three plus (+++) or greater measurement, a 24 hour urine sample should be collected. If urine dipstick or 24 hour urine protein is classified as CTC Grade 3 (4+ or 3.5 g/24 hours), the general guidance in Section 3.4.4.1 should be followed.

In most clinical studies, bevacizumab was interrupted for ≥2 g of proteinuria/24 hours and resumed when proteinuria was <2 g/24 hours. Patients with moderate to severe proteinuria based on 24 hour collections should be monitored regularly until improvement and/or resolution is observed.

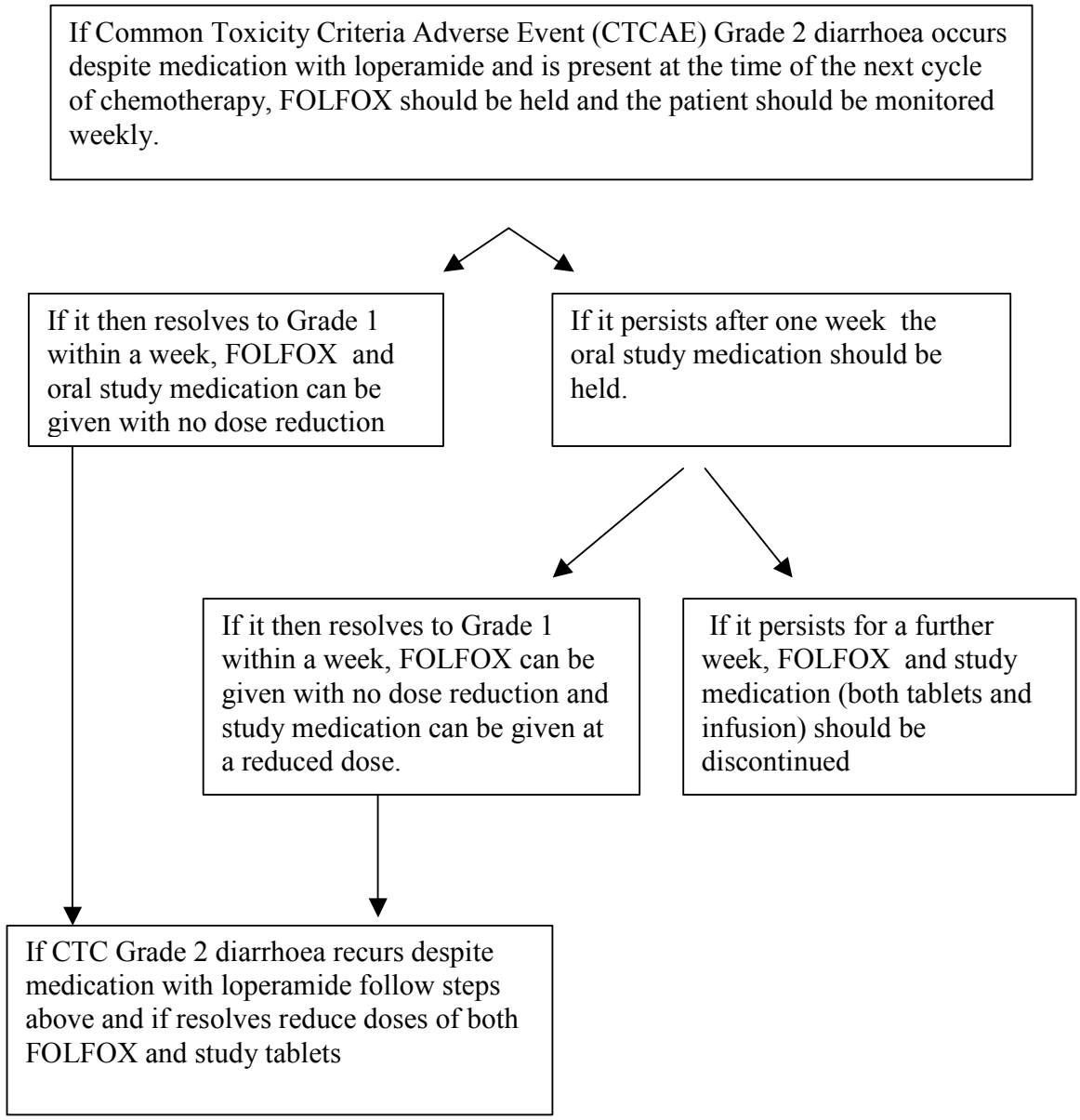
If nephrotic syndrome occurs, cediranib/bevacizumab should be permanently discontinued.

**Management of abnormal thyroid function tests**

If reductions in thyroxine are observed, replacement levothyroxine should be given when clinically indicated to normalise the thyroxine level to within the normal range and before the patient becomes clinically symptomatic. Replacement levothyroxine therapy may also be considered in patients with TSH increases (and thyroxine levels within the normal range), together with AEs and symptoms suggestive of incipient hypothyroidism. Thyroid function should be monitored frequently and the dose of levothyroxine should be titrated as required. The blinded study medication should be continued at the same dose for as long as possible with the replacement levothyroxine therapy.

**Management of diarrhoea**

Diarrhoea may be caused by any of the medications used in this study. Please use the following diarrhoea management plan as guidance; its emphasis is on treating diarrhoea at an early stage and, therefore, preventing episodes of severe diarrhoea and dehydrations, since these may be particularly hazardous in patients with chemotherapy–induced neutropenia.




For CTCAE Grade 3-4 diarrhoea refractory to oral anti-diarrhoeal medication, all treatment will be held. If ≥ CTCAE Grade 3 diarrhoea persists after 2 weeks, both FOLFOX and study medication should be discontinued. If the toxicity resolves to ≤ CTCAE Grade 1, then FOLFOX will be restarted and the dose reduced by 20%; study medication may also be restarted at a reduced dose. If ≥ CTCAE Grade 3 diarrhoea recurs FOLFOX and study medication should be discontinued.

### 3.4.4.4 Management of FOLFOX toxicity

**General Guidance**

Dose interruptions should be used as the first approach to managing toxicity. For any CTCAE Grade 3 or more, dosing should be interrupted. If one component of the chemotherapy is delayed, all components should be delayed.

If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same doses of 5-FU and oxaliplatin along with appropriate continuing supportive care.

If the symptoms of the toxicity are considered related to oxaliplatin and/or 5-FU and do not resolve to Grade 1 or below with maximum supportive care and following an appropriate dose interruption period, dose reductions of either or both components may be instituted.

If symptoms do not resolve following two dose reductions, and it is considered medically appropriate, investigators may choose to permanently discontinue the chemotherapy.

If oxaliplatin must be discontinued due to toxicity, 5-FU and folinic acid should be continued until progression along with the blinded study medication. If both chemotherapy agents must be discontinued, the blinded study medications should still be continued.

**Oxaliplatin**

Investigators are expected to be familiar with AEs related to oxaliplatin and are advised to read the National SmPC for the oxaliplatin being used in the study. The latest version of the SmPC available at the time of writing this protocol is presented in Appendix G; however, investigators are requested to refer the manufacturer's website for the latest version.

The most common adverse reactions to oxaliplatin are peripheral sensory neuropathies, fatigue, neutropenia, nausea, emesis and diarrhoea. Older patients may be more susceptible to diarrhoea, dehydration, hypokalaemia, leucopenia, fatigue and syncope. Hypersensitivity and anaphylactic/anaphylactoid reactions to oxaliplatin have been reported (<2% Grades 3/4) in clinical studies. These allergic reactions can be fatal, can occur at any cycle, and were similar in nature and severity to those reported with other platinum-containing compounds. Symptoms may include rash, urticaria, flushing of the face, diarrhoea, erythema, pruritis, shortness of breath, chest pains, disorientation and syncope and, rarely, bronchospasm and hypotension. These reactions should be managed with appropriate supportive therapy (epinephrine, corticosteroid and antihistamine therapy). Patients should be permanently discontinued from oxaliplatin if they develop a severe hypersensitivity reaction. Patients should be instructed to contact their physician if signs of an allergic reaction occur.

**Neuropathy:** Overall, neuropathy has been reported in 82% (all grades) and 19% (Grades 3/4) of patients previously untreated for advanced CRC and in 74% (all grades) and 7% (Grades 3/4) of previously treated patients. Oxaliplatin is associated with two types of neuropathy:

- An acute, reversible, primarily peripheral, sensory neuropathy that is of early onset, occurring within hours or 1-2 days of dosing, that resolves within 14 days, and that frequently recurs with further dosing. The symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paraesthesia, dysaesthesia and hypoesthesia in the hands, feet, perioral area or throat. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain and a feeling of chest pressure have also been observed. The acute, reversible pattern of sensory neuropathy was observed in about 56% of study patients who received oxaliplatin with 5-FU/leucovorin. An acute syndrome of pharyngolaryngeal dysaesthesia was seen in 1-2% (Grades 3/4) of patients and was characterised by subjective sensations of dysphagia or dyspnoea, without any laryngospasm or bronchospasm (no stridor or wheezing).

- Ice (mucositis prophylaxis) should be avoided during the infusion because cold temperature can exacerbate acute neurological symptoms. Patients should be informed that the acute neurosensory toxicity may be precipitated or exacerbated by exposure to cold or cold objects. Patients should be instructed to avoid cold drinks, use of ice and should cover exposed skin prior to exposure to cold temperature or cold objects.

- A persistent (>14 days), primarily peripheral, sensory neuropathy that is usually characterised by paraesthesias, dysaethesias, hypoaesthesias, but may also include deficits in proprioception that can interfere with daily activities (eg, writing, buttoning, swallowing and difficulty walking from impaired proprioception).

These forms of neuropathy occurred in 48% of the study patients receiving oxaliplatin with 5-FU/leucovorin. Persistent neuropathy can occur without any prior acute neuropathy event. The majority of the patients (80%) who developed Grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events.

Dose modifications for neurologic toxicity are allowed in this study as shown in Table 6. The toxicity scale for sensory neuropathies associated with oxaliplatin is shown in Table 7.

**Table 6 Oxaliplatin dose modifications for neurologic toxicity**

| Toxicity | Duration ≤7 days | Duration >7 days | Duration >14 days or persistent at next cycle |
|---|---|---|---|
| Grade 1 | No change | No change | No change |
| Grade 2 | No change | No change | Dose reduce 20% |
| Grade 3 | Dose reduce 20% | Dose reduce 20% | Stop |
| Grade 4 | Stop | Stop | Stop |
| Pharyngo-laryngeal dysaesthesias | No change | Increase infusion duration to 6 hours | Increase infusion duration to 6 hours |

**Table 7 Toxicity Scale for the Sensory Neuropathies Associated with Oxaliplatin**

| Grade | Symptoms |
|---|---|
| Grade 1 | Paraesthesias/dysaesthesias[a] of short duration that resolve and do not interfere with function |
| Grade 2 | Paraesthesias/dysaesthesias[a] interfering with function but not activities of daily living |
| Grade 3 | Paraesthesias/dysaesthesias[a] with pain or functional impairment that interfere with activities of daily living |
| Grade 4 | Persistent paraesthesias/dysaesthesias[a] that are disabling or life-threatening |

[a] May be cold-induced

Management of diarrhoea is discussed in Section 3.4.4.3.

**Myelosuppression:** Thrombocytopenia was frequently reported with the combination of oxaliplatin and 5-FU/leucovorin. The incidence of Grade 3/4 thrombocytopenia in patients previously untreated for advanced CRC and previously treated patients was 3-5%.

Neutropenia was frequently observed with the combination of oxaliplatin and 5-FU/leucovorin, with Grade 3 and 4 events reported in 35% and 18% of patients previously untreated for advanced CRC, respectively. Grade 3 and 4 events were reported in 27% and 17% of previously treated patients, respectively. The incidence of febrile neutropenia in patients previously untreated for advanced CRC was 4% (less than 1% of cycles) in the oxaliplatin and 5-FU/leucovorin combination arm. Additionally, in this same population, infection with Grade 3 or 4 neutropenia was 8%.

- If the nadir neutrophil count is $<500/mm^3$ or the nadir platelet count is $<50,000/mm^3$, the oxaliplatin and 5-FU doses will be reduced by 20%.

- Two further dose reductions of 20% of oxaliplatin or 5-FU for persistent nadir neutrophil count <500/mm$^3$ or nadir platelet count <50,000/mm$^3$ will be allowed.

**Pulmonary toxicity:** Oxaliplatin has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal. The combined incidence of cough, dyspnoea and hypoxia was 43% (any grade) and 7% (Grades 3 and 4) in the oxaliplatin plus 5-FU/leucovorin arm compared to 32% (any grade) and 5% (Grades 3 and 4) in the irinotecan plus 5-FU/leucovorin arm of unknown duration for patients with previously untreated CRC. If unexplained respiratory symptoms occur, such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis. Patients should be instructed to contact their physician if cough or breathing difficulties occur.

In this study, when oxaliplatin is discontinued due to toxicity, treatment should continue with 5-FU and the blinded study medication until documented disease progression or other criteria for discontinuation are met.

**5-FU**

The most common AEs associated with 5-FU are diarrhoea, myelosuppression, hand-foot syndrome and mucositis. The management of diarrhoea is discussed in Section 3.4.4.3 and management of myelosuppression is discussed above:

- For CTCAE Grade 3-4 mucositis or hand foot syndrome, the 5-FU infusion will be interrupted and not re-started during that cycle. In the subsequent cycle, if the toxicity has improved to ≤ CTCAE Grade 1, the 5-FU doses should be reduced by 20%.

**Folinic Acid**

The dose of folinic acid (leucovorin or equivalent preparation) will not be adjusted due to toxicity. The dose will be given immediately prior to each 5-FU dose, thus, if 5-FU is delayed, leucovorin (or equivalent folinic acid preparation) will also be delayed. Likewise, if any component of the cycle must be delayed, the entire cycle must be delayed (daily dosing with cediranib/placebo should continue).

### 3.4.5 Labelling

Bevacizumab (25 mg/mL) will be supplied in 4 mL or 16 mL single-use glass vials packaged in the commercial presentation. .

Cediranib and cediranib placebo will be packed into white high-density polyethylene bottles with child resistant, tamper evident closures.

Each container of cediranib or placebo will have an investigational-use label permanently affixed to the outside and will be labelled in accordance with local regulations, stating that the

drug is for investigational use only and should be kept out of reach of children. Instructions stating that the tablets should be taken at the same time each day will be included.

It is the investigator's responsibility to ensure the patient receives the correct dose. Patients should be instructed to take their medication at the same time of day, except on days they have a study visit, at which time they should not take their study medication until after their assessments.

In addition both products distributed through the IVRS system will be labelled with a unique 6 digit medication ID number to allow drug tracking.

### 3.4.6 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the investigational product bottle label and in the latest version of the Investigator's Brochure for cediranib (Investigator's Brochure).

Bevacizumab, oxaliplatin, 5-FU and leucovorin (or equivalent folinic acid preparation) will be stored according to the manufacturer's instructions.

The investigator will instruct the patient about storage requirements for study medication.

### 3.4.7 Accountability

The medication provided for this study is for use only as directed in the protocol. It is the investigator/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, so as to ensure that:

- Deliveries of such products from AstraZeneca are correctly received by a responsible person.
- Such deliveries are recorded.
- Study treatments are handled and stored safely and properly.
- Study treatments are only dispensed to study patients in accordance with the protocol.
- Any unused products should be destroyed locally, if this is not possible arrangements for disposal should be made through their Clinical Research Associate (CRA).

## 3.5 Method of assigning patients to treatment groups

Patient eligibility will be established before treatment randomisation. Patients will be randomised strictly sequentially, as patients are eligible for randomisation.

Data from other clinical studies in patients with CRC, including the bevacizumab EPAR (European Agency for the Evaluation of Medicinal Products. Bevacizumab European Public Assessment Report.), have shown that high baseline ALP and/or low baseline albumin are predictors of poor prognosis. To ensure balance with respect to these prognostic factors, the randomisation scheme will be stratified by WHO PS (0 vs. 1), baseline albumin (<4 vs. ≥4 g/dl) and baseline ALP (≤160 U/L vs. >160 U/L). Within each strata, patients will be randomised in an equal ratio to the treatment arms. If a patient discontinues from the study, the patient number will not be reused, and the patient will not be allowed to re-enter the study.

Patients will be assigned to treatment groups using an Interactive Voice Response System (IVRS). Details of the IVRS procedures will be documented.

## 3.6 Blinding and procedures for unblinding the study

### 3.6.1 Methods for ensuring blinding

All study personnel will be unaware of the randomised treatment until all decisions on the evaluability of the data from all patients have been made and documented, except for the un-blinded site staff responsible for the dispensing of medication (eg, the pharmacist), who will prepare the bevacizumab or placebo to match bevacizumab and so will not be blinded to bevacizumab treatment allocation. Each country will have an unblinded monitor to perform drug accountability and discuss any issues with the pharmacist to prevent the study monitors from becoming unnecessarily unblinded.

Cediranib active and placebo tablets will be supplied to the pharmacist blinded and will be dispensed by the pharmacy. Bevacizumab will be dispensed by the pharmacy and prepared as directed on the label (ie, diluted for infusion in saline solution). Bevacizumab placebo will be prepared following the same procedure used to prepare bevacizumab; however, bevacizumab will be omitted.

The active and placebo tablets will appear identical and will be presented in the same packaging to ensure blinding of the medication. Similarly, the bevacizumab and saline placebo infusions will appear identical to ensure that the blind is maintained. The IVRS system will provide the pharmacist or un-blinded site personnel with details as to the kit number for cediranib/placebo and if the patient should be dispensed bevacizumab or placebo.

### 3.6.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists through the IVRS system.

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomisation. The investigator(s) must document and report to AstraZeneca any breaking of the treatment code. AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

## 3.7 Pre-study, concomitant and post-study treatment(s)

Patients entering into the study must not have received prior treatment for metastatic disease.

All prior treatments for cancer and all drugs given to, or taken by, the patient at entry and during the study must be clearly documented in the appropriate eCRF page.

The following treatment restrictions apply:

- Caution in the concomitant use of any medication that may markedly affect renal function. Such medications may, however, be used with caution if deemed essential for treatment of a particular infection or continued if patients are using them prior to commencing the study with no effect on renal function demonstrable on blood or urine testing.

- Caution in the concomitant use of any medication that may affect hepatic P450 drug metabolising activity by way of enzyme induction (eg, phenytoin) or inhibition (eg, ketoconazole, ritonavir, erythromycin) within 2 weeks of the first dose of cediranib and throughout the study period.

- Patients who require oral anticoagulants (coumadin, warfarin) are eligible provided there is increased vigilance with respect to monitoring INR. IF medically appropriate and treatment available, consider switching to low molecular weight heparin.

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the electronic case report form (eCRF).

Following completion of the study, patients who are judged to benefit from treatment will be given the opportunity to continue treatment in a subsequent extension protocol.

## 3.8 Treatment compliance

The investigator or pharmacy must retain records of all study drugs administered. The CRA will check these records to confirm the compliance with the protocol administration schedule.

Any dose reductions will be documented, along with reasons for the dose reduction.

# 4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

## 4.1 Primary variable

The primary variable for this study is PFS. Further detail is given in Section 6.2.1. PFS is used as the basis for the sample size calculation (see Section 6.5).

## 4.2 Screening and demographic measurements

Investigators should refer to the Study Plan (Table 1) for the list of procedures and assessments to be performed at screening and their relative timings prior to randomisation.

Before entering the study, patients will be assessed to ensure that they meet the eligibility criteria (see Sections 3.3.2 and 3.3.3).

Written informed consent must be obtained prior to any study specific assessments. Procedures that are part of standard care may occur before informed consent is obtained.

Each patient will undergo screening procedures within 2 weeks prior to randomisation, unless otherwise specified below. The data listed below will be collected on the appropriate eCRF:

- Demographic details (date of birth and race)
- Past medical and surgical history, including histological subtype of tumour and duration of response to first treatment
- Biomarker assay data (archived tumour sample and blood sample)
- Physical examination to assess all conditions that are current and ongoing, including BP
- Vital signs
- 12-lead ECG
- Haematology, clinical chemistry and urinalysis (Baseline albumin required for randomisation).
- Creatinine clearance (Cockcroft-Gault)
- WHO performance status (PS)
- FACT-C and EQ-5D

- Radiological and clinical tumour assessments as per RECIST criteria within 4 weeks of starting randomised treatment, but as close as possible to starting the treatment(see Appendix C).
- AEs and tolerability data
- Concurrent medication.

Baseline albumin and ALP will be centrally assessed and used in conjunction with the WHO PS for stratification of subsequent randomisation.

Pregnancy tests will be performed as clinically indicated within 3 days prior to randomisation and the results will be recorded on the eCRF.

## 4.3 Patient-Reported Outcomes (PROs)

The methods for collecting Patient Reported Outcomes (PRO) data are presented below.

QoL/disease related symptoms will be assessed using the Functional Assessment of Cancer Therapy – Colorectal (FACT-C) questionnaire and the FACT Colorectal Symptom Index (FCSI) symptom sub-scale (Appendix D).

Patient Health status will be assessed by the EuroQol 5 Dimension Health Status Measure (EQ-5D; Appendix E).

The patient should complete each questionnaire at the Screening visit (Visit 1), Week 4 (Visit 5), Week 8 (Visit 7), Week 16 (Visit 9), Week 24 (Visit 11) and then at 12-weekly intervals until objective progression regardless of whether randomised treatment is discontinued. The patient should also complete a questionnaire at their treatment discontinuation visit. If any scheduled QoL assessment is not completed the reason for non-completion should be documented on the eCRF.

Each centre should allocate responsibility for QoL assessment to a specific individual (eg, a research nurse). The AstraZeneca designee will provide training for the relevant personnel in the administration of QoL questionnaires to help avoid the key problem of missing data. Before patients are randomised, they must be informed of the rationale for the study and the study details, including the QoL questionnaire.

The patients should be instructed on how to complete the questionnaire and, if necessary, assisted with completion of a training questionnaire that must be destroyed after completion. It is important that the value and relevance of QoL data are explained carefully to participating patients so that they are motivated to comply with data collection. The research nurse or appointed individual should also stress that the information is confidential. Therefore, if the patient has any medical problems he or she should discuss them with the doctor or research nurse separately from their QoL assessment. The questionnaire should be completed before the RECIST scans.

### 4.3.1 FACT-C and FCSI

#### 4.3.1.1 Methods of assessment

The FACT-C questionnaire consists of the FACT-G (general) QoL tool for cancer patients plus the Colorectal Cancer Subscale (CCS). The FACT-G is a self-administered instrument consisting of 27 items covering 4 domains of global QoL: physical well-being, social/family well-being, emotional well-being, and functional well-being. The CCS subscale (labelled 'Additional Concerns' in the FACT-C questionnaire) consists of 9 items of potential concern to patients receiving therapy for CRC (swelling or cramps, loss of weight, control of bowels, digestion, diarrhoea, appetite, body appearance, difficulties with ostomy appliance).

A symptom subscale (the FCSI) consisting of a subset of 9 items from the FACT-C will be used to assess changes in disease related symptoms. These items consist of questions relating to lack of energy, pain, loss of weight, diarrhoea, nausea, swelling or cramps, appetite, enjoyment of life and contentment. Patients rate each item on a scale from 0 (not at all) to 4 (very much) according to how much that item pertains to them. Higher FACT-C scores indicate good QoL, whereas low scores indicate poor QoL. FACT-C was chosen for this study because it is reliable and has been validated in patients with CRC (Ward WL et al 1999).

#### 4.3.1.2 Derivation or calculation of variable

Time to worsening of QoL will be assessed by the Trial Outcomes Index (TOI), the total FACT-C score, and the CCS.

The TOI score is the sum of the total scores from the physical well-being, functional well-being, and the CCS domains of the FACT-C. The total FACT-C score is the sum of the scores from the entire FACT-C questionnaire. The CCS is the total score from the 'Additional Concerns' domain of the FACT-C.

Time to worsening of QoL, as measured by the TOI, the total FACT-C score, and the CCS, will be defined as the time when a sustained clinically important deterioration in these scores has been recorded. A sustained clinically important deterioration in these end-points will be defined as a decrease in scores from baseline of greater than or equal to 6, 8 and 3 respectively (based on Yost KJ et al 2005), which is confirmed at the next completed assessment.

Time to worsening of symptoms, as measured by the FACT colorectal symptom index (FCSI), will be defined as the time when a sustained clinically important deterioration in the total score from the FCSI has been recorded. A sustained clinically important deterioration will be defined as a decrease in scores from baseline of greater than or equal to 4 (based on Yost KJ and Eton DT 2005), which is confirmed at the next completed assessment.

Patients without a baseline FACT-C assessment will be excluded from any quality of life/symptom analyses.

Patients who progress or die before quality of life/symptoms decline by the values specified above will be defined as deteriorating at the time of progression or death as appropriate. Therefore quality of life/symptoms data will not be colleted beyond objective progression.

Patients who do not experience documented deterioration in quality of life/symptoms, disease progression or death will be treated as censored observations at the time of the last quality of life/symptom assessment.

Further details of the analysis will be presented prospectively in the Statistical Analysis Plan.

### 4.3.2 Patient Health Status

Patient health status will be assessed by the EQ-5D, a validated and well-known utility measure, which consists of 5 questions (The EuroQol Group. 1990). This measure has been translated into multiple languages.

Details of the analysis of EQ-5D will be presented prospectively in the SAP.

### 4.3.3 Administration of PRO questionnaires

The instructions for completion of questionnaires are:

- Questionnaires must be completed before any investigations (including RECIST scans) or discussions about the status of the patient's disease with the clinic staff.
- The patient must complete the questionnaire his- or herself without any intervention from family, friends, centre staff etc.
- The only exception to the above point is if the patient is blind or illiterate. In this case, the questionnaire may be read to the patient verbatim; however, the reader must not aid in the interpretation of questions or in the selection of answers.
- Only one answer to every question should be checked.
- Centre personnel should not review the responses to the questionnaire with the patient or with any other centre staff.
- Following completion, the nurse or appointed individual may quickly scan the questionnaire for completeness and should confirm verbally with the patient that the questionnaire has been completed fully.

## 4.4 Health Economic measurements and variables

Whilst it is intended that data from this and other studies will be used in a health economic assessments of cediranib, all such analyses will be performed as part of a separate Health Economics analysis plan.

## 4.5 Pharmacokinetic measurements and variables (Not applicable)

## 4.6 Efficacy and pharmacodynamic measurement and variables

Following initial randomised study treatment on Day 1, subsequent visits and assessments should occur ±3 days of the protocol-specified visit times except for tumour assessments, which can occur ±2 weeks of the specified visit date. Patients will be considered lost to follow-up if they miss their visit and the investigator confirms that the patient is lost to follow-up.

Baseline radiological tumour assessments should be performed no more than 4 weeks before the start of study treatment, but should be as close as possible to the start of study treatment. Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments at Week 8 (Visit 7), Week 16 (Visit 9), Week 24 (Visit 11) and then every 12 weeks until disease progression or death. RECIST measurements must be using CT or MRI scans covering chest, abdomen and pelvis. The RECIST criteria will be used to determine PFS and ORR (CR and PR). The RECIST criteria are presented in Appendix C (Therasse P et al 2000).

It is important to follow the assessment schedule as closely as possible because biases in analysis can occur if 1 treatment group is examined more often or sooner than the other. If an unscheduled radiological and clinical tumour assessment is performed and the patient has not progressed, the next scheduled tumour assessment should still be performed at the planned time (as detailed in the study plan). This schedule is to be followed in order to minimise any unintentional bias caused by some patients being monitored at a different frequency than other patients.

Tumour assessments will be performed in accordance with the protocol schedule until evidence of one of the following:

- Progression of disease (patients will be followed for subsequent therapy and death).
- Death without evidence of progression.

If a patient has surgery for liver metastases, that patient should continue to be assessed for progression.

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions, recorded and measured at baseline. These target lesions, which must be measurable (as defined in Appendix C), will be monitored by the investigator throughout the study, and tumour measurements will be collected. Lesions previously irradiated or within previous radiation target volume will not be considered as measurable lesions. All other (non target) lesions will also be monitored throughout the study and an overall assessment of non target lesions will be made and recorded as “present”, “present with progression” or “absent”.

A patient will be determined to have progressed if they have progression of target lesions, clear progression of existing non-target lesions or the appearance of one or more new lesions (see Appendix C). Death will be regarded as a progression event in those patients who die before disease progression.

Lesions must be assessed using the same method and technique on each occasion. Lesions will be recorded on the eCRF page in the same order as they were recorded at screening. Details of any new lesions will also be collected. Response will be calculated in comparison to the baseline tumour measurements obtained before starting treatment. Progression will be calculated in comparison to when the tumour burden was at a minimum. Repeat assessments to confirm RECIST response should be performed at the next protocol scheduled assessment.

If the investigator is in doubt as to whether progression has occurred, particularly with respect to non-target lesions or the appearance of a new lesion, it is advisable to pursue treatment for a further 4 weeks and then repeat the RECIST assessment. If the patient has not progressed, all subsequent assessments should be carried out to the original schedule for the RECIST assessments.

**Tumour markers must not be used to assign progression or objective response (see RECIST, Appendix C).**

After progression, patients should be followed up for survival every 12 weeks as outlined in the study plan, unless the patient withdraws consent. Adherence to the study plan should be observed whenever possible.

### 4.6.1 Progression free survival

#### 4.6.1.1 Methods of assessment

The RECIST criteria will be used to assess tumours at Screening (Visit 1), Week 8 (Visit 7), Week 16 (Visit 9), Week 24 (Visit 11) and then every 12 weeks until disease progression or death.

Any patients discontinuing from all study treatment prior to progression must still be followed for RECIST as per the schedule above, until progression.

#### 4.6.1.2 Derivation or calculation of outcome variable

PFS will be calculated as the interval from randomisation to the earlier date of objective disease progression, per RECIST criteria, or death. A detailed definition of PFS is provided in Section 6.2.1.

### 4.6.2 Overall survival

#### 4.6.2.1 Methods of assessment

Overall survival will be assessed by recording the exact date that patient death occurs. Following disease progression, all patients should be followed for survival every 12 weeks.

Unblinding should not occur unless essential for subsequent patient management.
Eg, unblinding to determine suitability of patients for entry into second line clinical studies following D8480C00013 would only be necessary if prior treatment with named agents were not permitted. If second line clinical studies specifically exclude patients with prior treatment with VEGF inhibitors, then all patients participating in study D8480C00013 would be ineligible for such a study. To avoid unnecessary unblinding, the blind should only be broken AFTER:

- Objective progression has been observed and documented.
- The randomised study treatment has been permanently discontinued for the required length of time to allow introduction of a subsequent VEGF inhibitor.
- Confirmation that all other entry criteria for the subsequent clinical study have been met.

All patients should be followed regardless of whether they have progressed, stopped treatment or received other cancer treatment.

#### 4.6.2.2 Derivation or calculation of outcome variable

The OS (or time to death) will be calculated as the interval from the date of randomisation to the date of patient death (any cause). Patients who have not died at the time of the final analysis, who are lost to follow-up or who withdraw consent will be censored at the last date the patient was known to be alive.

### 4.6.3 Response Rate

#### 4.6.3.1 Methods of assessment

Categorisation of response rate will be based on the RECIST criteria using the following response categories: CR, PR, stable disease and progressive disease (see Appendix C).

#### 4.6.3.2 Derivation or calculation of outcome variable

The RECIST criteria will be used to assess the response rate. For the phase III analysis, a patient will be deemed to be a responder if the RECIST criteria for a confirmed CR or PR are satisfied at any time up to and including the defined analysis cut-off point. For the analysis of response rate in the phase II part of the study, a patient will be deemed to be a responder if they have a CR or PR prior to the analysis cut-off. For both the phase II and III analyses, any treated patient who does not satisfy the conditions to be a responder will be deemed to be a non-responder. Further details of response rate and duration of response are provided in Section 6.2.1.

## 4.7 Safety measurements and variables

The methods for collecting safety data are described below.

### 4.7.1 Adverse events (AEs)

#### 4.7.1.1 Definitions

The definitions of AEs, SAEs and other significant AEs (OAEs) are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

**AE**

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Any events that are unequivocally due to progression of disease must not be reported as an AE. Signs and symptoms clearly associated with the disease under study should not be reported as AEs unless they are newly emergent (ie, not previously observed in the patient), judged by the investigator to be unusually severe or accelerated or if the investigator considers deterioration of disease-related signs and symptoms to be caused directly by the drug. If there is any uncertainty about an AE being solely due to the disease under study, it should be reported as an AE or SAE as appropriate.

**SAE**

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- results in death
- is immediately life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer "yes" or "no" to the question "*Do you consider that there is a reasonable possibility that the event may have been caused by the drug?*" For further guidance on the definition of an SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol.

Any events, except AEs that are unequivocally due to progression of disease, must be reported as an SAE.

**OAE**

OAEs will be identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment, will be classified as OAEs. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

### 4.7.1.2 Recording of AEs

Any detrimental change in a patient's condition subsequent to their entering the study should be considered an AE, except those unequivocally due to progression of disease.

**Method of detecting AE/SAEs**

At each visit, the method of detecting AEs and SAEs will be by:

- Information volunteered by the patient or carer.
- Open-ended and non-leading verbal questioning of the patient at every visit such as the following: "*How are you feeling? Have you had any (other) medical problems since your last visit?"*.
- Observation by the investigational team, other care providers or relatives.

**Time period for collection of AEs/SAEs**

AEs will be collected throughout the study and will be recorded from the time of informed consent and followed up to resolution or for 30 days after the last administration of study treatment.

All study related toxicities and SAEs must be followed until resolution, unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

All new AEs occurring for up to 30 days after the last dose of study medication must be reported to AstraZeneca. All study-related AEs and all SAEs occurring up to 30 days after the last dose of study medication must be reported and must be followed until resolution where possible.

If a patient discontinues from treatment for reasons other than disease progression and, therefore, continues to have tumour assessments using RECIST, drug- or procedure-related SAEs must be captured until the patient is considered to have progressive disease and, therefore, will have no further RECIST assessments.

**Post study events**

After the patient has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study patients. However, if an investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to the investigational product, the investigator should notify AstraZeneca, Drug Safety.

**Handling of unresolved AEs and SAEs**

During the course of the study, all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion. All AEs assessed by the investigators as being related to study treatment or procedure and all SAEs occurring up to 30 days after the last dose of study medication must be followed-up until resolution, unless the event is considered by the investigator to be unlikely to resolve due to the patient's underlying disease.

All patients who have any CTC Grade 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must have further tests performed until the lab values have returned to CTC Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

AstraZeneca reserves the right to ask for further information/clarification on any AE that may be considered of interest.

**Collection of AE data**

All AEs will be recorded on the eCRFs provided. A description of the event, including its date of onset and resolution, whether it constitutes an SAE or not, any action taken (eg, changes to study treatment, other treatment given, and follow-up tests) and outcome, should be provided along with the investigator's assessment of causality (the relationship to the study treatment). AEs will be graded according to National Cancer Institute (NCI) CTCAE Version 3.0 and changes tracked on the relevant eCRF.

For selected AEs of special interest, further information concerning each event may be captured using additional forms or questionnaires.

### Causality

For an AE to be a suspected drug-related event there should be at least a reasonable possibility of a causal relationship between the study medicinal product and the AE (see Appendix B for guidelines on interpretation of causality).

Any detrimental change in a patient's condition subsequent to their entering the study and during the 30-day follow up period should be considered an AE.

### Disease progression

Worsening of disease related symptoms could be thought of as a worsening of a patient's condition attributable to the disease for which the investigational product is being given. This worsening may be an increase in the severity of the disease or symptoms of the disease. Expected progression of the disease being studied, including signs and symptoms of the progression, should not be reported as an AE unless more severe in intensity or more frequent than expected for the patient's condition.

Symptoms of the disease under study that are newly emergent on study treatment or worsen on study treatment should only be reported as AEs (or SAEs as appropriate) if they are not considered to be expected progression of the disease under study.

Any events that are unequivocally due to progression of disease must **not** be reported as an AE.

### Lack of efficacy

When there is a deterioration in the condition for which the study treatment is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless AstraZeneca or the reporting physician considers that study treatment contributed to the deterioration or local regulations state to the contrary, the deterioration would be considered a lack of efficacy.

### New cancers

The development of a new cancer should be regarded as an SAE. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study.

### Deaths

All deaths that occur during the study, or within the protocol defined follow up period after the administration of the last dose of study treatment, must be reported as follows:

Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the eCRF but should not be reported as an SAE.

Where death is not due (or not clearly due) to progression of disease under study, the AE causing the death must be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

Deaths with an unknown cause should always be reported as an SAE. A post-mortem may be helpful in the assessment of the cause of death and, if performed, a copy of the post-mortem results should be forwarded to AstraZeneca, Drug Safety within the usual timeframes.

**Abnormal laboratory findings/vital signs**

The reporting of protocol mandated laboratory/vital signs abnormalities as both laboratory/vital signs findings and AEs should be avoided.

Laboratory/vital signs abnormalities should only be reported as AEs if any criterion for an SAE is fulfilled or study treatment is discontinued, or requires dose modification. In addition, vital signs abnormalities that require treatment should be reported as AEs.

**Pregnancy**

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 9.4, Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. If the partner of a male patient becomes pregnant, this should also be reported.

#### 4.7.1.3 Reporting of SAEs

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (ie, immediately but no later than the end of the next business day) of when he or she becomes aware of it.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by day one for all fatal and life-threatening cases and by Day 5 for all other SAEs. Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above.

All SAEs have to be reported, whether or not considered causally related to the investigational product. All SAEs will be recorded in the case report form. The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

### 4.7.2 Laboratory safety measurements and variables

#### 4.7.2.1 Methods of assessment

During the conduct of this study, the local laboratory in each centre will be used to perform the laboratory assessments required by the protocol (clinical chemistry (Table 8), haematology (Table 9), and urinalysis (Table 10).

The analysis of the primary efficacy endpoint, PFS, will be stratified by baseline albumin and alkaline phosphatase (ALP); therefore, these parameters will be assessed centrally by calibrating local laboratories.

For the purpose of assessing eligibility, patients may be screened within 1 week prior to randomisation by a local laboratory. Results from the local laboratory will be used to determine eligibility. Samples will be assessed at the time points detailed in the study plan (see Table 1).

The local laboratory will supply all venepuncture equipment, sample containers and labels. Procedures for sampling, handling and shipping of these samples will be provided in the Laboratory Handbook for Investigators to be provided to each site.

Routine haematology and clinical chemistry parameters will be investigated at Screening and then at 2-weekly intervals. Other selected clinical chemistry parameters will be measured every 8 weeks up to 24 weeks the every 12weeks. Troponin and CKMB will be assessed only if cardiac ischaemia is suspected (eg, if indicated by abnormal ECG). Selected haematology parameters will be measured at baseline and then only in the event of a bleed/thrombotic event. See Section 4.8 for the total volume of blood samples to be collected.

**Table 8 Clinical chemistry**

| Every 2 weeks[a]: | Every 8 weeks to 24 weeks then every 12 weeks: | In the event of suspected cardiac ischaemia: | Optional tests for site:<br>In the event of suspected muscle weakness | Optional tests for site:<br>In the event of suspected cardiac ischaemia or dysfunction |
|---|---|---|---|---|
| Albumin | Triiodothyronine $T_3$ (free) | Troponin T or I | Total CK | Brain natriuretic peptide |
| ALP | Thyroxine $T_4$ (free) | CKMB | CKMM | |
| AST | TSH | | | |
| ALT | LDH | | | |
| Bilirubin | CEA | | | |
| Urea | | | | |
| Calcium(uncorrected) | | | | |
| Creatinine (creatinine clearance) | | | | |
| Magnesium | | | | |
| Potassium | | | | |
| Sodium | | | | |

[a] These tests are to be performed prior to each chemotherapy session, ie, every 2 weeks.

**Table 9 Haematology**

| At Screening only: | Every 2 weeks[a]: | In the event of a bleed/thrombotic event: |
|---|---|---|
| International normalised ratio (INR) | Haemoglobin | INR |
| Activated partial thromboplastin time (APTT) | Platelet count | APTT |
| | Haematocrit | |
| | Red blood cells | |
| | Leucocyte differential count | |
| | Mean cell volume | |
| | White blood cells | |

[a] These tests are to be performed prior to each chemotherapy session, ie, every 2 weeks.

**Table 10 Urinalysis**

| | |
|---|---|
| Blood | Ketones |
| Bilirubin | Protein |
| Glucose | pH |

#### 4.7.2.2 Derivation or calculation of outcome variables

Section 4.7.1.2 provides details of how AEs based on laboratory tests will be recorded and reported.

Creatinine clearance will be estimated using the Cockcroft-Gault equation:

**Males:**

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

**Females:**

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

### 4.7.3 Vital signs, ECG and physical examination

#### 4.7.3.1 Methods of assessment

Vital signs and physical examination will be performed at Screening, Day 1, then after 1, 2, 4 and 8 weeks and then at 4-weekly intervals up to and including the discontinuation visit).

Blood pressure monitoring will be performed at each visit, prior to commencing iv infusions, every 2 weeks throughout the duration of randomised treatment.

ECGs will be recorded routinely at Screening, Day 1 and Week 2. Further ECGs will be performed only in the event of a cardiac AE. The same method of assessment should be used throughout. ECGs will be evaluated locally. Any clinically significant abnormal findings observed and recorded during the study will be recorded as AEs.

Physical examinations will be performed and will also include the WHO PS.

WHO PS will be recorded as follows:

0 = Fully active, able to carry out all usual activities without restrictions and without the aid of analgesia.

1 = Restricted in strenuous activity, but ambulatory and able to carry out light work or pursue a sedentary occupation. This group also contains patients who are fully active, as in Grade 0, but only with the aid of analgesics.

2 = Ambulatory and capable of all self-care, but unable to work. Up and about more than 50% of waking hours.

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

4 = Completely disabled, unable to carry out any self-care and confined totally to bed or chair.

## 4.8 Volume of blood sampling and handling of biological samples

The total volume of blood that will be drawn from each patient in this study depends on the length of time that the patient receives study medication. Table 11 is a guide to the approximate volume of blood that will be drawn from each patient, based on the assumption that each patient will receive study treatment for 10 months. Local laboratories will be used for analysis of blood samples.

**Table 11 Volume of blood to be drawn from each patient**

| Assessment | | Sample volume (mL) | Number of samples | Total volume (mL) |
|---|---|---|---|---|
| Safety | Clinical chemistry | 9.0 mL | 23 | 207.0 mL |
| | Haematology | 4.0 mL | 23 | 92.0 mL |
| Biomarkers of angiogenesis | plasma | 4.0mL | 7 | 28.0 mL |
| | serum | 7.0mL | 7 | 49.0 mL |
| Genotyping | | 10.0 mL | 1 | 10.0 mL |
| **Total** | | 34.0 mL | 61 | 386.0 mL |

Note: a median PFS time of 11 months (ie, 47 or 48 weeks) has been assumed with laboratory tests performed every 2 weeks (ie, 23 or 24 samples) based on data for bevacizumab in combination with FOLFOX/XELOX in the first line setting (Cassidy J et al 2006).

### 4.8.1 Analysis of biological samples

#### 4.8.1.1 Clinical chemistry samples

The analyte stability limits defined by each local laboratory will be applied to all analyses performed on behalf of AstraZeneca. Local laboratories will not analyse samples that fall outside these stability limits. Analytical data will not be reported if found to have been derived from a sample that fell outside these stability limits. The standards of procedure followed by each local laboratory may be amended in accordance with its Standard Operating

Procedures. Each local laboratory will inform AstraZeneca of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

If a local laboratory chooses to sub-contract the analytical work to another laboratory, the local laboratory must assure itself and provide assurance to AstraZeneca that the other laboratory will apply defined stability limits to all analyses performed on behalf of AstraZeneca. Samples falling outside these limits must not be analysed or data reported. The other laboratory will inform AstraZeneca of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

## 4.9 Genetic measurements and co-variables

For centres who participate in the collection of blood samples for genetic analysis, patients will be invited to provide a 10 mL blood sample at Visit 2 for the extraction of DNA for potential genetic analysis. Genotype is a stable parameter, therefore, if for any reason the blood sample is not drawn at Visit 2, it may be taken at any visit until the last study visit

Further details regarding blood sample collection, storage, extraction of DNA and analysis are available in Appendix F.

For patients who consent, part of the archived tumour specimen may be used for DNA extraction and analysis. Details for the collection of tumour samples will be provided in a separate handbook.

## 4.10 Collection of tissue samples for biomarker assays

An archived tumour specimen will be obtained during screening for the analysis of tumour VEGFR and protein expression.

Instructions for tumour and blood sample collection, transport and storage in biomarker studies will be provided in a separate handbook.

# 5. DATA MANAGEMENT

eCRFs will be provided for the recording of data. Data are to be recorded onto the eCRFs. Corrections should be made by approved personnel; the reasons for significant changes must be provided.

Any electronic data will be electronically loaded into the database by the CRO and checked for validity.

The method of distribution and processes for data queries will be documented in the study Data Management Plan. On receipt of the data query by data management at the CRO, the database will be edited appropriately.

# 6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 6.1 Statistical evaluation – general aspects

A comprehensive SAP will be prepared before unblinding of the data.

## 6.2 Description of outcome variables in relation to objectives and hypotheses

The primary objective of the study is to determine the efficacy of cediranib in combination with FOLFOX compared to the efficacy of bevacizumab in combination with FOLFOX. This objective will be assessed by the primary variable of PFS, which is defined in Section 6.2.1. Whilst the study has been powered on the basis of showing superiority, the non-inferiority of cediranib compared to bevacizumab will also be tested. The non-inferiority margin has been pre-specified in Section 6.4.3.

A secondary objective of the study is to compare cediranib in combination with FOLFOX to bevacizumab in combination with FOLFOX for OS, ORR, duration of response, QoL and disease related symptoms.

The objective of the phase II part of this study is to assess the tolerability of each dose of cediranib in combination with FOLFOX, and obtain an initial assessment of the relative efficacy of cediranib and bevacizumab when given in combination with FOLFOX. The study will continue unless there is a reasonable probability that cediranib is inferior to bevacizumab, according to prospectively defined criteria defined in the IDMC charter. These criteria consider tolerability and response rate data from this study in conjunction with tolerability and PFS data from a second line CRC phase II study (D8480C00041) that includes the same 3 treatment groups. If both doses of cediranib satisfy the criteria, only one dose arm will be selected for further study. The IDMC will analyse the phase II data and if continuation criteria are met analysis results will not be disclosed. The IDMC may also review tolerability and PFS data from a third, placebo-controlled, cediranib study in first line CRC (D8480C00051) if the results from this study (D8480C00013) and the phase II study are equivocal.

The incorporation of data from the second line CRC study enables the relative efficacy of the agents to also be assessed using a PFS endpoint instead of solely relying on response rate data. If the phase II decision were to be based solely on PFS data from this study, many more patients would be exposed before being able to assess the likelihood that the study might achieve its primary objective.

### 6.2.1 Progression free survival

PFS is defined as the time from randomisation to the earlier date of objective progression or death. Patients who are still alive at the time of the analysis, without a progression event, will be censored at the date of their last evaluable objective tumour assessment.

This study is double-blind and patients are to have radiological scans until confirmation of objective progression. In light of the design, the dates of progression and death, and the evaluability of data will be handled as follows:

- A evaluable visit includes the following scenarios:

1. Visits where a complete set of target lesion assessments are performed

2. A new lesion is detected

- Progression of target lesions includes situations where:

  – All target lesions have been assessed and a response of progression can be assigned.

- In the following situations, patient will be censored:

  - Patients who progress, or die in the absence of progression, following two or more consecutive non-evaluable tumour assessment visits, will be censored at the date of the last evaluable assessment (or at randomisation if no evaluable tumour assessments have been performed post-randomisation).

  - Patients that start another anti-cancer therapy prior to progression will be censored at the date of the last evaluable tumour assessment visit prior to starting the new therapy.

  Otherwise, the actual date of progression or death will be used on the analysis, regardless of whether the patient had discontinued all or part of their randomised therapy.

- Date of Progression:

  If radiological assessments take place on multiple dates at a visit, the date used for analysis will be defined as the earliest of the following:

  – Date of radiological assessment showing a new lesion (if progression is based on a new lesion)

  – Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions).

– Date of the last assessment of non-target lesions (if progression is based on the non-target lesion response)

Whilst the planned primary analysis does not include progression events occurring after a patient has started another anti-cancer therapy, all patients must continue to be followed until objective progression, regardless if they discontinue all or part of their randomised therapy, or start another anti-cancer therapy, in order to support the planned sensitivity analyses.

Two sensitivity analyses will be performed to support the primary analysis of PFS:

For the primary analysis, objective progression will be calculated programmatically based on the tumour measurements and assessments provided on the eCRF. To investigate the sensitivity of the primary analysis, a supportive analysis will be performed using the tumour assessment data from an independent central review. For consistency with the primary analysis, patients who progress, or die in the absence of progression, following two or more consecutive non-evaluable tumour assessment visits, will be censored at the date of the last evaluable assessment (or at randomisation if no evaluable tumour assessments have been performed post-randomisation).

To assess the sensitivity of the primary analysis to possible time-assessment bias, a supportive analysis will be performed that does not incorporate the PFS time. This analysis will compare the proportion of patients who have either progressed or died before a fixed calendar date (subject to a pre-defined time window) coinciding with the time of the final PFS analysis. This analysis will be performed using the definition of PFS outlined in Section 6.2.1, using the tumour measurements and assessments provided on the eCRFs. In addition to the events included in the primary analysis, this analysis will include progression events occurring after 2 or more missed tumour assessment visits.

### 6.2.2 Secondary endpoints

Overall survival is defined as the time from randomisation to the date of death from any cause. Patients who have not died at the time of analysis will be censored at the last date the patient was known to be alive.

For the analysis of response rate in the phase III part of the study, a patient will be defined as a responder if they have a confirmed PR or CR as defined by RECIST criteria at any point prior to the data cut-off for the primary analysis. For the analysis of response rate in the phase II part of the study, a patient will be defined as a responder if they have a PR or CR prior to the analysis cut-off.

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the patient progresses, regardless of whether the patient is still taking study medication. Non-responders will be excluded from the summary of response duration.

QoL and disease related symptom endpoints will be assessed using the FACT-C questionnaire (see Section 4.3.1.2). Time to worsening of QoL and disease related symptoms will be defined as the time to a clinically important deterioration in the endpoint of interest. The definition of a clinically important deterioration is defined in Section 4.3.1.2.

## 6.3 Description of analysis sets

The primary statistical analysis of the efficacy of cediranib will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Therefore, all efficacy and QoL data will be summarised and analysed on an ITT basis.

When assessing tolerability, summaries will be produced based on study treatment actually received for all patients who received at least one dose of randomised study medication (termed the evaluable for safety [EFS] population).

The final analysis of the study will include all data from patients recruited into both the phase II and phase III parts of the study; however, data from the cediranib dose discontinued at the end of phase II will not be included.

## 6.4 Method of statistical analysis

### 6.4.1 Analysis of primary endpoint

PFS will be analysed using a log-rank test stratified by PS (0 or 1), baseline albumin and baseline ALP, in accordance with the stratification used at randomisation. Baseline albumin and ALP will each be stratified by creating two levels for each covariate. The stratification levels for baseline albumin will be <4 and ≥4 g/dL and the stratification levels for baseline ALP will be ≤160 and >160 U/L. The effect of treatment will be estimated by the adjusted HR together with its 95% confidence interval (CI), which will be calculated from a Cox proportional hazards model fitting for the same covariates defined in an identical manner to the log-rank test. Kaplan-Meier plots of PFS will be presented by treatment group.

The existence of any treatment by covariate interactions will be investigated by the difference in the log likelihoods for the full (including interactions) and reduced (excluding interactions) models. This investigation will include a calculation of the HR within each stratum, using a Cox model fitted separately for each stratum. If the difference in log likelihoods is found to be significant (p<10%), an attempt to determine the cause and type of interaction will be made. If the interaction is found to be quantitative, the interaction terms will be dropped and the model refitted. If it is found to be qualitative (Gail M and Simon R 1985), the extent of the interaction will be investigated by estimating the HR for different values of the covariate.

The assumption of proportionality will be assessed using plots of complementary log-log event times versus log time.

The primary analysis will use tumour measurements and assessments provided on the eCRFs. To assess the sensitivity of the primary analysis, a supportive analysis will be performed, which uses the tumour assessments data provided by an independent central review. This analysis will use the same methodology and model as the primary analysis.

A further supportive analysis will compare the number of patients who have had a PFS event at, or before the final PFS analysis, based on a calculated assessment of progression, using the tumour assessment data provided on the eCRFs. The event rates will be analysed using a binary model with a complementary log-log link function so that the results can be approximated as a HR. An adjusted analysis will be performed allowing for the effect of treatment and the same covariates used for PFS. Treatment comparisons will be summarised using the estimated HR from the adjusted binary analysis together with its 95% CI. The event rate in each group will also be reported.

The final analysis of the study will include all data from patients recruited into both the phase II and phase III parts of the study; however, data from the cediranib dose discontinued at the end of phase II will not be included. Since PFS data from patients recruited into the phase II part of the study will be used in the phase III analyses, and data from the phase II part will be used to select the phase III dose, the Todd and Stallard methodology (Todd S and Stallard N 2005) will be used to adjust the type 1 error for the primary analysis.

### 6.4.2 Analysis of secondary endpoints

The analysis of OS will use the same methodology and model as described for PFS. An interim assessment of OS will be performed at the time of the primary analysis of PFS. A final analysis of OS will be performed when 950 deaths have occurred. An O'Brien and Fleming spending function (O'Brien PC and Fleming TR 1979) will be used to control the family-wise type 1 error rate, between the interim and final analyses of OS.

Response rate will be analysed using logistic regression, adjusting for the same set of covariates as PFS. The effect of treatment will be estimated using the adjusted odds ratio and its 95% CI together with the response rate in each treatment group.

The duration of response will not be formally analysed. All data will be summarised by treatment group. Non-responders will be excluded from the summaries.

The analysis of time to worsening of QoL and time to worsening of disease related symptoms will use the same methodology as described for PFS.

### 6.4.3 Assessment of non-inferiority of cediranib compared to bevacizumab

Non-inferiority will be demonstrated if the upper 2 sided 95% confidence limit for the PFS HR is less than 1.2. This criterion requires that the point estimate is 1.05 or less. The absolute benefit of cediranib will be assessed in Study D8480C00051, which compares cediranib with placebo and is running concurrently to study D8480C00013.

## 6.5 Determination of sample size

### 6.5.1 Phase II analysis

The phase II analysis of data will be performed when a total of 225 patients (75 per group) have been followed for 3 months. A prospectively defined algorithm, based on the observed HR in study D8480C00041 and the observed response rate in this study, will be applied by the IDMC to determine whether the study should continue and if so, which dose of cediranib should be selected. Details of the algorithm will be provided in the IDMC charter. The number of patients in the phase II part of this study is considered sufficient to assess the tolerability of each dose of cediranib and to assess the relative efficacy of cediranib to bevacizumab prior to phase III. For example, with 75 patients per group if the response rate for either cediranib arm is 10% greater than the bevacizumab group, assuming a response rate of 45% in the bevacizumab group, there is only an 11% probability of observing such an outcome if the true response rates were identical. Similarly, based on the same assumptions, if the response rate for either cediranib arm were more than 10% inferior to the bevacizumab group, this result would indicate that for the given dose of cediranib there is approximately a 90% probability that cediranib was truly inferior to bevacizumab. In addition to response rate, the algorithm for continuation of the study will take account of the HR in study D8480C00041 and safety and tolerability data for each dose.

### 6.5.2 Phase III analysis

The final PFS analysis will be performed after 850 PFS events have occurred. If the true HR for cediranib:bevacizumab is equal to 0.8, this analysis will have 90% power to demonstrate a statistically significant difference at a 2-sided 5% level. An observed HR of 0.87 or less will be required to demonstrate statistical significance.

An interim analysis of the secondary endpoint, OS, will be performed at the time of the final PFS analysis, and it is anticipated that approximately 501 patients will have died at this time (assuming a 25 month median OS). This will enable calculation of a sufficiently precise estimate of the treatment effect in order to provide reassurance regarding the relative effect on OS. For example, if a HR of 1 is observed for OS, its 95% CI would range from 0.84 to 1.19. In other words, a 19% increase in OS (approximately 4.75 months assuming a median OS of 25 months for patients on bevacizumab) would be significant.

It is intended that approximately 1400 patients will receive either bevacizumab or the cediranib dose selected for phase III expansion. Together with patients in the cediranib dose group dropped after the phase II analysis, it is expected a total of approximately 1600 patients will be recruited into the study.

If the median PFS for the bevacizumab + FOLFOX group is 11 months, it is predicted the 850 PFS events will occur 37 months after the first patient has entered the study.

The final analysis of OS update is planned after a total of 950 deaths, which is predicted to occur about 18 months later (58 months after the first patient has been recruited into the study).

## 6.6 Interim analyses

The trigger for, and estimated timing of, the planned efficacy analyses for this study are summarised in (Table 12). A review of safety in the current study, D8480C00013, and the concurrent second line study, D8480C00041, will be performed at a time agreed with the IDMC, approximately 9 months after the first patient is entered into study D8480C00041. This time point is expected to occur approximately 3 months after the first patient is recruited into study D8480C00013. An additional review of safety will be performed, at a point agreed with IDMC, after the phase II analysis and before the final PFS analysis.

**Table 12 Trigger for and Timing of planned efficacy analyses**

| Description | Objective | Trigger[a] | Approximate Time[b] |
|---|---|---|---|
| Phase II analysis | Initial assessment of tolerability and comparative efficacy data, and dose selection. Continue study guided by prospectively defined criteria. If both doses satisfy criteria, choose one dose. | 225 patients followed for 3 months | 11 months |
| Final PFS analysis | Final analysis of PFS and secondary endpoint ORR. Interim analysis of OS. | 850 PFS events | 37 months |
| Final OS analysis | Final analysis of OS | 950 deaths | 58 months |

PFS = progression free survival, OS = overall survival
[a] These criteria will determine the time analyses are performed. The final column gives an approximate time if the assumptions detailed below hold.
[b] Times are from first patient entered until the required events occur and do not include time to collate and analyse data. It is also assumed that the median PFS for the bevacizumab + FOLFOX group is 11 months. If these assumptions do not hold, times will vary.

- The phase II decision will be made when both 225 patients have been followed for 3 months in this study and 120 PFS events have occurred in the companion second line study. These 2 timings are planned to coincide. The criteria for continuation will be used for each dose of cediranib separately and prospectively defined in the IDMC charter.

## 6.7 Independent Data Monitoring Committee

The IDMC is responsible for safeguarding the interests of study participants, via review of accumulating safety and efficacy data, for this study and the companion, second line, phase II Study D8480C0041. The IDMC will provide AstraZeneca with ongoing guidance and recommendations for action with respect to study conduct and the management of patients treated under the auspices of the study protocols. Additionally, the IDMC will review efficacy and tolerability data from the phase II portion of this study in conjunction with data from Study D8480C0041, and provide AstraZeneca with a recommendation whether to continue this study according to prospectively defined criteria and if so, which cediranib arm should be continued.

Data from a third, placebo-controlled, cediranib study, D8480C00051, may be used by the IDMC for the decision of whether to continue into phase III if the results of this study and Study D8480C00041 are equivocal.

The IDMC will be composed of therapeutic area experts and statisticians who do not have significant conflicts of interests and therefore, will neither be study investigators or individuals employed by AstraZeneca. The interim analyses, including the phase II analysis, will be conducted by the IDMC who will not disclose results if the recommendation is to continue the study.

# 7. STUDY MANAGEMENT

## 7.1 Monitoring

Before the first patient enters into the study, a representative of AstraZeneca will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.
- Discuss the specific requirements of the genetic research with the investigator(s) (and other personnel involved with the study).

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.

- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the eCRFs and investigational product accountability checks are being performed.

- Perform source data verification (SDV; a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each patient (eg, clinic charts).

- Perform source verification of the genetic consent of participating patients and ensure that the investigational team is adhering to the specific requirements of this genetic research.

The monitor or another AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre need information and advice.

## 7.2 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the centre to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her centre.

## 7.3 Training of staff

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

## 7.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the Co-ordinating Investigator and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (Amended Protocol) will need to be reviewed by FDA as part of the Special Protocol Approval and will not be implemented until feedback is obtained from FDA, then the protocol must be notified to or approved by each IRB or IEC, and if applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's IRB or IEC must be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB or IEC is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to each principal investigator(s), who in turn is responsible for the distribution of these documents to his or her IRB or IEC, and to the staff at his or her centre. The distribution of these documents to the regulatory authority will be handled according to local practice.

## 7.5 Study agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

Specific reference to the genetic requirements for this study will be included in the study agreements (s).

## 7.6 Study timetable and end of study

Before a patient's enrolment in the study and any study-related procedures are undertaken the following should be fulfilled:

- Signed Clinical Study Protocol and other agreements between AstraZeneca and the Principal Investigator/Study Site.
- Approval of the study by the IRB/IEC.
- Approval of the study, if applicable, by the regulatory authority.

The first patient is to be recruited by approximately July 2006. Recruitment is expected to be completed by October 2008. Investigators will be notified by AstraZeneca (or company representing AstraZeneca) when recruitment to the study has been completed.

The final PFS analysis will occur when 850 PFS events have occurred. This analysis is predicted to occur approximately 37 months after the first patient has entered the study. A final analysis of OS data is planned after 950 deaths, which is predicted to occur approximately 58 months after the first patients has entered the study.

Based on the above assumptions, the last patient is expected to have completed the study by January 2011.

# 8. ETHICS

## 8.1 Ethics review

AstraZeneca will provide IECs and Principal Investigators with safety updates/reports according to local requirements.

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to AstraZeneca before he or she can enrol any patient into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC annually, as local regulations require.

This study will be conducted under a Food and Drug Administration (FDA) Investigational New Drug (IND) at centres in the USA only, and at each centre in the USA, the Principal Investigator is also responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

## 8.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

## 8.3 Informed consent

The principal investigator(s) at each centre will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any procedure specifically for the study, including the following:

The principal investigator(s) must store the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

## 8.4 Patient data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorise the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by centre/randomisation number and initials.

The Master Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an IRB or IEC may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

# 9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

## 9.1 AstraZeneca emergency contact procedure

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. In case advice needs to be sought from the study team, contact one of the following team members:



## 9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.1.**

## 9.3 Procedures in case of overdose

Use of study medication in doses in excess of that specified in the protocol should not be recorded in the eCRF as an AE of 'Overdose' unless there are associated symptoms or signs.

- An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the eCRF.
- An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the eCRF. In addition, the

overdose should be reported on the separate AstraZeneca "Clinical Study Overdose Report Form."

- An overdose without associated symptoms should not be recorded as an AE in the eCRF. The overdose should be reported on the separate AstraZeneca "Clinical Study Overdose Report Form".

## 9.4 Procedures in case of pregnancy

### 9.4.1 Maternal exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report form.

### 9.4.2 Paternal exposure

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented. The outcomes of any conception occurring during the study must be followed up and documented.

All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report form.

# 10. REFERENCES

**Bardelli A et al 2003**
Bardelli A, Parsons DW, Silliman N, Ptak J, Szabo S, Saha S et al. Mutational analysis of the tyrosine kinome in colorectal cancers. Science 2003;300:949.

**Batchelor TT et al 2007**
Batchelor TT, Sorensen AG, di Tomaso E, Zhang W-T, Duda DG, Cohen KS. AZD2171, a Pan-VEGF receptor tyrosine kinase inhibitor, normalises tumour vasculature and alleviates edema in glioblastoma patients. Cancer Cell 2007;11:83-5.

**Bleiberg H 1999**
Bleiberg H. CPT-11 in gastrointestinal cancer. Eur J Cancer 1999;35:371-9.

**Brooks R 1996**
Brooks R. EuroQol: the current state of play. Health Policy 1996;37(1):53-72.

**Cassidy J et al 2006**
Cassidy J, Clarke S, Diaz Rubio E et al. First efficacy and safety results from XELOX-1/NO16966, a randomised 2x2 factorial phase III trial of XELOX vs FOLFOX4 plus bevacizumab or placebo in first-line metastatic colorectal cancer (MCRC). Ann Oncol 2006;17 (suppl. 9):Abstract LBA3.

**Chen E et al 2007**
Chen E, Jonker D, Gauthier I, MacLean M, Wells J, Powers J, et al. Phase I study of AZD2171 in combination with oxaliplatin and infusional 5-FU (mFOLFOX6) in patients (pts) with advanced colorectal cancer (CRC). Submitted for ECCO 14, 2007.

**De Gramont A et al 2000**
De Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000;18:2938-47.

**Dolan P 1997**
Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35(11):1095-108.

**Drevs J et al 2007**
Drevs J, Siegert P, Medinger M et al. Phase I Clinical Study of AZD2171, a highly potent oral vascular endothelial growth factor signaling inhibitor, in patients with advanced solid tumors. J Clin Oncol 2007;25:3045-54.

**Duval M et al 2003**
Duval M, Bedard-Goulet S, Delisle C, Gratton JP. Vascular endothelial growth factor dependent down regulation of flk-1/kdr involves cbl mediated ubiquitination. J Biol Chem 2003;278:20091-7.

**European Agency for the Evaluation of Medicinal Products. Bevacizumab European Public Assessment Report.**
European Agency for the Evaluation of Medicinal Products. Bevacizumab European Public Assessment Report. Available from URL: http://www.emea.eu.int/humandocs/PDFs/EPAR/avastin/17199204en6.pdf. Accessed August 2007.

**Fan F et al 2005**
Fan F, Wey JS, McCarty MF, Belcheva A, Liu W, Bauer TW et al. Expression and function of vascular endothelial growth factor receptor-1 on human colorectal cancer cells. Oncogene 2005;24(16):2647-53.

**Gail M and Simon R 1985**
Gail M, Simon R. Testing for qualitative interactions between treatment effects and patient subsets. Biometrics 1985;41:361-72.

**Giantonio BJ et al 2005**
Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP et al. High-dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200. Gastrointestinal Cancers Symposium 2005;Abstract 169a.

**Goldberg RM 2004**
Goldberg RM. Current approaches to first-line treatment of advanced colorectal cancer. Clin Colorectal Cancer 2004;4 Suppl 1:S9-15.

**Graeber TG et al 1996**
Graeber TG, Osmanian C, Jacks T, Housman DE, Koch CJ, Lowe SW et al. Hypoxia mediated selection of cells with diminished apoptotic potential in solid tumours. Nature 1996;379:88-91.

**Grothey A et al 2007**
Grothey A, Sugrue M, Hedrick E et al. Association between exposure to bevacizumab (BV) beyond first progression (BBP) and overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC): Results from a large observational study (BRiTE). J Clin Oncol 2007, ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007:Abstract 4036.

**Hecht JR et al 2005**
Hecht JR, Trarbach T, Jaeger E, Hainsworth J, Wolff R, Lloyd K et al. A randomized, double-blind, placebo-controlled, phase III study in patients (Pts) with metastatic adenocarcinoma of the colon or rectum receiving first-line chemotherapy with oxaliplatin/5-fluorouracil/leucovorin and PTK787/ZK 222584 or placebo (CONFIRM-1). 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement), 2005:Abstract 3.

**Hurwitz H et al 2004**
Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.

**Investigator's Brochure**
Investigator's Brochure AZD2171, Current Edition 2007. Note: Investigators are requested to refer to the latest version of the Investigator's Brochure, in case of any changes.

**Kabbinavar F et al 2003**
Kabbinavar F, Hurwitz HI, Fehrenbacher L et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 2003;21:60-5.

**Kind P et al 1999**
Kind P, Hardman G, Macran S. UK Population norms for EQ-5D. York Centre for Health Economics Discussion Paper 1999;Nov;172.

**Maindrault-Goebel F 2006**
Maindrault-Goebel F. Lledo G, Chibaudel B, et al. OPTIMOX2, a large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MRC). A GERCOR study. J Clin Oncol 2006; ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006:Abstract 3504.

**Mayer RJ 2000**
Mayer RJ. Moving beyond fluorouracil for colorectal cancer. N Engl J Med 2000;343:963-4.

**Morgan B et al 2003**
Morgan B, Thomas AL, Drevs J, Hennig J, Buchert M, Jivan A, et al. Dynamic contrast-enhanced magnetic resonance imaging as a biomarker for the pharmacological response of PTK787/ZK222584, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinases, in patients with advanced colorectal cancer and liver metastases: results from two phase I studies. J Clin Oncol 2003;21(21):3955-64.

**O'Brien PC and Fleming TR 1979**
O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.

**Parkin DM et al 2001**
Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94(2):153-6.

**Renner W et al 2000**
Renner W, Kotschan S, Hoffmann C, Obermayer-Pietsch B, Pilger E. A common 936 C/T mutation in the gene for vascular endothelial growth factor is associated with vascular endothelial growth factor plasma levels. J Vascular Research 2000;37:443-8.

**Roset M et al 1999**
Roset M, Badia X, Mayo NE. Sample size calculations in studies using the EuroQol 5D. Qual Life Res 1999;8(6):539-49.

**Saltz LB et al 2007a**
Saltz LB, Clark S, Diaz-Rubio E Scheithauer W, Figer A, Wong R et al. Bevacizumab in combination with XELOX or FOLFOX4: Efficacy results from XELOX-1/NO16966, a randomized phase III trial in the first-line treatment of metastatic colorectal cancer (MCRC). ASCO Gastrointestinal Cancers Symposium, Orlando 2007:Abstract 238.

**Saltz LB et al 2007b**
Saltz LB Clark S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R et al. Bevacizumab (Bev) in combination with XELOX or FOLFOX4: Updated efficacy results from XELOX-1/ NO16966, a randomized phase III trial in first-line metastatic colorectal cancer. J Clin Oncol 2007, ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007:Abstract 4028.

**Saltz LB et al 2000**
Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. New Engl J Med 2000;343:905-14.

**Semenza GL 2002**
Semenza GL. Signal transduction to hypoxia-inducible factor 1. Biochemical Pharmacology 2002;64:993-8.

**Sridhar SS et al 2007**
Sridhar SS, Hotte SJ, Mackenzie MJ, Kollmannsberger C, Haider MA, Pond GR, et al. Phase II study of the angiogenesis inhibitor AZD2171 in first-line, progressive, unresectable, advanced metastatic renal cell carcinoma (RCC): A trial of the PMH Phase II Consortium. J Clin Oncol, 2007 ASCO Annual Meeting Proceedings Part 1. Vol 25, No 18S (June 20 Supplement) 2007:Abstract 5093.

**Stevens A et al 2003**
Stevens A, Soden J, Brenchley PE, Ralph S, Ray DW. Haplotype analysis of the polymorphic human vascular endothelial growth factor gene promoter. Cancer Research 2003;63:812-6.

**Tanimoto K et al 2003**
Tanimoto K, Yoshiga K, Eguchi H, Kaneyasu M, Ukon K, Kumazaki T et al. Hypoxia-inducible factor-1α polymorphisms associated with enhanced transactivation capacity, implying clinical significance. Carcinogenesis 2003;24:1779-83.

**The EuroQol Group. 1990**
The EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199-208.

**Therasse P et al 2000**
Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J Natl Cancer Inst 2000;92(3):205-16.

**Todd S and Stallard N 2005**
Todd S, Stallard N. A New Clinical Trial Design Combining Phases 2 and 3: Sequential Designs with Treatment Selection and a Change of Endpoint. DIJ 2005;39:109-18.

**Tournigand C et al 2004**
Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. J. Clin. Oncol 2004;22:229-37.

**Ward WL et al 1999**
Ward WL, Hahn EA, Mo F, Hernandez L, Tulsky DS, Cella D. Reliability and validity of the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) quality of life instrument. Quality of Life Research 1999;8(3):181-95.

**Watson CJ et al 2000**
Watson CJ, Webb NJ, Bottomley, MJ, Brenchley PE. Identification of polymorphisms within the vascular endothelial growth factor (VEGF) gene: correlation with variation in VEGF protein production. Cytokine 2000;12:1232-5.

**Wattanapitayakul SK et al 2001**
Wattanapitayakul SK, Mihm MJ, Young AP, Bauer JA. Therapeutic implications of human endothelial nitric oxide synthase gene polymorphism. Trends Pharmacol Sci. 2001 Jul;22(7):361-8.

**Wedge SR et al 2005**
Wedge SR, Kendrew J, Hennequin LF, Valentine PJ, Barry ST, Brave SR, et al. AZD2171: A Highly Potent, Orally Bioavailable, Vascular Endothelial Growth Factor Receptor-2 Tyrosine Kinase Inhibitor for the Treatment of Cancer. Cancer Res 2005;65(10):4389-400.

**Willett CG et al 2004**
Willett CG, Boucher Y, di Tomaso E, Duda DG, Munn LL, Tong RT, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nature Medicine 2004;10:145-7.

**Yost KJ et al 2005**
Yost KJ, Cella D, Chawla A, Holmgren E, Eton DT, Ayanian JZ et al. Minimally important differences were estimated for the Functional Assessment of Cancer Therapy – Colorectal

(FACT-C) instrument using a combination of distribution- and anchor-based approaches. J. Clin Epidemiol 2005;58:1241-51.

**Yost KJ and Eton DT 2005**
Yost KJ, Eton DT. Combining distribution- and anchor-based approaches to determine minimally important differences. Evaluation and The Health Professions 2005;28:172-91.

**Yu JL et al 2002**
Yu JL, Rak JW, Coomber BL, Hicklin DJ, Kerbel RS. Effect of p53 status on tumour response to antiangiogenic therapy. Science 2002;295:1526-8.

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**Clinical Study Protocol: Appendix B**

| | |
|---|---|
| Drug Substance | AZD2171 |
| Study Code | D8480C00013 |
| Appendix Edition Number | 1.0 |
| Appendix Date | 21 November 2005 |

# Appendix B
# Additional Safety Information

# FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)



## Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

## Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious adverse event (SAE), although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

## Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These events should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous (iv) hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

# A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or, could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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| **Clinical Study Protocol: Appendix C** | |
|---|---|
| Drug Substance | AZD2171 |
| Study Code | D8480C00013 |
| Appendix Edition Number | 1.0 |
| Appendix Date | 03 February 2006 |

# Appendix C
# Objective Tumour Response Criteria (RECIST)

# 1. DEFINITION OF MEASURABLE AND NON-MEASURABLE LESIONS

**Measureable**: Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan provided reconstruction of 5 mm intervals.

**Non-measurable**: All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly non-measurable lesions.

Lesions that are considered as truly non-measurable include the following:

- Bone lesions;
- Leptomeningeal disease;
- Ascites;
- Pleural / pericardial effusion;
- Inflammatory breast disease;
- Lymphangitis cutis/pulmonis;
- Abdominal masses that are not confirmed and followed by imaging techniques;
- Cystic lesions.

Note: Lesions previously irradiated or within previous radiation treatment target volume will not be considered as measurable lesions.

# 2. METHODS OF MEASUREMENT

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

## 2.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

In the D8480C00013 (AZD2171) study, it is recommended that examinations of the chest, abdomen and pelvis will be collected as part of the scheduled RECIST assessments.

## 2.2 Clinical lesions

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

In the D8480C00013 (AZD2171) study clinical assessment will not be used as part of RECIST as CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment.

## 2.3 Chest x-ray

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

In the D8480C00013 (AZD2171) study, chest x-ray will not be used as part of RECIST as CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment.

## 2.4 Ultrasound

Ultrasound (US) should not be used to measure tumor lesions for objective response evaluation. It is however a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

As ultrasound is not appropriate for assessing objective response, it will not be used as part of the RECIST assessment in the D8480C00013 (AZD2171) study.

## 2.5 Endoscopy and laparoscopy

The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in

reference centers. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

As these methods have not been validated for assessing objective response, they will not be used as part of the RECIST assessment in the D8480C00013 (AZD2171) study.

## 2.6 Tumor markers

Tumor markers alone cannot be used to assess response.

Tumor markers, although measured in trial D8480C00013, will not contribute to the response assessment.

## 2.7 Cytology and histology

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). However, cytology and histology are not relevant to confirmation of residual benign tumors in colorectal cancer and will not be used in this context in the D8480C00013 (AZD2171) study.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Where cytology findings are not available, pleural effusion that worsens or appears, this will be considered to be progression of non-target lesions, or disease progression due to new lesions.

# 3. TUMOUR RESPONSE EVALUATION

## 3.1 Assessment of overall tumor burden and measurable disease

To assess the objective response during the study, it is necessary to estimate the overall tumour burden at baseline. Only subjects with measurable disease at baseline should be included where measurable disease is defined by the presence of at least one measurable lesion.

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

### 3.1.1 Documentation of “target” and “non-target” lesions

All measurable lesions up to a maximum of 10 lesions representative of all involved organs (maximum of 5 lesions per organ) should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions

with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD.

The longest diameter will be measured and recorded for all target lesions identified at baseline at follow-up assessments and the sum LD calculated.

If a lesion splits into two or more parts, then the sum of the LDs of those parts is recorded.

If two or more lesions merge, then the LD of the combined lesion should be recorded for one of the lesions and zero recorded for the other lesion.

If a lesion becomes to small to measure, then the size below which measurement cannot be accurately obtained should be substituted for the LD and used in the sum LD.

If a lesion cannot be measured accurately due to progression, then the maximum measurable LD should be used in the sum LD and response assessment.

If a lesion has become non measurable or evaluable for some other reason and it is not possible to assign an estimate of the longest diameter then this lesion should be excluded from response assessment.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "absent" or "present with progression" at subsequent visits.

# 4. RESPONSE CRITERIA

## 4.1 Evaluation of target lesions

| | |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions |
| Partial Response (PR) | At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD. |
| Progressive Disease (PD) | At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded (either at baseline or at previous assessment since treatment began). |
| Stable Disease (SD) | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. |

Note: Appearance of new lesions only counts towards the overall visit response, not towards the response of target or non-target lesions.

## 4.2 Evaluation of non-target lesions

| | |
|---|---|
| Complete Response (CR) | Disappearance of all non-target lesions |
| Non-Complete Response (non-CR/Non-Progression [non-PD]) | Persistence of one or more non-target lesion or/and maintenance of tumor marker level above the normal limits. |
| Progression (PD) | Unequivocal progression of existing non-target lesions. |

Note: Appearance of new lesions only counts towards the overall visit response, not towards the response of target or non-target lesions.

## 4.3 Evaluation of Overall response

### 4.3.1 Best Overall Response

The best overall response will be calculated by the sponsor.

### 4.3.2 Overall Visit Response

For each visit where tumour response evaluation assessments are performed, the sponsor will derive the overall visit response, using the algorthim shown below, based on the response of the target lesions, the non-target lesions and the presence or absence of new lesions.

| Target lesions | Non-target lesions | New lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| PR | Non-PD | No | PR |
| SD | Non-PD | No | SD |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease. See text for more details.

Note:

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to ensure "symptomatic

deterioration" subjects continue to have objective tumor assessments at withdrawal from trial and until progression is confirmed by imaging.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

# 5. CONFIRMATORY MEASUREMENT

## 5.1 Confirmation

The main goal of confirmation of objective response is to minimize the risk of overestimation of the response rate. This aspect of response evaluation is particularly important in non-randomized trials where response is the primary endpoint. In this setting, to be assigned a status of PR or CR, changes in tumor measurements must be confirmed at the next scheduled imaging visit (no less than 4 weeks after the criteria for response were first met ).

## 5.2 SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies and as such these protocols for computed tomography (CT) and magnetic resonance imaging (MRI) scanning may differ from those employed in clinical practice at various institutions. The use of standardized protocols allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

## 5.3 CT

CT scans of the thorax, abdomen and pelvis should be contiguous throughout the anatomical region of interest. As a rule of thumb, the minimum size of the lesion should be no less than double the slice thickness. Lesions smaller than this are subject to significant "partial volume" effects and such a lesion may appear to have "responded" or "progressed" on subsequent examinations, when in fact they remain the same size. This minimum lesion size for a given slice thickness at baseline ensures that any lesion appearing smaller on subsequent examinations will truly be decreasing in size.

The type of CT scanner is important regarding the slice thickness and minimum sized lesion. For spiral (helical) CT scanners, the minimum size of any given lesion at baseline may be 10 mm, provided the images are reconstructed contiguously at 5mm intervals. For conventional CT scanners, the minimum sized lesion should be 20 mm using a contiguous slice thickness of 10 mm.

The fundamental difference between spiral and conventional CT is that conventional CT acquires the information only for that particular slice thickness scanned, which is then expressed as a two dimensional representation of that thickness or volume as a gray scale image. The next slice thickness needs to be scanned before it can be imaged and so on. Spiral

CT acquires the data for the whole volume imaged, typically the whole of the thorax or upper abdomen in a single breath hold of about 20-30 seconds. To view the images, a suitable reconstruction algorithm is selected, by the machine, so the data are appropriately imaged. As suggested above, for spiral CT, 5 mm re-constructions can be made thereby allowing a minimum sized lesion of 10 mm.

Spiral CT is now the "standard" in most hospitals involved in cancer management in US, Europe and Japan, so the comments related to spiral CT are pertinent. However, some institutions involved in clinical trials will have conventional CT, but the number of these scanners will decline as they are replaced by spiral CT.

Other body parts, where CT scans are of different slice thickness, (such as the neck, which are typically of 5 mm thickness) or in the young pediatric population, where the slice thickness may be different, the minimum sized lesion allowable will be different. However, it should be double the slice thickness. The slice thickness and the minimum sized lesion should be specified in the study protocol.

In subjects in whom the abdomen and pelvis have been imaged, oral contrast agents should be given to accentuate the bowel from other soft tissue masses. This is almost universally undertaken routinely.

Intra-venous (IV) contrast agents should also be given, unless contra-indicated for medical reasons, such as allergy. This is to accentuate vascular structures from adjacent lymph node masses and to help enhance liver and other visceral metastases. Although in clinical practice its use may add little, in the context of a clinical study where objective response rate based on measurable disease is the endpoint, unless an IV contrast agent is given, a significant number of otherwise measurable lesions will not be measurable. In subjects in whom the disease is apparently restricted to the periphery of the lungs, for example, the use of IV contrast agents appears unnecessary, but the aim of a clinical study is to ensure lesions are truly resolving, and there is no evidence of new disease at other sites scanned, eg, small metastases in the liver.

The method of administration of IV contrast agents is variable. Rather than try to institute rigid rules regarding methodology of administration of contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be given such that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given subject.

All images from each examination should be included and not "selected" images of the apparent lesion. This is to ensure that if a review is undertaken, the reviewer can satisfy him/herself that no other abnormalities co-exist. All window settings should be included, particularly in the thorax where lung and soft tissue windows should be considered.

When measuring lesions, lesions should be measured on the same window setting on each examination. It is not acceptable to measure a lesion on lung windows on one examination, then on soft tissue settings on the next. In the lung, it does not really matter whether lung or

soft tissue windows are used for intra-parenchymal lesions, provided a thorough assessment of nodal and parenchymal disease has been undertaken and the target lesions are measured as appropriate using the same window settings for repeated examinations throughout the study.



## 5.4 MRI

MRI is a complex issue. MRI is entirely acceptable and capable of providing images in different anatomical planes. It is important therefore that when it is used lesions must be measured in the same anatomical plane using the same imaging sequences on subsequent examinations. MRI scanners vary in the images produced. Some of the factors involved include the magnet strength (high field magnets require shorter scan times, typically 2-5 minutes), the coil design and subject co-operation. Wherever possible, the same scanner should be used. For instance, the images provided by a 1.5T scanner will differ from those using a 0.5T scanner. Although, a comparison can be made, it is not ideal.

Moreover many subjects with advanced malignancy are in pain, so their ability to remain still for the duration of a scan sequence, in the order of 2-5 minutes is limited. Any movement during the scan time leads to motion artifacts, degradation of image quality such that the examination will probably be useless.

For these reasons, CT is at this point in time the imaging modality of choice.

The same imaging modality must be used throughout the study to measure disease. Different imaging techniques have differing sensitivities, so any given lesion may have different dimensions at any given time if measured with different modalities. It is therefore, not acceptable to interchange different modalities throughout a trial and use these measurements. It must be the same technique throughout.

## REFERENCES

Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. Journal of the National Cancer Institute. 2000;92(3):205-216

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| Clinical Study Protocol: Appendix D | |
|---|---|
| Drug Substance | AZD2171 |
| Study Code | D8480C00013 |
| Appendix Edition Number | 1.0 |
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# Appendix D
# FACT-C Quality of Life Questionnaire Including FCSI Subscale

# FACT-C (VERSION 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>**

| | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|
| **<u>PHYSICAL WELL-BEING</u>** | | | | | |
| I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP1 I have nausea | 0 | 1 | 2 | 3 | 4 |
| GP2 Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| GP3 I have pain | 0 | 1 | 2 | 3 | 4 |
| GP4 I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| GP5 I feel ill | 0 | 1 | 2 | 3 | 4 |
| GP6 I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

## SOCIAL/FAMILY WELL-BEING

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GS1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |

*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*

| | | | | | | |
|---|---|---|---|---|---|---|
| GS7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

**By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>**

## EMOTIONAL WELL-BEING

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GE1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| | I worry that my condition will get worse | 0 | 1 | 2 | 3 | 4 |

## FUNCTIONAL WELL-BEING

| | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|
| GF1 I am able to work (include work at home) | 0 | 1 | 2 | 3 | 4 |
| GF2 My work (include work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| GF3 I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| GF4 I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GF5 I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |

**By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>**



## ADDITIONAL CONCERNS

| | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|
| I have swelling or cramps in my stomach area ..... C1 | 0 | 1 | 2 | 3 | 4 |
| I am losing weight..... C2 | 0 | 1 | 2 | 3 | 4 |
| I have control of my bowels ..... C3 | 0 | 1 | 2 | 3 | 4 |
| I can digest my food well..... C4 | 0 | 1 | 2 | 3 | 4 |
| I have diarrhea ..... C5 | 0 | 1 | 2 | 3 | 4 |
| I have a good appetite ..... C6 | 0 | 1 | 2 | 3 | 4 |
| I like the appearance of my body | 0 | 1 | 2 | 3 | 4 |
| Do you have an ostomy appliance? *(Check one box)* | ☐ No | or | ☐ Yes | | |
| ***If yes**, please answer the next two items:* | | | | | |
| I am embarrassed by my ostomy appliance C8 | 0 | 1 | 2 | 3 | 4 |
| Caring for my ostomy appliance is difficult C9 | 0 | 1 | 2 | 3 | 4 |

# FCSI SYMPTOM SUBSCALE



| ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|
| GP1 I have lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP4 I have pain | 0 | 1 | 2 | 3 | 4 |
| C2 I am losing weight | 0 | 1 | 2 | 3 | 4 |
| C5 I have diarrhea | 0 | 1 | 2 | 3 | 4 |
| GP2 I have nausea | 0 | 1 | 2 | 3 | 4 |
| C1 I have swelling or cramps in my stomach area | 0 | 1 | 2 | 3 | 4 |
| C6 I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| GF3 I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| GF7 I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |

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| Clinical Study Protocol: Appendix E | |
|---|---|
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| Study Code | D8480C00013 |
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# Appendix E
# EuroQol-5 Dimension Health Status Measure

# EQ - 5D

## HEALTH QUESTIONNAIRE

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

**Mobility**

| | |
|---|---|
| I have no problems in walking about | ❑ |
| I have some problems in walking about | ❑ |
| I am confined to bed | ❑ |

**Self-Care**

| | |
|---|---|
| I have no problems with self-care | ❑ |
| I have some problems washing or dressing myself | ❑ |
| I am unable to wash or dress myself | ❑ |

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

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

**Pain/Discomfort**

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

**Anxiety/Depression**

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

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| **Clinical Study Protocol: Appendix F** | |
|---|---|
| Drug Substance | AZD2171 |
| Study Code | D8480C00013 |
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# Appendix F
# Pharmacogenetics

# PHARMACOGENETICS RESEARCH SYNOPSIS

**A Randomised, Double-blind, Multicentre Phase II/III Study to Compare the Efficacy of AZD2171 in Combination with 5-fluorouracil. Leucovorin, and Oxaliplatin (FOLFOX) to the Efficacy of Bevacizumab in Combination with FOLFOX in Patients with Previously Untreated Metastatic Colorectal Cancer**

The pharmacogenetic research described in this appendix will be submitted for regulatory approval (where applicable) and ethical approval, and implemented with the Clinical Study Protocol. All sections of the clinical study protocol apply to the pharmacogenetics research described in this appendix. This appendix details additional procedures and considerations for inclusion of patients in the pharmacogenetic component of the study.

**Study centre(s) and number of patients who may be enrolled in this genetic research**

The pharmacogenetic part of the study will be conducted in as many centres as possible that are participating in the main study.

**Objectives**

1. To obtain archival tumour samples for DNA extraction and exploratory retrospective mutational analysis of genes involved in the response to AZD2171 taken in combination with FOLFOX.

2. To obtain blood samples for DNA extraction and exploratory retrospective pharmacogenetic analysis of the response to AZD2171 taken in combination with FOLFOX.

**Study Design**

It is proposed to collect an optional blood sample and archival tumour samples for exploratory retrospective genetic analysis. Provision of blood and archival tumour samples will be optional for all patients entering the study and will involve a separate consent procedure. A patient's acceptance of this procedure will not be a requirement for his or her participation in the main study.

The archival tumour samples, blood samples and data for pharmacogenetic analysis in this study will be coded. Each sample will be labelled with study number and patient enrolment number (E-code). Only the investigator will be able to link the sample to the individual patient. The samples and data will not be labelled with a personal identifier.

DNA samples may be stored for up to 15 years after completion of the main study, after which the samples will be destroyed.

**Target Population**

All consenting patients in all centres participating in the pharmacogenetic part of the study

**Co-variables**

- Retrospective analysis of genes that may be involved in the response to AZD2171 and drugs taken in combination with AZD2171 (ie, FOLFOX), including the VEGF and KDR genes and other genes in the pathways targeted by AZD2171.

- Retrospective mutational analysis of genes that may be involved in the response to AZD2171 and drugs taken in combination with AZD2171 (ie, FOLFOX) using DNA isolated from archival tumour samples.

In addition, it is likely that additional information will become available on genes involved in the response to AZD2171 and drugs taken in combination with AZD2171 in metastatic colorectal cancer. It is, therefore, important to retain the possibility of investigating additional genes in the context of AZD2171 and drugs taken in combination with AZD2171.

**Statistical Methods**

The number of patients who will agree to participate in the pharmacogenetic component of the study is unknown. It is, therefore, not possible to establish whether sufficient data will be generated. A statistical analysis plan will be prepared where appropriate.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS FOR PHARMACOGENETICS

| Abbreviation or special term | Explanation |
|---|---|
| μm | Micrometer |
| $^{o}$C | Degrees Celsius |
| DNA | Deoxyribonucleic acid |
| EDTA | Ethylenediamine tetra-acetic acid |
| ERCC | Excision Repair Cross-Complementing |
| GSTP1 | Glutathione S-transferase P1 |
| ICH | International conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| KDR | Kinase insert domain- containing Receptor |
| LIMS | Laboratory information management system |
| mL | Millilitre |
| pCRF | Paper case record form |
| TS | Thymidylate synthase |
| VEGF | Vascular endothelial growth factor |
| XPD | Xeroderma Pigmentosum Group D |

# 1. BACKGROUND

AstraZeneca plans to include investigations into genetic variations and their effect on drug response as part of the drug development programme for all projects where it is considered to be appropriate. By using this information, the aim is to better understand the impact of genetic variation and how it can be utilised to bring better drugs to market.

To achieve this goal a systematic collection of DNA for genetic analysis (derived from blood samples taken from consenting study patients) will be implemented across a broad range of relevant clinical studies. The ability to acquire appropriate consent to collect blood samples to establish an archive and allow future meta-analysis of data derived from a number of studies for AZD2171 is of the utmost importance. This genetic research forms part of this strategy.

AZD2171 has been developed as a potent inhibitor of kinase insert domain-containing receptor (KDR), fms-like tyrosine kinase (Flt-1) and fms-like tyrosine kinase-4 (Flt-4) in vitro, and of VEGF –driven human umbilical vein endothelial cell (HUVEC) proliferation. AZD2171 is expected at chronic oral dosing to inhibit VEGF-driven angiogenesis and, as a consequence, constrain tumour growth. Since angiogenesis is necessary for the growth and metastasis of most tumours and VEGF is believed to have a pivotal role in this process, AZD2171 treatment may have broad-spectrum clinical utility.

To investigate the relationship between blood and tumour biomarkers and clinical efficacy and tolerability, pharmacogenetic analysis will be performed on samples from patients who have given informed consent. It is proposed that initial analysis should focus on variants of genes in the pathways targeted by AZD2171 but the scope of the informed consent will allow the analysis of additional genes. In addition to *kdr/flk-1*, the target of AZD2171, genes in this pathway encode proteins that are either biomarkers themselves (VEGF-A) or regulate the expression of biomarkers themselves (HIF1$\alpha$, microvessel density). Knowledge of variation in these genes will assist in the interpretation of biomarker data. Genes regulated by this pathway also include candidates for genetic factors predisposing to the development of hypertension in response to anti-angiogenic therapy.

Genes associated with the response to FOLFOX therapy have recently been described (Stoehlmacher et al, 2004). Variants of the XPD, ERCC1, GSTP1 and TS genes were associated with improved survival and delayed time to progression in patients with colorectal cancer treated with FOLFOX.

Somatic mutations in the tyrosine kinase domain of *kdr/flk-1* have been described in colorectal tumours (Bardelli et al, 2003). There are no data on the functional consequences of these mutations but one of the mutations would result in a truncated protein.

Retrospective analysis of p53 mutation status may assist in the classification of tumours likely to respond to anti-angiogenic therapy. The frequency of p53 mutations varies with tumour type and mutations leading to inactivation of wild type p53 tumour suppressor gene may render cells less susceptible to apoptosis induce by hypoxic stress (Graeber et al 1996).

## 1.1 Rationale for genetic research

AstraZeneca intends to apply pharmacogenetics to the AZD2171 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD2171.

# 2. GENETIC RESEARCH OBJECTIVES

## 2.1 Archival tumour tissue samples

Genes that may be investigated include:

- Retrospective mutational analysis of the KDR gene and other genes (ie, k-ras, p53) in slides, sections or blocks of archival tumour samples

In addition to above named genes, which it is believed may influence therapeutic response to AZD2171 and drugs taken in combination with AZD2171, it is likely that additional information on other genes important for this drug and for the response to AZD2171 in metastatic colorectal cancer for which the drug is being developed will become available in the future. It is, therefore, important to retain the possibility of investigating additional genes in the context of AZD2171 and drugs taken in combination with AZD2171.

## 2.2 Blood sample

Genes that may be investigated include:

- Retrospective genotyping of the VEGF and KDR genes and other genes in pathways targeted by AZD2171 and drugs taken in combination with AZD2171 (ie, FOLFOX).

In addition to above named genes, which it is believed may influence therapeutic response to AZD2171 and drugs taken in combination with AZD2171, it is likely that additional information on other genes important for this drug and for the response to AZD2171 in metastatic colorectal cancer for which the drug is being developed will become available in the future. It is, therefore, important to retain the possibility of investigating additional genes in the context of AZD2171 and drugs taken in combination with AZD2171.

# 3. GENETIC RESEARCH PLAN AND PROCEDURES

## 3.1 Genetic research plan

This appendix to the Clinical Study Protocol has been subjected to peer review according to AstraZeneca standard procedures.

The patient will be asked to participate in this pharmacogenetic component. If the patient agrees to participate, archival tumour samples will be collected from patients who allow consent for their samples to be used for pharmacogenetic analysis. A 9 mL ethylenediaminetetra-acetic acid (EDTA) blood sample will also be collected prior to dosing with AZD2171.

## 3.2 Selection of genetic research population

### 3.2.1 Study selection record

All patients at centres participating in the pharmacogenetic part of this study will be asked to participate in the genetic research. Participation in this genetic component of the clinical study is voluntary and if a patient declines to participate in the genetic research component of the study there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in the main body of the clinical study protocol.

### 3.2.2 Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the study protocol **and:**

- Provide informed consent for the genetic sampling and analyses

### 3.2.3 Exclusion criteria

Not applicable

### 3.2.4 Discontinuation of patients from this genetic research

#### 3.2.4.1 Criteria for discontinuation

Specific reasons for discontinuing a patient from this genetic research are:

- Withdrawal of consent for genetic research. Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment.

#### 3.2.4.2 Procedures for discontinuation

Patients who discontinue from the main study should always be asked specifically whether they are withdrawing or continuing their consent for this genetic research. It must be established whether the patient:

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic research in the future.

- Withdraws consent for the sample to be kept for genetic research in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The Principal Investigator is responsible for providing written notification to AstraZeneca of any patient who has withdrawn consent for the use of the sample taken for genetic research. AstraZeneca will provide written confirmation to the investigator of the actions taken with the sample, which must be filed in the Investigator Study File.

# 4. GENETIC MEASUREMENTS AND CO-VARIABLES

## 4.1 Summary of genetics objectives and analysis

The purpose of this genetic research is to generate data for use in future retrospective analyses. Future analyses will explore genetic factors that may influence the response to AZD2171 taken in combination with FOLFOX in metastatic colorectal adenocarcinoma in this study. The results of this genetic research will not form part of the clinical study report for this study. The results may be pooled with genetic data from other studies on AZD2171 to generate hypotheses to be tested in future studies.

## 4.2 Collection of samples for genetic research

### 4.2.1 Archival tumour samples

Patients will be asked to provide consent for AstraZeneca to collect and analyse sample(s) of their archival tumour material.

The Principal Investigator will be asked to provide one of the following for each consenting patient, depending on which format is more convenient:

- Six re-cut sections from a formalin-fixed paraffin-embedded tumour tissue block, presented on slides, including 1 stained with haematoxylin and eosin. Each section to be 20 μm thick.

or

- Six re-cut sections from a tumour tissue block, presented in an Eppendorf tube, all unstained. Each section to be 20 μm thick

or

- Formalin-fixed, paraffin-embedded tumour tissue blocks.

Samples will be labelled with the protocol study number, centre number, patient enrolment number (E-code), sample ID and date of sample preparation. No personal identifiers (patient name, initials, or date of birth) will be placed on the tube or accompanying documentation. A record of the date of consent to the genetic research, the date the archival samples were obtained, and the sample site (primary or metastatic, and if metastatic, which site) will be recorded. A copy of the record should accompany the shipment and a duplicate retained at the site for monitoring.

### 4.2.2 Blood sample

A single venous blood sample (10 mL) will be collected into a polypropylene tube containing EDTA and gently inverted a minimum of 5 times to mix thoroughly. Tubes will be labelled with the protocol study number, centre number, patient enrolment number (E-code) and date of sample collection. No personal identifiers (patient name, initials, or date of birth) will be placed on the tube or accompanying documentation. A record of the date of consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the paper case record form (pCRF).

Genotype is a stable parameter, therefore if for any reason the blood sample is not drawn at visit 2, it may be taken at any study visit until the last study visit. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

### 4.2.3 Sample processing and shipping

Tumour samples will be transferred at ambient temperature to AstraZeneca or its designee for analysis. Where possible, samples should be shipped in batches and shipment will be coordinated with the receiving laboratory to ensure that samples arrive within working hours, on normal working days. A record of the date of the patient consent, protocol study number, centre number, sample site, enrolment code and date and time of sample collection, should accompany the shipment.

Blood samples will be stored frozen (-20$^{o}$C or below) at the site and sent to AstraZeneca or its designee for DNA extraction. Samples must remain frozen at all times. Alternatively, if samples can be transferred to the DNA extraction laboratory within 48

hours of collection, it is acceptable to refrigerate the samples (+4$^{o}$C or below) and transport them to the relevant DNA extraction laboratory on wet ice or equivalent.

### 4.2.4 Storage and coding of DNA samples

The processes adapted for the coding and storage of samples for pharmacogenetic analysis are important to maintain patient confidentiality.

For all samples irrespective of the type of coding used, the DNA will be extracted from the tumour and blood samples. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will be used to identify the sample and corresponding data at the AstraZeneca pharmacogenetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any AstraZeneca employee working with the DNA.

The tumour and blood samples and data for pharmacogenetic analysis in this study will be coded. Each sample will be labelled with the study number and patient enrolment number (E-code). Only the investigator will be able to link the tumour sample to the individual patient. The sample and data will not be labelled with a personal identifier.

All DNA samples will be stored under secure conditions with restricted access at AstraZeneca or the contracted laboratory. The tumour, DNA samples or date derived from the samples may be made available to groups or organisations working with AstraZeneca on this study or as part of the drug development project. However, the samples and any results will remain the property of AstraZeneca at all times. AstraZeneca will not give tumour, blood or DNA samples or data derived from the samples to any other parties, except as required by law.

# 5. MANAGEMENT OF GENETIC RESEARCH DATA

Only the date the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded on the pCRF and in AstraZeneca's Clinical Study database (AMOS). The genotypic data will not be merged with the clinical dataset collected from the patient population for statistical analysis. The genotypic data generated from the study will be stored in the AstraZeneca Laboratory Information Management System (LIMS) database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the dataset from the main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis.

## 5.1 Reporting of genotypic results

Results from any pharmacogenetic research performed will be reported separately from the clinical study report. AstraZeneca will not provide individual results to patients, their

family members, any insurance company, an employer, clinical study investigator, general physician or any other third party, unless required to do so by law. The patient's tumour or blood DNA will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

# 6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of patients who will agree to participate in the genetic research is unknown. It is, therefore, not possible to establish whether a statistically relevant number of patients will consent to provide sufficient data to be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

# 7. STUDY MANAGEMENT

## 7.1 Monitoring

Before first patient entry into the study, a representative of AstraZeneca will visit the investigational study site. In addition to the requirements described in the main study, this genetic research will be discussed.

During the study, a representative of AstraZeneca will have regular contacts with the investigational site. One of the purposes of these visits will be to perform source verification of the genetic consent of participating patients and to ensure that the investigational team are adhering to the specific requirements of this genetic research.

## 7.2 Training of staff

Before the first patient is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA and genetic research with a representative of AstraZeneca. The ethical considerations specific to genotyping and the importance of the informed consent process will be made clear. The requirements for the collections of the patient's sample will also be made clear.

## 7.3 Changes to the protocol

Any changes to the genetic research will comply with the principles described in Section 7 of the main body of the protocol.

## 7.4 Study Agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail. Specific reference to requirements relating to this genetic research will be included in the study agreement(s).

# 8. ETHICS

## 8.1 Ethics Review

In addition to documenting Institutional Review Board/ Independent Ethics Committee (IRB/IEC) approval of the main study, approval must be obtained for this genetic research and the associated genetic informed consent from the relevant IRB or IEC. It must be clearly stated in the approval that this genetic research is approved. The investigator must submit written approval to AstraZeneca before any patient participates in this genetic research.

## 8.2 Ethical conduct of the study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation of Good Clinical Practice (ICH-GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics.

For studies including genetic analysis special precautions are taken as described in Section 4.2.4 of this Appendix.

## 8.3 Informed Consent

The pharmacogenetic component of this study is optional and the patient may participate in other components of the study without participating in the pharmacogenetic component. To participate in the pharmacogenetic component of the study, the patient or legal representative must sign and date a separate informed consent form (see Section 10). Copies of signed and dated consent forms must be given to the patient or legal representative and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient or legal representative understands that they may freely discontinue the pharmacogenetic aspect of the study at any time.

## 8.4 Patient data protection

All data protection and confidentiality principles, described in the main study protocol, are applicable to this genetic research.

Reference to participation in this genetic research should not be recorded into the patient's general medical record. All notes should be kept within the clinical study records.

Due to the exploratory nature of this genetic research, there will be no routine communication of results to patients. AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient; however, it must be recognised that there are exceptional circumstances where individuals may see both genetic data and a patients personal identifier, for example in the case of a medical emergency, when AstraZeneca physicians and investigators might know the patient's identity and might have access to the genetic data, or during regulatory audit where designated authorities must be permitted access to the relevant files.

# 9. REFERENCES

Bardelli A, Parsons DW, Silliman N, Ptak J, Szabo S, Saha S et al. Mutational analysis of the tyrosine kinome in colorectal cancers. Science 2003; 300: 949.

Graeber TG, Osmanian C, Jacks T, Housman DE, Koch CJ, Lowe SW et al. Hypoxia mediated selection of cells with diminished apoptotic potential in solid tumours. Nature 1996; 379:88-91.

Stoehlmacher J, Park DJ, Zhang W, Yang D, Groshen S, Zahedy S et al. A multivariate analysis of genomic polymorphisms: prediction of clinical outcome to 5FU/oxaliplatin chemotherapy in refractory colorectal cancer. British Journal of Cancer 2004; 91:344-354.

# 10. INFORMED CONSENT

## 10.1 Informed Consent for the US

## Genetic Research Addendum to Informed Consent Form for use in the US

Subject Initials: << >> Enrolment code: << >>

Study Title: **A Randomised, Double-blind, Multicentre Phase II/III Study to Compare the Efficacy of AZD2171 in Combination with 5-fluorouracil, Leucovorin and Oxaliplatin (FOLFOX) to the Efficacy of Bevacizumab in Combination with FOLFOX in Patients with Previously Untreated Metastatic Colorectal Cancer**

**An optional part of this study involves the collection of a blood sample from you for genetic (DNA) research.**

**Section 1. What is the Background to and Purpose of the Genetic Research?**

Cells in your body contain a type of molecule called deoxyribonucleic acid, or DNA for short. DNA is what your genes are made of. Genes are inherited and direct growth, development, and how the body functions. For example, some genes control the colour of your hair or eyes. Scientists have learned a lot about how genes work. There are many differences, or variations, in DNA from one person to another. These variations may affect a person's chance of suffering from a particular disease or the way a person responds to a particular drug. You are being asked to donate a blood sample, and a sample of your tumour tissue, for genetic research that will determine part of the structure of your DNA and enable us compare it to medical information about you. You are being asked to do this because you are already taking part in **A Randomised, Double-blind, Multicentre Phase II/III Study to Compare the Efficacy of AZD2171 in Combination with 5-fluorouracil, Leucovorin and Oxaliplatin (FOLFOX) to the Efficacy of Bevacizumab in Combination with FOLFOX in Patients with Previously Untreated Metastatic Colorectal Cancer,**

which we will call "the main study" in the rest of this document. We will use the words "this genetic research" for the genetic research we are now asking you to take part in.

We are asking you and other patients participating in the main study to donate a blood sample and a sample of your tumour tissue because we want to study how genetic variations may influence the way people respond to AZD2171 when taken in combination with 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX).We will not use the blood sample you donate for other purposes.

The purpose of this genetic research is not to provide you with test results. The study sponsor (AstraZeneca) will not make any results available to you, any insurance company, your employer, your family, the study doctor, or any other physician who treats you now or in the future. You should be aware that the study sponsor has no obligation to conduct this genetic research, or any additional research on your blood or tumour sample or DNA.

**Section 2. Study Procedure**

If you decide to donate part of your tumour sample, we will contact the pathologist where your sample is kept and ask them to send part of your sample to a laboratory

If you decide to donate a sample, we will draw about 2 teaspoons (10 ml) of blood from you at your second visit. DNA will be extracted from your blood sample. In this process, most of the original blood sample will be used up but a small amount will be kept as a "backup" in case of problems in the testing of your DNA.

The DNA sample and the remaining tumour and blood sample will be stored with similar samples from other people at a secure central laboratory owned by AstraZeneca and located within the European Union. DNA and blood samples from this genetic research will be destroyed 15 years after the main study is completed. Your DNA may be studied at any time before this. The pattern of variations in your DNA may be compared with medical information collected in the main study, but only as this information relates to the research goals described above. The results from this genetic research may be analyzed along with results from other research.

**Section 3. Risks and Inconveniences**

These are no different from those experienced by you in having blood taken in the main study. There are no additional tests or assessments that you will be asked to take part in. The tumour sample needed will be cut from your tumour sample already taken and stored at the hospital as part of your original diagnosis and the blood sample will be drawn from you as part of this main study and does not involve a separate procedure. You will only be asked to sign this consent form, which shows that you have agreed to your samples being collected, stored and tested.

**Section 4. Possible Benefits**

There is no direct benefit to you in taking part in this genetic research. However, this research may contribute to our understanding of the treatment of metastatic colorectal cancer, and may eventually lead to improvements in treatment.

**Section 5. Taking Part is Voluntary**

It is up to you whether to donate a sample for genetic research or not. You may refuse to donate a sample at any time without penalty or loss of benefits to which you are otherwise entitled. You will receive the same treatment and care in the main study whether or not you donate your tumour and blood samples for genetic research as described in this document. **If you decide not to donate a sample, you can still take part in the main study**.

## Section 6. No Payment for Taking Part

You will not be paid for donating a sample for use in this genetic research.

## Section 7. Rights to the Results of Genetic Research

Any information derived directly or indirectly from this genetic research, as well as any patents, diagnostic tests, drugs, or biological products developed directly or indirectly as a result of this genetic research, are the sole property of the study sponsor (and its successors, licensees, and assigns) and may be used for commercial purposes. You have no right to this property or to any share of the profits that may be earned directly or indirectly as a result of this genetic research. However, in signing this form and donating part of your tumour samples and giving a blood sample for genetic research, you do not give up any rights that you would otherwise have as a participant in research.

## Section 8. Confidentiality and Authorization to Collect, Use and Disclose Your Protected Information

In this section ("the Authorization") you are being asked for permission to use and share certain information about you so that the genetic research described in this document may be carried out. This section describes:

- how your protected information will be collected, used, and shared with certain other persons involved in this genetic research,
- how your confidentiality will be protected,
- your rights.

### What is Your "Protected Information"?

In a file at the study site, the code number used to label your tumour and blood sample will be recorded next to your name. For this reason, information obtained from your tumour and blood sample, including the results of research on your DNA, are considered protected information. Special precautions will therefore be taken to ensure that the genetic research described in this document will be carried out with a very high degree of confidentiality.

### Will Anyone be Able to Identify You?

Your tumour sample and blood sample will not be labelled with your name but, as mentioned above, only with the same code that is given to you in the main study. As an added level of security, your DNA, when it is extracted from your tumour sample and blood sample and the results of any research on your DNA will receive a second code number. A file linking the first and second codes will be kept in a secure place at AstraZeneca with restricted access. If you change your mind about participating in this genetic research, this link will allow us to locate your samples and destroy them. The link will be destroyed 15 years after the main study is completed, at the same time that your DNA sample and any remaining tumour and blood are destroyed.

The coding of samples and results is to ensure that genetic research results are kept confidential by keeping your identity and these results separate. Very few people will be able to connect your identity and the results of research on your DNA, and only for special reasons. If there should be a medical emergency, an AstraZeneca doctor whose job it is to find out what caused the problem might know your identity and might also have access to the results of research on your DNA. AstraZeneca staff whose job it is to make sure the research has been done properly by checking the records at the study doctor's site, will also be able to identify you from your medical files but will not have access to the results of this genetic research. Apart from these persons, other research staff at AstraZeneca will not know your identity. Regulatory authorities, who also may wish to check that this genetic research has been done properly, will also have access to your files and know your identity.

The data and results of this genetic research may be reviewed with collaborators and published. Neither your name nor any other information that identifies you personally will appear in any publications or reports.

**Use and Disclosure of Your Protected Information**

If you sign this form and donate a tumour sample and a blood sample, you allow the study doctor to use your protected information to carry out the genetic research described in this document. As noted above, there are special precautions taken to ensure that persons looking at the results of research on your DNA should not be able to identify you personally. Subject to those precautions, the study doctor may nonetheless share your protected information with:

- the study sponsor, including its affiliates, its representatives, and its contractors who work on behalf of the study sponsor to carry out this genetic research;
- other doctors and health care professionals who are involved in this genetic research;
- the Institutional Review Board (IRB) that watches over the main study; and
- government agencies overseeing this genetic research.

The blood samples that are donated to the study sponsor, and the DNA prepared from them, will not be given or sold to anyone else, nor will they be used for purposes other than the genetic research described in this document.

**Notice on Redisclosure of Protected Information**

The study doctor can only share your protected information with persons whom you have permitted to see it, and only in the ways you have permitted. However, if you sign this form those persons may share your protected information with other persons. Federal law does not protect you against this, but the laws of your state may provide additional protection. However, the study sponsor will only share your protected information with its and its affiliates' staff involved in this genetic research and with the persons whom you permit to receive it under this form.

## Section 9. Withdrawing your Consent and Authorization

You may withdraw your consent to the use of your sample in genetic research at any time. If you withdraw your consent **before** your tumour sample and blood sample are sent for genetic research, the study doctor will arrange to have them destroyed. If you withdraw your consent **after** your tumour sample and blood sample have been sent for genetic research the study sponsor and the study doctor will ensure that your tumour sample and blood sample and any DNA that has been extracted from them are destroyed. However, if genetic research has already been performed the study sponsor is not obliged to destroy results of this research.

You may withdraw your Authorization (permission) regarding the use and disclosure of your protected information at any time by writing to the study doctor at the following address: <<>>. If you withdraw this Authorization, the study doctor will no longer use your protected information or share it with others under the Authorization for this genetic research, unless the study doctor needs to do so to protect the research results. However, the study sponsor may still use information about you that was shared with the study sponsor before you withdrew your Authorization.

If you withdraw your Authorization, you can continue to take part in the main study unless you withdraw your Authorization for the main study.

### Expiration of Your Authorization

In signing this form, you authorize the use and disclosure of your protected information as necessary to carry out the genetic research described in this document. Your Authorization will expire 15 years after the main study is completed.

## Section 10. Whom to Ask if You Have Questions

If you have questions about donating a sample, any study-related injury, or your rights as a subject, you may contact the personnel identified in the main study form.

## Section 11. Informed Consent Statement and Authorization

I, _____ (name of subject), have read and I understand all the information in this informed consent and authorization form. I have been given the chance to discuss it and ask questions. All my questions have been answered to my satisfaction. I voluntarily consent to take part in this genetic research. I understand I will receive a copy of this informed consent and authorization form.

By signing this informed consent and authorization form, I have not given up any of the legal rights, which I otherwise would have as a subject in a research study. I authorize the collection, use and disclosure of my personal information in accordance with this form.

## Section 11. Informed Consent Statement and Authorization

I, _____ (name of subject), have read and I understand all the information in this informed consent and authorization form. I have been given the chance to discuss it and ask questions. All my questions have been answered to my satisfaction. I voluntarily consent to

take part in this genetic study. I understand I will receive a copy of this informed consent and authorization form.

By signing this informed consent and authorization form, I have not given up any of the legal rights, which I otherwise would have as a subject in a research study. I authorize the collection, use and disclosure of my medical information in accordance with this form.

| _____ | _____ |
|---|---|
| Signature of Subject | Date of Signature |

_____
Printed name of Subject

_____
Name of Patient's Legally Authorized Representative (If Applicable) (Please Print)

| _____ | _____ |
|---|---|
| Authority of Representative To Act For Patient (If Applicable) | Date of Signature |

| _____ | _____ |
|---|---|
| Signature of Person Administering this Consent | Date |

_____
Printed Name of Person
Administering this Consent

I do not consent to provide a blood sample under the conditions described in this section.

| _____ | _____ | _____ |
|---|---|---|
| Printed Name | Signature | Date |

| _____ | _____ | _____ |
|---|---|---|
| Printed Name of Person Administering this Consent | Signature of Person Administering this Consent | Date |

## 10.2 Informed Consent for the Rest of World

# GENETIC RESEARCH ADDENDUM TO INFORMED CONSENT FORM FOR USE GLOBALLY (EXCEPT IN THE US)

Study Code: D8480C00013 Subject Initials: << >>

Centre No: << >> Enrolment code and/or randomisation code: << >>

Study Title: **A Randomised, Double-blind, Multicentre Phase II/III Study to Compare the Efficacy of AZD2171 in Combination with 5-fluorouracil, Leucovorin and Oxaliplatin (FOLFOX), to the Efficacy of Bevacizumab in Combination with FOLFOX in Patients with Previously Untreated Metastatic Colorectal Cancer**

**An optional part of this study involves the collection of a blood sample, and a sample of your tumour tissue, from you for genetic (DNA) research.**

**What is the Background to and Purpose of the Genetic Research?**

Cells in your body contain a type of molecule called deoxyribonucleic acid, or DNA for short. DNA is what your genes are made of. Genes are inherited and direct growth, development, and how the body functions. For example, some genes control the colour of your hair or eyes. Scientists have learned a lot about how genes work. There are many differences, or variations, in DNA from one person to another. These variations may affect a person's chance of suffering from a particular disease or the way a person responds to a particular drug. You are being asked to donate a blood sample for genetic research that will determine part of the structure of your DNA and to allow us to compare it with medical information about you. You are being asked to do this because you are already taking part in a clinical study for metastatic colorectal cancer (known as D8480C00013), which we will call "the main study" in the rest of this document. We will use the words "this genetic study" for the genetic research we are now asking you to take part in.

We are asking you and other patients participating in the main study to donate a blood sample and a sample of your archived tumour tissue because we want to study how genetic variation may influence the way people respond

You should be aware that the study sponsor has no obligation to conduct this research, or any additional research on your blood sample or DNA.

**What will Happen to me if I take Part?**

If you decide to donate part of your tumour sample, we will contact the pathologist where your sample is kept and ask them to send part of your sample to a laboratory.

If you decide to take part, we will draw about 2 teaspoons (10 ml) of blood from you at your second visit. DNA will be extracted from your blood sample. In this process, most of the original blood sample will be used up but a small amount will be kept as a "backup" in case of problems in the testing of your DNA.

The DNA sample and the remaining tumour and blood sample will be stored with similar samples from other people at a secure central laboratory owned by AstraZeneca and located within the European Union. All DNA and blood samples from this genetic study will be destroyed 15 years after the main study is completed. Your DNA may be studied at any time before this. The pattern of variations in your DNA may be compared with medical information collected in the main study, but only as this information relates to the research goals described above. The research results from this genetic study may be analysed along with results from other research.

**What are the Possible Risks and Inconveniences of Taking Part?**

These are no different from those experienced by you in having blood taken in the main study. There are no additional tests or assessments that you will be asked to take part in. The tumour sample needed will be cut from your tumour sample already taken and stored at the hospital as part of your original diagnosis and the blood sample will be drawn from you as part of the main study and does not involve a separate procedure. You will only be asked to sign this consent form which shows that you have agreed to your samples being collected, stored and tested.

**What are the Possible Benefits of Taking Part?**

There is no direct benefit to you in taking part in this research. However, this research may contribute to our understanding of the treatment of metastatic colorectal cancer, and may eventually lead to improvements in treatment.

**Do I have to Take Part?**

It is up to you whether to take part in this study or not. You may refuse to take part or stop taking part in this genetic study at any time without penalty or loss of benefits to which you are otherwise entitled. You will receive the same treatment and care in the main study whether or not you donate a blood sample for genetic research as described in this document. **If you decide not to donate a sample, you can still take part in the main study**.

**Do I Receive a Payment for Taking Part?**

You will not be paid for taking part in this genetic study.

**What Rights do I have to see the Results of the Genetic Research and Personal Data?**

The purpose of this genetic study is not to provide you with test results. The study sponsor (AstraZeneca) will not make any results available to you, any insurance company, your employer, your family, the study doctor, or any other physician who treats you now or in the future.

You have the right to request information about any personal data that the Study Doctor or the Sponsoring Company may hold about you. You also have the right to request that any inaccuracies in your personal data be corrected. If you wish to make a request, then please contact the Study Doctor in the first instance, who can help you contact the Sponsoring Company if necessary. The Sponsoring Company may transfer your Study Data to countries outside the European Union for these purposes and for providing data to regulatory authorities.

**What Rights Do I have to the Results of the Genetic Research?**

Any information derived directly or indirectly from this genetic study, as well as any, patents, diagnostic tests, drugs, or biological products developed directly or indirectly as a result of this study, are the sole property of the study sponsor (and its successors, licensees, and assigns) and may be used for commercial purposes. You have no right to this property or to any share of the profits that may be earned directly or indirectly as a result of this study. However, in signing this form and donating a blood sample for genetic research, you do not give up any rights that you would otherwise have as a participant in a research study.

**What Steps are Taken to Ensure the Genetic Results are Kept Confidential?**

Special precautions are taken to ensure that the research in this genetic study will be carried out with a very high degree of confidentiality. Your tumour sample and blood sample will be labelled with the same code that is given to you in the main study, but not with personal identifiers such as your name. As an added level of security, your DNA when it is extracted from your tumour and blood samples, and the results of any research on your DNA will also receive a second code number. A file linking the first and second codes will be kept in a secure place at AstraZeneca with restricted access. If you change your mind about participating in this genetic research, this link will allow us to locate your sample and destroy it. The link will be destroyed 15 years after the main study is completed, at the same time that your DNA sample and any remaining blood are destroyed.

The coding of samples and results is to ensure that genetic research results are kept confidential by keeping your identity and these results separate. Very few people will be able to connect your identity and the results of research on your DNA, and only for special reasons. If there should be a medical emergency, an AstraZeneca doctor whose job it is to find out what caused the problem might know your identity and might also have access to the results of research on your DNA. AstraZeneca staff whose job it is to make sure the study has been done properly by checking the records at the study doctor's site, will also be able to identify you from your medical files but will not have access to the results of the genetic research in this study. Apart from these persons, other research staff at AstraZeneca will not know your identity. Regulatory authorities, which also may wish to check that the study has been done properly, will also have access to your files and know your identity.

The data and results of this genetic study may be reviewed with collaborators and published. Neither your name nor any other personal identifiers will appear in any publications or reports.

## Can I Withdraw my Consent?

You may withdraw your consent at any time. If you withdraw your consent **before** your tumour and blood samples are sent for genetic research, the study doctor will arrange to have them destroyed. If you withdraw your consent **after** your blood sample has been sent for genetic research the study sponsor and the study doctor will ensure that your tumour and blood samples and any DNA that has been extracted from them are destroyed. However, if genetic research has already been performed the study sponsor is not obliged to destroy results of this research. In this case, only the tumour and blood samples and any DNA extracted will be destroyed.

## Whom Should I Contact If I Need more Information or Help?

If you have questions about donating a sample, any study-related injury, or your rights as a subject, you may contact the personnel identified in the main study form.

**Informed Consent Statement**

I, _____ (name of subject), have read and I understand all the information in this informed consent. I have been given the chance to discuss it and ask questions. All my questions have been answered to my satisfaction. I voluntarily consent to take part in this genetic study. I understand I will receive a copy of this informed consent.

By signing this informed consent, I have not given up any of the legal rights, which I otherwise would have as a subject in a research study. I authorise the collection, use and disclosure of my medical information in accordance with this form.

_____ _____
Signature of Subject Date of Signature

_____
Printed name of Subject

_____
Name of Patient's Legally Authorised Representative (If Applicable) (Please Print)

_____ _____
Authority of Representative Date of Signature
To Act For Patient (If Applicable)

_____ _____
Signature of Person Date
Administering this Consent

_____
Printed Name of Person
Administering this Consent

I do not consent to provide a blood sample under the conditions described in this section.

_____ _____ _____
Printed Name Signature Date

_____ _____ _____
Printed Name of Person Signature of Person Date
Administering this Consent Administering this Consent

AstraZeneca

| **Clinical Study Protocol Appendix G** | |
|---|---|
| Drug Substance | Cediranib (RECENTIN, AZD2171) |
| Study Code | D8480C00013 |
| Appendix Edition Number | 01 |
| Appendix Date | 07 September 2007 |

# Appendix G
# Summary of Product Characteristics

# 1. SUMMARY OF PRODUCT CHARACTERISTICS FOR AVASTIN

Accessed September 2007:

http://www.emea.europa.eu/humandocs/PDFs/EPAR/avastin/H-582-PI-en.pdf

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Avastin 25 mg/ml concentrate for solution for infusion.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bevacizumab 25 mg per ml. Each vial contains 100 mg of bevacizumab in 4 ml and 400 mg in 16 ml respectively.

Bevacizumab is a recombinant humanised monoclonal antibody produced by DNA technology in Chinese Hamster ovary cells.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear to slightly opalescent, colourless to pale brown liquid.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Avastin (bevacizumab) in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

Avastin in combination with paclitaxel is indicated for first-line treatment of patients with metastatic breast cancer.

### 4.2 Posology and method of administration

**General**

Avastin must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

It is recommended that treatment be continued until progression of the underlying disease.

The initial dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30-minutes.

The initial dose should be administered following chemotherapy, all subsequent doses can be given before or after chemotherapy.

Do not administer as an intravenous push or bolus.

Instructions for the preparation of Avastin infusions are described in section 6.6. Avastin infusions should not be administered or mixed with glucose solutions (see section 6.2).

**Metastatic carcinoma of the colon or rectum (mCRC)**

The recommended dose of Avastin is 5 mg/kg of body weight given once every 14 days as an intravenous infusion. Dose reduction for adverse events is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended as described in section 4.4.

**Metastatic breast cancer (mBC)**

The recommended dose of Avastin is 10 mg/kg given once every 2 weeks or 15 mg/kg given once every 3 weeks as an intravenous infusion.

*Special populations*

*Children and Adolescents:* The safety and efficacy in children and adolescents have not been studied. Avastin is not recommended for use in children and adolescents due to a lack of data on safety and efficacy (see section 5.3).

*Elderly:* No dose adjustment is required in the elderly.

*Renal impairment*: The safety and efficacy have not been studied in patients with renal impairment.

*Hepatic impairment*: The safety and efficacy have not been studied in patients with hepatic impairment.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to Chinese hamster ovary (CHO) cell products or other recombinant human or humanised antibodies.
- Pregnancy (see section 4.6).
- Avastin is contraindicated in patients with untreated CNS metastases (see sections 4.4 and 4.8).

## 4.4 Special warnings and precautions for use

*Gastrointestinal perforations* (see section 4.8)
Patients may be at an increased risk for the development of gastrointestinal perforation when treated with Avastin. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.

*Wound Healing Complications* (see section 4.8)
Avastin may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery.

*Hypertension* (see section 4.8)
An increased incidence of hypertension was observed in Avastin-treated patients. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. There is no information on the effect of Avastin in patients with uncontrolled hypertension at the time of initiating therapy. Therefore, caution should be exercised before initiating therapy in these patients. Monitoring of blood pressure is generally recommended during therapy.

In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. Avastin should be permanently

discontinued, if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.

*Reversible Posterior Leukoencephalopathy Syndrome (RPLS)* (see section 4.8)
There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of RPLS requires confirmation by brain imaging. In patients developing RPLS, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of Avastin. The safety of reinitiating Avastin therapy in patients previously experiencing RPLS is not known.

*Proteinuria* (see section 4.8)
Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with Avastin. There is evidence suggesting that Grade 1 [US National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0] proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Therapy should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome).

*Arterial Thromboembolism* (see section 4.8)
In five randomised clinical trials, the incidence of arterial thromboembolic events including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) was higher in patients receiving Avastin in combination with chemotherapy compared to those who received chemotherapy alone.

Patients, receiving Avastin plus chemotherapy, with a history of arterial thromboembolism or age greater than 65 years have an increased risk of developing arterial thromboembolic events during therapy. Caution should be taken when treating these patients with Avastin.

Therapy should be permanently discontinued in patients who develop arterial thromboembolic events.

*Haemorrhage*
The risk of CNS haemorrhage in patients with CNS metastases receiving Avastin could not be fully evaluated, as these patients were excluded from clinical trials. Thus, Avastin should not be used in these patients (see sections 4.3 and 4.8).

Patients treated with Avastin might have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Avastin should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during Avastin therapy (see section 4.8).

There is no information on the safety profile of Avastin in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting Avastin treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of serious bleeding when treated with a full dose of warfarin and Avastin concomitantly.

*Pulmonary Haemorrhage/Haemoptysis*
Patients with non-small cell lung cancer treated with Avastin may be at risk of serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/ haemoptysis (> 2.5 ml of red blood) should not be treated with Avastin.

*Congestive Heart Failure (CHF)* (see section 4.8)
Events consistent with CHF were reported in clinical trials. The symptoms ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or

hospitalisation. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines.

Caution should be exercised when treating patients with clinically significant cardiovascular disease or pre-existing congestive heart failure with Avastin.

*Neutropenia* (see section 4.8)
Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus Avastin in comparison to chemotherapy alone.

## 4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies with other antineoplastic agents have been conducted. However, the existing data suggest that bevacizumab does not affect the pharmacokinetics of 5-fluorouracil (5-FU), carboplatin, paclitaxel, and doxorubicin to a clinically relevant extent.

In one study, irinotecan concentrations were similar in patients receiving Irinotecan/5-FU/folinic acid (IFL) alone and in combination with bevacizumab. Concentrations of SN38, the active metabolite of irinotecan, were analysed in a subset of patients (approximately 30 per treatment arm). Concentrations of SN38 were on average 33% higher in patients receiving IFL in combination with bevacizumab compared with IFL alone. Due to high inter-patient variability and limited sampling, it is uncertain if the increase in SN38 levels observed was due to bevacizumab. There was a small increase in diarrhoea and leucopenia adverse events (known adverse drug reactions of irinotecan), and also more dose reductions of irinotecan were reported in the IFL + bevacizumab-treated patients.

Patients who develop severe diarrhoea, leucopenia or neutropenia with bevacizumab and irinotecan combination should have irinotecan dose modifications as specified in the Summary of Product Characteristics for the medicinal product containing irinotecan.

## 4.6 Pregnancy and lactation

***Pregnancy***
There are no data on the use of Avastin in pregnant women. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). IgGs are known to cross the placenta, and Avastin is anticipated to inhibit angiogenesis in the foetus, and thus is suspected to cause serious birth defects when administered during pregnancy. Avastin is contraindicated (see section 4.3) in pregnancy. Women of childbearing potential have to use effective contraception during (and up to 6 months after treatment).

***Lactation***
It is not known whether bevacizumab is excreted in human milk. As maternal IgG is excreted in milk and bevacizumab could harm infant growth and development (see section 5.3), women must discontinue breast-feeding during therapy and not breast feed for at least six months following the last dose of Avastin.

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, there is no evidence that Avastin treatment results in an increase in adverse events that might lead to impairment of the ability to drive or operate machinery or impairment of mental ability.

## 4.8 Undesirable effects

The overall safety profile of Avastin is based on data from over 1000 patients with various malignancies, predominantly treated with Avastin in combination with chemotherapy in clinical trials.





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The most serious adverse drug reactions were:

- Gastrointestinal perforations (see section 4.4).
- Haemorrhage, including pulmonary haemorrhage/haemoptysis, which is more common in non-small cell lung cancer patients (see section 4.4).
- Arterial thromboembolism (see section 4.4).

The most frequently observed adverse drug reactions across clinical trials in patients receiving Avastin were hypertension, fatigue or asthenia, diarrhoea and abdominal pain.

Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with Avastin therapy are likely to be dose-dependent.

Table 1 lists adverse drug reactions associated with the use of Avastin in combination with different chemotherapy regimens in multiple indications. These reactions had occurred either with at least a 2% difference compared to the control arm (NCI-CTC grade 3-5 reactions) or with at least a 10% difference compared to the control arm (NCI-CTC grade 1-5 reactions), in at least one of the major clinical trials.

The adverse drug reactions listed in this table fall into the following categories: Very Common (≥ 10%) and Common (≥ 1% - < 10%). Adverse drug reactions are added to the appropriate category in the table below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping adverse drug reactions are presented in the order of decreasing seriousness. Some of the adverse drug reactions are reactions commonly seen with chemotherapy, however, an exacerbation by Avastin therapy can not be excluded.

**Table 1: Very Common and Common Adverse Drug Reactions**

| ***System Organ Class (SOC)*** | ***NCI-CTC Grade 3-5 Reactions (≥ 2 % difference between the study arms in at least one clinical trial)*** | | ***All Grade Reactions (≥ 10 % difference between the study arms in at least one clinical trial)*** |
|---|---|---|---|
| | ***Very common*** | ***Common*** | ***Very Common*** |
| ***Infections and infestations*** | | Sepsis<br>Abscess<br>Infection | |
| ***Blood and the lymphatic systems disorders*** | Leucopenia | Febrile neutropenia<br>Anaemia<br>Thrombocytopenia | |
| ***Metabolism and nutrition disorders*** | | Dehydration | Anorexia |
| ***Nervous system disorders*** | Peripheral sensory neuropathy | Cerebral ischaemia<br>Syncope<br>Somnolence<br>Headache | Dysgeusia |
| ***Eye disorders*** | | | Eye disorder |
| ***Cardiac disorders*** | | Cardiac failure congestive<br>Supraventricular tachycardia | |
| ***Vascular disorders*** | Hypertension | Thromboembolism (arterial)* | Rectal haemorrhage<br>Hypertension |

| *System Organ Class (SOC)* | *NCI-CTC Grade 3-5 Reactions (≥ 2 % difference between the study arms in at least one clinical trial)* | | *All Grade Reactions (≥ 10 % difference between the study arms in at least one clinical trial)* |
|---|---|---|---|
| | *Very common* | *Common* | *Very Common* |
| | | Deep vein thrombosis | |
| ***Respiratory, thoracic and mediastinal disorders*** | | Dyspnoea<br>Hypoxia | Dyspnoea<br>Epistaxis<br>Rhinitis |
| ***Gastrointestinal disorders*** | Diarrhoea | Ileus<br>Intestinal obstruction<br>Abdominal pain<br>Gastrointestinal disorder | Constipation<br>Stomatitis |
| ***Skin and subcutaneous tissue disorders*** | | | Exfoliative dermatitis<br>Dry skin<br>Skin discolouration |
| ***Musculoskeletal, connective tissue and bone disorders*** | | Muscular weakness | |
| ***Renal and urinary disorders*** | | Proteinuria<br>Urinary Tract Infection | |
| ***General disorders and administration site conditions*** | Asthenia<br>Fatigue | Pain | Pyrexia<br>Asthenia<br>Pain |

** Pooled arterial thromboembolic events including cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic events.*
*Data are unadjusted for the differential time on treatment.*

***Further information on selected serious adverse drug reactions:***

*Gastrointestinal perforations* (see section 4.4):
Avastin has been associated with serious cases of gastrointestinal perforation or fistulae.

Gastrointestinal perforation have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer and non-squamous non-small cell lung cancer, and in up to 2.0% in metastatic colorectal cancer patients. Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforations, which represents between 0.2%-1% of all Avastin treated patients.

The presentation of these events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumour necrosis, diverticulitis, or chemotherapy-associated colitis.

*Wound healing* (see section 4.4):
As Avastin may adversely impact wound healing, patients who had major surgery within the last 28 days were excluded from participation in phase III clinical trials.

In clinical trials of metastatic carcinoma of the colon or rectum, there was no increased risk of post-operative bleeding or wound healing complications observed in patients who underwent major surgery

28-60 days prior to starting Avastin. An increased incidence of post-operative bleeding or wound healing complication occurring within 60 days of major surgery was observed if the patient was being treated with Avastin at the time of surgery. The incidence varied between 10% (4/40) and 20% (3/15).

In locally recurrent and metastatic breast cancer, Grade 3-5 wound healing complications were observed in 1.1% of patients receiving Avastin + paclitaxel and in none of the patients receiving paclitaxel alone.

*Nasal Septum Perforations:*
Very rare cases of nasal septum perforations have been reported in patients treated with Avastin.

*Hypertension* (see section 4.4):
An increased incidence of hypertension of up to 34% has been observed in Avastin-treated patients in clinical trials compared with up to 14% in those treated with comparator. Grade 3 and 4 hypertension (requiring oral anti-hypertensive medication) in patients receiving Avastin ranged from 8% to 16%. Grade 4 hypertension (hypertensive crisis) occurred in up to 0.5% of patients treated with Avastin and chemotherapy compared to with up to 0.2% of patients treated with the same chemotherapy alone.

In clinical trials in metastatic colorectal cancer, mean increases in diastolic and systolic blood pressure were observed at week 24 in the Avastin containing treatment arms relative to baseline, ranging from +4.1 mmHg to +5.4 mmHg for diastolic and + 5.5 mmHg to +8.4 mmHg for systolic blood pressure measurements.

Hypertension was generally adequately controlled with oral anti-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. It rarely resulted in discontinuation of Avastin treatment or hospitalisation.

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal.

The risk of Avastin-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

*Reversible Posterior Leukoencephalopathy Syndrome (RPLS)* (see section 4.4)
There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a rare neurological disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension.

*Proteinuria* (see section 4.4):
In clinical trials, proteinuria has been reported in up to 38% of patients receiving Avastin. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome, with the great majority as Grade 1 proteinuria. Grade 3 proteinuria was reported less frequently (< 3% of treated patients). Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. The proteinuria seen in clinical trials was not associated with renal dysfunction and rarely required permanent discontinuation of therapy.

*Haemorrhage* (see section 4.4):
In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 5% in Avastin treated patients, compared with up to 2.9% of patients in chemotherapy control group.

The haemorrhagic events that have been observed in clinical studies were predominantly tumour-associated haemorrhage (see below) and minor mucocutaneous haemorrhage (e.g. epistaxis).

***Tumour-associated haemorrhage*** was observed in Avastin studies.

Major or massive pulmonary haemorrhage/haemoptysis has been observed primarily in patients with non-small cell lung cancer. These events occurred suddenly and presented as major or massive pulmonary haemorrhage/haemoptysis. Among the possible risk factors evaluated (including squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, Avastin therapy, previous medical history of atherosclerosis, central tumour location and cavitation of tumours during therapy), the only variables that showed statistically significant correlations with bleeding were Avastin therapy and squamous cell histology.

Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent studies, while patients with unknown tumour histology were included. In NSCLC, Grade 3-5 pulmonary haemorrhage/haemoptysis has been observed in up to 2.3% of patients treated with Avastin + carboplatin–paclitaxel as compared with < 1% with carboplatin-paclitaxel alone. Two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome. Following the occurrence of one fatal pulmonary haemorrhage in the first 56 patients treated with Avastin in a clinical trial for NSCLC, patients with gross prior pulmonary haemorrhage/haemoptysis were subsequently excluded.

Gastrointestinal haemorrhages, including rectal bleeding and melaena have been reported in colorectal cancer patients, and have been assessed as tumour-associated haemorrhages.

Tumour-associated haemorrhage was also seen rarely in other tumour types and locations, including a case of central nervous system (CNS) bleeding in a patient with hepatoma with occult CNS metastases (see section 4.3) and another patient who developed continuous oozing of blood from a thigh sarcoma with necrosis.

Across all clinical trials, ***mucocutaneous haemorrhage*** has been seen in 20% - 40% of Avastin-treated patients. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in Avastin treatment regimen.

There have also been less common events of minor mucocutaneous haemorrhage in other locations, such as gingival bleeding or vaginal bleeding.

*Thromboembolism* (see section 4.4):

*Arterial thromboembolism:*
An increased incidence of arterial thromboembolic events was observed in patients treated with Avastin across indications, including cerebrovascular accidents, myocardial infarction, transient ischemic attacks, and other arterial thromboembolic events.

In clinical trials, the overall incidence of arterial thromboembolic events ranged from 0.8% to 3.6% in the Avastin containing arms compared with up to 1.4% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving Avastin compared to 0.5% in patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischemic attacks) were reported in up to 2.3% of patients treated with Avastin in combination with chemotherapy compared to 0.5% of patients treated with chemotherapy alone. Myocardial infarction was reported in 1.4% of patients treated with Avastin in combination with chemotherapy compared to 0.7% of patients treated with chemotherapy alone.

In one clinical trial, AVF2192g, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan were included. In this trial arterial thromboembolic events were observed in 10% (10/100) of patients compared to 5.8% (6/104) in the chemotherapy control group.

*Venous thromboembolism:*
The incidence of venous thromboembolic events in clinical trials was similar in patients receiving Avastin in combination with chemotherapy compared to those receiving the control chemotherapy

alone. Venous thromboembolic events include deep venous thrombosis, pulmonary embolism and thrombophlebitis.

In clinical trials across indications, the overall incidence of venous thromboembolic events ranged from 2.8% to 17.3% of Avastin-treated patients compared with 3.2% to 15.6% in the controls. In the clinical trials in NSCLC an increase of the overall incidence of venous thromboembolic events with Grade 3-5 severity was observed of up to 5.6% in the Avastin containing arm compared with 3.2% in the chemotherapy control arm. One event (0.2%) was fatal on the Avastin containing arm compared to none in the carboplatin-paclitaxel arm.

Patients who have experienced a venous thromboembolic event may be at higher risk for a recurrence if they receive Avastin in combination with chemotherapy versus chemotherapy alone.

*Congestive Heart Failure (CHF)*
In clinical trials with Avastin, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. In one phase III study (AVF2119g) in patients with metastatic breast cancer an increase of CHF with Avastin (3.5% vs.1%) was seen. The CHF events varied in severity from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF requiring treatment or hospitalisation. Most of the patients who developed CHF had received prior anthracyclines, prior radiotherapy to the left chest wall or had other risk factors for the development of CHF, e.g. pre-existing heart disease or concomitant cardiotoxic therapy. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In most clinical trials of Avastin, patients with pre-existing CHF of NYHA (New York Heart Association (NYHA) II-IV were excluded, therefore, no information is available on the risk of CHF in this population.

Prior anthracyclines exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF

*Elderly Patients*
In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events, including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs), grade 3-4 leucopenia, neutropenia, diarrhoea and fatigue as compared to those aged ≤ 65 years when treated with Avastin (see sections 4.4 and 4.8 under *Thromboembolism*).

No increase in the incidence of other reactions, including gastrointestinal perforation, wound healing complications, hypertension, proteinuria, congestive heart failure, and haemorrhage was observed in elderly patients (> 65 years) receiving Avastin as compared to those aged ≤ 65 years treated with Avastin.

*Laboratory Abnormalities:*
Decreased neutrophil count, decreased white blood cell count and presence of urine protein may be associated with Avastin exposure.

Across all clinical trials, the following Grade 3 and 4 laboratory abnormalities were seen with an increased (≥ 2%) incidence in patients treated with Avastin in combination with chemotherapy regimen compared those in the control group: decreased neutrophil count, decreased white blood cell count, decreased haemoglobin, protein urine present, decreased blood potassium, increased blood potassium, prothrombin time prolonged, decreased blood phosphorus, increased blood glucose and increased blood alkaline phosphatase.





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### 4.9 Overdose

The highest dose tested in humans (20 mg/kg of body weight, intravenous) was associated with severe migraine in several patients.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibody, ATC code: L01X C07

*Mechanism of action*
Bevacizumab binds to vascular endothelial growth factor (VEGF) and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF reduces the vascularisation of tumours, thereby inhibiting tumour growth.

*Pharmacodynamic effects*
Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

*Clinical efficacy*

**Metastatic carcinoma of the colon or rectum (mCRC)**

The safety and efficacy of the recommended dose (5 mg/kg of body weight every two weeks) in metastatic carcinoma of the colon or rectum were studied in three randomised, active-controlled clinical trials in combination with fluoropyrimidine-based first-line chemotherapy. Avastin was combined with two chemotherapy regimens:

- **AVF2107g**: A weekly schedule of irinotecan/bolus 5-fluorouracil/folinic acid (IFL) for a total of 4 weeks of each 6 week-cycle (Saltz regimen).
- **AVF0780g**: In combination with bolus 5-fluorouracil/ folinic acid (5-FU/FA) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen).
- **AVF2192g**: In combination with bolus 5-FU/FA for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen) in patients who were not optimal candidates for first-line irinotecan treatment.

All three trials evaluated Avastin at a dose of 5 mg/kg of body weight every two weeks and enrolled patients with previously untreated metastatic carcinoma of the colon or rectum.

**Avastin in Combination with IFL Chemotherapy for First-Line Treatment of Metastatic Carcinoma of the Colon or Rectum (AVF2107g):** This was a phase III randomised, double-blind, active-controlled clinical trial evaluating Avastin in combination with IFL as first-line treatment for metastatic carcinoma of the colon or rectum. Eight hundred and thirteen patients were randomised to receive IFL + placebo (Arm 1) or IFL + Avastin (5 mg/kg every 2 weeks, Arm 2) (see Table 2). A third group of 110 patients received bolus 5-FU/FA+Avastin (Arm3). Enrollment in Arm 3 was discontinued, as pre-specified, once safety of Avastin with the IFL regimen was established and considered acceptable. All treatments were continued until disease progression. The overall mean age was 59.4 years; 56.6% of patients had an ECOG performance status of 0, 43% had a value of 1 and 0.4% had a value of 2. 15.5% had received prior radiotherapy and 28.4% prior chemotherapy.

**Table 2 Treatment regimens in study AVF2107g**

| | Treatment | Starting Dose | Schedule |
|---|---|---|---|
| Arm 1 | Irinotecan | 125 mg/m$^2$ IV | Given once weekly for 4 weeks every 6 weeks |
| | 5-Fluorouracil | 500 mg/m$^2$ IV | |
| | Folinic acid | 20 mg/m$^2$ IV | |
| | Placebo | IV | Every 2 weeks |
| Arm 2 | Irinotecan | 125 mg/m$^2$ IV | Given once weekly for 4 weeks every 6 weeks |
| | 5-Fluorouracil | 500 mg/m$^2$ IV | |
| | Folinic acid | 20 mg/m$^2$ IV | |
| | Avastin | 5 mg/kg IV | Every 2 weeks |
| Arm 3 | 5-Fluorouracil | 500 mg/m$^2$ IV | Given once weekly for 6 weeks every 8 weeks |
| | Folinic acid | 500 mg/m$^2$ IV | |
| | Avastin | 5 mg/kg IV | Every 2 weeks |
| *5-Fluorouracil:* *IV bolus injection immediately after* folinic acid. | | | |
| folinic acid*:* *IV bolus injection (over 1–2 minutes) immediately after each irinotecan dose.* | | | |

The primary efficacy variable of the trial was duration of survival. The addition of Avastin to IFL resulted in a statistically significant increase in overall survival (see Table 3). The clinical benefit, as measured by overall survival, was seen in all pre-specified patient subgroups, including those defined by age, sex, performance status, location of primary tumour, number of organs involved and duration of metastatic disease.

The efficacy results of Avastin in combination with IFL-chemotherapy are displayed in Table 3.

**Table 3 Efficacy results for study AVF2107g**

| | AVF2107g | |
|---|---|---|
| | **Arm 1** **IFL + Placebo** | **Arm 2** **IFL + Avastin[a]** |
| Number of Patients | 411 | 402 |
| Overall survival | | |
| Median time (months) | 15.6 | 20.3 |
| 95% Confidence Interval | 14.29 – 16.99 | 18.46 – 24.18 |
| Hazard ratio[b] | | 0.660 |
| p-value | | 0.00004 |
| Progression-free survival | | |
| Median time (months) | 6.2 | 10.6 |
| Hazard ratio | | 0.54 |
| p-value | | < 0.0001 |
| Overall response rate | | |
| Rate (%) | 34.8 | 44.8 |
| 95% CI | 30.2–39.6 | 39.9–49.8 |
| p-value | | 0.0036 |
| Duration of response | | |
| Median time (months) | 7.1 | 10.4 |
| 25–75 percentile (months) | 4.7–11.8 | 6.7–15.0 |

[a] 5 mg/kg every 2 weeks.
[b] Relative to control arm.

Among the 110 patients randomised to Arm 3 (5-FU/FA + Avastin), the median overall survival was 18.3 months, median progression free survival was 8.8 months, overall response rate was 39% and median duration of response was 8.5 months.

**Avastin in Combination with 5-FU/FA Chemotherapy for the First-Line Treatment of Metastatic Carcinoma of the Colon or Rectum in patients who were not optimal candidates for first-line irinotecan treatment (AVF2192g)**: This was a phase II randomised, double-blind, active-controlled clinical trial evaluating the efficacy and safety of Avastin in combination with 5-FU/FA as first-line treatment for metastatic colorectal cancer in patients who were not optimal candidates for first-line irinotecan treatment. Patients had to be either more susceptible to irinotecan toxicity (≥ 65 years, prior radiotherapy to pelvis or abdomen) or less likely to benefit from irinotecan treatment (PS ≥ 1, baseline albumin < 3.5 g/dl) in order to be eligible for enrolment. One hundred and five patients were randomised to 5-FU/FA + placebo arm and 104 patients to 5-FU/FA + Avastin (5 mg/kg every 2 weeks) arm. All treatments were continued until disease progression. The overall mean age was 71 years; 28.2% of patients had a ECOG performance status of 0, 65.1% had a value of 1 and 6.7% had a value of 2. The addition of Avastin 5 mg/kg every two weeks to 5-FU/FA resulted in higher objective response rates, significantly longer progression-free survival, and a trend in longer survival, compared to 5-FU/FA chemotherapy alone (see Table 4). These efficacy data were consistent with the results observed in studies AVF2107g and AVF0780g.

**Avastin in Combination with 5-FU/FA Chemotherapy for the First-Line Treatment of Metastatic Carcinoma of the Colon or Rectum (AVF0780g):** This was a phase II randomised, active-controlled, open-labelled clinical trial investigating Avastin in combination with 5-FU/FA as first-line treatment of metastatic colorectal cancer. The median age was 64 years. 19% of the patients had received prior chemotherapy and 14% prior radiotherapy. Seventy-one patients were randomised to receive bolus 5-FU/FA or 5-FU/FA + Avastin (5 mg/kg every 2 weeks). A third group of 33 patients received bolus 5-FU/FA + Avastin (10 mg/kg every 2 weeks). Patients were treated until disease progression. The primary endpoints of the trial were objective response rate and progression-free survival. The addition of Avastin 5 mg/kg every two weeks to 5-FU/FA resulted in higher objective response rates, longer progression-free survival, and a trend in longer survival, compared with 5-FU/FA chemotherapy alone (see Table 4). These efficacy data are consistent with the results from study AVF2107g.

The efficacy data from studies AVF0780g and AVF2192g investigating Avastin in combination with 5-FU/FA-chemotherapy are summarised in Table 4.

**Table 4: Efficacy results for studies AVF0780g and AVF2192g**

| | AVF0780g | | | AVF2192g | |
|---|---|---|---|---|---|
| | **5-FU/FA** | **5-FU/FA + Avastin[a]** | **5-FU/FA + Avastin[b]** | **5-FU/FA + placebo** | **5-FU/FA + Avastin** |
| Number of Patients | 36 | 35 | 33 | 105 | 104 |
| Overall survival | | | | | |
| Median time (months) | 13.6 | 17.7 | 15.2 | 12.9 | 16.6 |
| 95% Confidence Interval | | | | 10.35 - 16.95 | 13.63 – 19.32 |
| Hazard ratio[c] | - | 0.52 | 1.01 | | 0.79 |
| p-value | | 0.073 | 0.978 | | 0.16 |
| Progression-free survival | | | | | |
| Median time (months) | 5.2 | 9.0 | 7.2 | 5.5 | 9.2 |
| Hazard ratio | | 0.44 | 0.69 | | 0.5 |
| p-value | - | 0.0049 | 0.217 | | 0.0002 |
| Overall response rate | | | | | |
| Rate (percent) | 16.7 | 40.0 | 24.2 | 15.2 | 26 |

| | AVF0780g | | | AVF2192g | |
|---|---|---|---|---|---|
| | **5-FU/FA** | **5-FU/FA + Avastin[a]** | **5-FU/FA + Avastin[b]** | **5-FU/FA + placebo** | **5-FU/FA + Avastin** |
| 95% CI | 7.0 – 33.5 | 24.4 – 57.8 | 11.7 – 42.6 | 9.2 - 23.9 | 18.1 - 35.6 |
| p-value | | 0.029 | 0.43 | | 0.055 |
| Duration of response | | | | | |
| Median time (months) | NR | 9.3 | 5.0 | 6.8 | 9.2 |
| 25–75 percentile (months) | 5.5 – NR | 6.1 – NR | 3.8 – 7.8 | 5.59 - 9.17 | 5.88 - 13.01 |

[a] 5 mg/kg every 2 weeks.
[b] 10 mg/kg every 2 weeks.
[c] Relative to control arm.
NR = Not reached.

**Metastatic breast cancer (mBC)**

Study E2100 was an open-label, randomised, active controlled, multicentre clinical trial evaluating Avastin in combination with paclitaxel for locally recurrent or metastatic breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. Patients were randomised to paclitaxel alone (90 mg/m$^2$ IV over 1 hour once weekly for three out of four weeks) or in combination with Avastin (10 mg/kg IV infusion every two weeks). Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to study entry. Of the 722 patients in the study, the majority of patients had HER2-negative disease (90%), with a small number of patients with unknown (8%) or confirmed HER2-positive status (2%), who had previously been treated with or were considered unsuitable for trastuzumab therapy. Furthermore, 65% of patients had received adjuvant chemotherapy including 19% prior taxanes and 49% prior anthracyclines. Patients with central nervous system metastasis, including previously treated or resected brain lesions, were excluded.

In Study E2100, patients were treated until disease progression. In situations where early discontinuation of chemotherapy was required, treatment with Avastin as a single agent continued until disease progression. The patient characteristics were similar across the study arms. The primary endpoint of this trial was progression free survival (PFS), based on study investigators' assessment of disease progression. The results of this study are presented in Table 5.

**Table 5 Study E2100 Efficacy Results:**

| | **Paclitaxel (n=354)** | **Paclitaxel + Avastin (n=368)** |
|---|---|---|
| **Progression-Free Survival (Months)[a, b]** | | |
| Median | 6.7 | 13.3 |
| Hazard ratio | 0.48 | |
| 95% CI | (0.39, 0.59) | |
| p-value (log-rank test) | P<0.0001 | |
| **Overall survival (months)[c]** | | |
| Median | 23.8 | 25.7 |
| Hazard ratio | 0.82 | |
| 95% CI | (0.66, 1.03) | |
| p-value (log-rank test) | 0.082 | |
| CI= Confidence interval | | |

| | Paclitaxel (n=354) | Paclitaxel + Avastin (n=368) |
|---|---|---|
| [a]Intent to treat analysis<br>[b] As assessed by study investigators<br>[c] Based on an exploratory analysis of immature overall survival data, with 70% of events required for final analysis | | |

The clinical benefit of Avastin as measured by PFS was seen in all pre-specified subgroups tested (including disease-free interval, number of metastatic sites, prior receipt of adjuvant chemotherapy and estrogen receptor (ER) status). In an exploratory analysis, the extent of Avastin benefit was less pronounced in the subgroup of patients >65 years of age.

## 5.2 Pharmacokinetic properties

The pharmacokinetic data for bevacizumab are available from eight clinical trials in patients with solid tumours. In all clinical trials, bevacizumab was administered as an IV infusion. The rate of infusion was based on tolerability, with an initial infusion duration of 90 minutes. The pharmacokinetics of bevacizumab was linear at doses ranging from 1 to 10 mg/kg.

*Absorption*
Not applicable.

*Distribution*
Based on a population pharmacokinetic analysis of 491 subjects receiving Avastin weekly, every 2 weeks, or every 3 weeks, in doses ranging from 1 to 20 mg/kg, the volume of the central compartment ($V_c$) was 2.92 l. Results also indicated that, after correcting for body weight, male subjects had a larger $V_c$ (+ 22%) than females.

*Metabolism*
Assessment of bevacizumab metabolism in rabbits following a single IV dose of $^{125}$I-bevacizumab indicated that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF.

*Elimination*
Bevacizumab clearance was 0.231 l/day. The volume of the central compartment ($V_c$) and clearance correspond to an initial half-life of 1.4 days and a terminal half-life of about 20 days. This half-life is consistent with the terminal elimination half-life for human endogenous IgG, which is 18 to 23 days. In patients with low albumin (≤ 29g/l) and high alkaline phosphatase (≥ 484U/l) (both markers of disease severity), clearance was approximately 20% higher than in patients with median laboratory values.

***Pharmacokinetics in Special Populations***
The population pharmacokinetics were analysed to evaluate the effects of demographic characteristics. The results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age.

*Children and adolescents:* No studies have been conducted to investigate the pharmacokinetics of bevacizumab in paediatric patients.

*Renal impairment:* No studies have been conducted to investigate the pharmacokinetics of bevacizumab in renally impaired patients.

*Hepatic impairment:* No studies have been conducted to investigate the pharmacokinetics of bevacizumab in patients with hepatic impairment.





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### 5.3 Preclinical safety data

In studies of up to 26 weeks duration in cynomolgus monkeys, physeal dysplasia was observed in young animals with open growth plates, at bevacizumab average serum concentrations below the expected human therapeutic average serum concentrations. In rabbits, bevacizumab was shown to inhibit wound healing at doses below the proposed clinical dose. Effects on wound healing were shown to be fully reversible.

Studies to evaluate the mutagenic and carcinogenic potential of bevacizumab have not been performed.

No specific studies in animals have been conducted to evaluate the effect on fertility. An adverse effect on female fertility can however be expected as repeat dose toxicity studies in animals have shown inhibition of the maturation of ovarian follicles and a decrease/absence of corpora lutea and associated decrease in ovarian and uterus weight as well as a decrease in the number of menstrual cycles.

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and foetal body weights, an increased number of foetal resorptions and an increased incidence of specific gross and skeletal foetal malformations. Adverse foetal outcomes were observed at all tested doses, of which the lowest dose resulted in average serum concentrations approximately 3 times larger than in humans receiving 5 mg/kg every 2 weeks.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Trehalose dihydrate
Sodium phosphate
Polysorbate 20
Water for injections

### 6.2 Incompatibilities

A concentration dependent degradation profile of bevacizumab was observed when diluted with glucose solutions (5%).

### 6.3 Shelf life

2 years.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 30°C in sodium chloride 9 mg/ml (0.9%) solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

### 6.5 Nature and contents of container

Single-use vial (Type I glass) with a butyl rubber stopper containing 100 mg of bevacizumab in 4 ml of concentrate for solution for infusion.
Single-use vial (Type I glass) with a butyl rubber stopper containing 400 mg of bevacizumab in 16 ml of concentrate for solution for infusion.

Pack of 1 vial containing 4 ml.
Pack of 1 vial containing 16 ml.

### 6.6 Special precautions for disposal and other handling

Avastin does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

Avastin should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute with sodium chloride (0.9%) solution for injection, up to a total volume of 100 ml. For heavier patients receiving doses of 10 or 15 mg/kg, the dose may be made up to 200 or 250 ml with sodium chloride (0.9%) solution. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.
No incompatibilities between Avastin and polyvinyl chloride or polyolefine bags or infusion sets have been observed.

## 7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/300/001 – 100 mg/4 ml vial
EU/1/04/300/002 – 400 mg/16 ml vial

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 January 2005

## 10. DATE OF REVISION OF THE TEXT

**ANNEX II**

**A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OF THE MARKETING AUTHORISATION**

## A MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990
USA

Genentech, Inc.
1000 New Horizons Way
Vacaville, CA 95688
USA

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barrell-Str. 1,
D-79639 Grenzach-Wyhlen
Germany

## B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex: Summary of Product Characteristics, section 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

## A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Avastin 25 mg/ml concentrate for solution for infusion
Bevacizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 100 mg bevacizumab.

**3. LIST OF EXCIPIENTS**

Trehalose dihydrate, sodium phosphate, polysorbate 20, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Concentrate for solution for infusion
100 mg
1 vial of 4 ml

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous use after dilution
Read the package leaflet before use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

This medicinal product does not contain any preservative

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C – 8°C).
Do not freeze
Keep the vial in the outer carton

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/300/001

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Not applicable

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Avastin 25 mg/ml concentrate for solution for infusion
Bevacizumab

**2. METHOD OF ADMINISTRATION**

For intravenous use after dilution

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Batch

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

100 mg, 4 ml

**6. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Avastin 25 mg/ml concentrate for solution for infusion
Bevacizumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains 400 mg bevacizumab.

**3. LIST OF EXCIPIENTS**

Trehalose dihydrate, sodium phosphate, polysorbate 20, water for injections.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Concentrate for solution for infusion
400 mg
1 vial of 16 ml

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous use after dilution
Read the package leaflet before use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

This medicinal product does not contain any preservative

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator (2°C – 8°C).
Do not freeze
Keep the vial in the outer carton

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/300/002

## 13. BATCH NUMBER

Batch

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Not applicable

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Avastin 25 mg/ml concentrate for solution for infusion
Bevacizumab

## 2. METHOD OF ADMINISTRATION

For intravenous use after dilution

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Batch

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

400 mg, 16 ml

## 6. OTHER

**B. PACKAGE LEAFLET**

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**Avastin 25 mg/ml concentrate for solution for infusion**
**Bevacizumab**

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell you doctor or pharmacist.

**In this leaflet**:
1. What Avastin is and what it is used for
2. Before you use Avastin
3. How to use Avastin
4. Possible side effects
5. How to store Avastin
6. Further information

## 1. WHAT AVASTIN IS AND WHAT IT IS USED FOR

Avastin is used for the treatment of advanced cancer in the large bowel, i.e., in the colon or rectum. This medicine will be administered with chemotherapy, containing medicines called 5-fluorouracil and folinic acid. A medicine called irinotecan might also be part of the chemotherapy.

Avastin is also used for the treatment of metastatic breast cancer. When used for patients with breast cancer, it will be administered with a chemotherapy called paclitaxel.

Avastin contains the active substance bevacizumab, which is a humanised monoclonal antibody. Monoclonal antibodies are proteins which specifically recognise and bind to other unique proteins in the body. Bevacizumab binds selectively to a protein called human vascular endothelial growth factor (VEGF), which is found on the lining of blood and lymph vessels in the body. VEGF causes blood vessels to grow within tumours, these blood vessels provide the tumour with nutrients and oxygen. Once bevacizumab is bound to VEGF, it stops VEGF working properly. This has the effect of preventing tumour growth by blocking the growth of the blood vessels providing the nutrients and oxygen to the tumour.

Each pack of Avastin concentrate for solution for infusion contains one vial. This vial contains either 4 ml or 16 ml of a slightly opaque, colourless to pale brown sterile liquid concentrate. The concentrate must be diluted before use to make a solution for intravenous infusion.

## 2. BEFORE YOU USE AVASTIN

**Do not use Avastin if:**
- you are allergic (hypersensitive) to bevacizumab or to any of the other ingredients of Avastin.
- you are allergic (hypersensitive) to Chinese hamster ovary (CHO) cell products or to other recombinant human or humanised antibodies.
- you have cancer in your brain which has not been treated.
- you are pregnant.

**Take special care with Avastin:**

- if you have conditions causing inflammation inside the abdomen (e.g. diverticulitis, stomach ulcers, colitis associated with chemotherapy), as it is possible that Avastin may increase the risk of developing holes in the gut wall.

- if you are going to have an operation, if you have had major surgery within the last 28 days or if you still have an unhealed wound following surgery, you should not receive this medicine as Avastin can increase the risk of bleeding or increase the risk of problems with wound healing after surgery.

- if you have high blood pressure which is not well controlled with blood pressure medicines as Avastin can increase the incidence of high blood pressure.

- if you have high blood pressure, as you may have a higher risk of having protein in your urine.

- if you are over 65 years old and also have had blood clots in your arteries (a type of blood vessel) in the past, as these factors can increase the risk of further blood clots in the arteries.

- if you or your family tend to suffer from bleeding problems or you are taking medicines to thin the blood for the treatment of blood clots.

- if you have been coughing or spitting blood or had any bleeding in your lungs.

- if you have ever received anthracyclines (for example doxorubicin, a specific type of chemotherapy used to treat some cancers) or had radiotherapy to your chest, as Avastin can increase the risk of developing a weak heart.

Please consult your doctor, even if these statements were applicable to you at any time in the past.

**Using other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
If you are also taking irinotecan, another chemotherapy agent which may be used for the treatment of advanced cancer of the large bowel, your doctor may change the dose of irinotecan that you are given if you suffer from severe diarrhoea or a severe reduction in the number of white cells in your blood.

**Pregnancy and breast feeding**
You must not use this medicine if you are pregnant. Avastin may cause damage to your unborn baby as it may stop the formation of new blood vessels. Your doctor should advise you about using contraception during treatment with Avastin and for at least 6 months after the last dose of Avastin.

Tell your doctor straightaway if you are pregnant, become pregnant during treatment with this medicine, or plan to become pregnant in the near future.

You must not breast-feed your baby during treatment with Avastin and for at least 6 months after the last dose of Avastin, as this medicine may interfere with the growth and development of your baby.

Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines:**
Avastin has not been shown to impair your ability to drive or to use any tools or machines.

## 3. HOW TO USE AVASTIN

**Dosage and frequency of administration**
The dose of Avastin needed depends on your body weight and the kind of cancer to be treated. The recommended dose is 5, 10 or 15 mg per kilogram of your body weight. Your doctor will prescribe a dose of Avastin that is right for you. You will be treated with Avastin once every 2 or 3 weeks. The number of infusions that you receive will depend on how you are responding to treatment; you should continue to receive this medicine until Avastin fails to stop your tumour growing. Your doctor will discuss this with you.

**Method and route of administration**
Avastin is a concentrate for solution for infusion. Depending on the dose prescribed for you, some or all of the contents of the Avastin vial will be diluted with saline solution before use. A doctor or nurse will give you this diluted Avastin solution by intravenous infusion. The first infusion will be given to you over 90 minutes following the administration of your chemotherapy medicines. If this is well-tolerated the second infusion may be given over 60 minutes. Later infusions may be given to you over 30 minutes. After the first dose, Avastin can be administered before or after your chemotherapy medicines.

**Whilst you receive this medicine:**
The administration of Avastin should be temporarily discontinued:
- if you develop severe high blood pressure requiring treatment with blood pressure medicines,
- if you have problems with wound healing following surgery,
- if you undergo surgery.

The administration of Avastin should be permanently discontinued if you develop:
- severe high blood pressure which cannot be controlled by blood pressure medicines; or a sudden severe rise in blood pressure,
- presence of protein in your urine accompanied by swelling of your body,
- a hole in your gut wall,
- a blood clot in your arteries,
- any severe bleeding.

**If too much Avastin is given:**
- you may develop a severe migraine. If this happens you should talk to your doctor or pharmacist immediately.

**If a dose of Avastin is missed:**
- your doctor will decide when you should be given your next dose of Avastin. You should discuss this with your doctor.

**If you stop treatment with Avastin:**
Stopping your treatment with Avastin may stop the effect on tumour growth. Do not stop treatment with Avastin unless you have discussed this with your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, Avastin can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

The side effects listed below were seen when Avastin was given together with chemotherapy. This does not necessarily mean that these side effects were strictly caused by Avastin.

Side effects described as very common were experienced in more than 1 in 10 patients.
Side effects described as common were experienced by up to 1 in 10 patients.

The common (up to 1 in 10 patients) most serious side effects are:
- perforation of the gut,
- bleeding, including bleeding in the lungs in patients with non-small cell lung cancer,
- blocking of the arteries by a blood clot.

The severe side effects, which may be very common (more than 1 in 10 patients), include:
- high blood pressure,
- problems with wound healing after surgery,
- feeling of numbness or tingling in hands or feet.
- decreased number of white cells in the blood that help to fight against infections,
- lack of energy or tiredness.

The severe side effects which may be common (up to 1 in 10 patients), include:
- decreased number of cells in the blood, these include white cells (which may occur with a fever), red cells and cells that help the blood to clot,
- bleeding associated with the tumour,
- lack of energy,
- abdominal pain,
- dry mouth in combination with thirst and/or reduced or darkened urine,
- diarrhoea,
- pain, including headache,
- blood clots in the veins of the legs or difficulties in getting the blood to clot,
- localised pus collection,
- infection, and in particular infection in the blood or bladder,
- reduced blood supply to the brain,
- blood clots in the arteries, which can lead to a stroke and a heart attack,
- falling asleep or fainting
- problems with the heart with breathing difficulties,
- increase in heart rate (pulse),
- blockage in the gut or bowel,
- abnormal urine test (protein in the urine),
- shortness of breath or low levels of oxygen in the blood.

Rarely, such side effects as seizures (fits), headache, confusion or changes in vision may occur.

*You should seek help immediately if you suffer from any of the above mentioned side effects.*

The very common (more than 1 in 10 patients) side effects which were not severe, include:
- high blood pressure,
- pain,
- lack of energy,
- constipation, bleeding from the lower part of the large bowel, inflammation of the mouth,
- loss of appetite,
- protein in the urine,
- nose bleed,
- fever.

The common (up to 1 in 10 patients) side effects which were not severe, include:
- shortness of breath,
- nose bleed,
- runny nose,
- dry skin, flaking and inflammation of the skin, change in skin colour,
- change in the sense of taste,

- problems with eye (tearing).

Other less common side effects of any severity which have been reported are heart failure and bleeding from the lining of the mouth or vagina.

There have been very rare reports of patients developing a hole in the septum of the nose – the structure, which separates the nostrils.

Some side effects are more common in elderly patients. These side effects include blood clot in the arteries which can lead to a stroke or a heart attack. In addition, elderly patients have a higher risk of a reduction in the number of white cells in the blood.

*You should seek help as soon as possible if you suffer from any of the above mentioned side effects.*

Avastin may also cause changes in laboratory tests carried out by your doctor. These include; a decreased number of white cells in the blood, in particular neutrophils (one type of white blood cell which helps protect against infections) in the blood; presence of protein in the urine; decreased blood potassium, sodium or phosphorous (a mineral); increased blood sugar; increased blood alkaline phosphatase (an enzyme); decreased haemoglobin (found in red blood cells, which carry oxygen), which may be severe.

## 5. HOW TO STORE AVASTIN

Keep out of the reach and sight of children.

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Keep the vial in the outer carton.

Do not use after the expiry date which is stated on the outer carton and on the vial label after the abbreviation EXP. The expiry date refers to the last day of that month.

Infusion solutions should be used immediately after dilution. Discard any unused medicine.

## 6. FURTHER INFORMATION

**What Avastin contains**

- The active substance is bevacizumab.
- The other ingredients are trehalose dihydrate, sodium phosphate, polysorbate 20 and water for injections.

**What Avastin looks like and contents of the pack**
Avastin is a clear, colourless to pale brown liquid in a glass vial with a rubber stopper. Each vial contains 100 mg bevacizumab in 4 ml of solution or 400 mg bevacizumab in 16 ml of solution.

**Marketing Authorisation Holder:**
Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW,
United Kingdom.

**Manufacturer:**
Roche Pharma AG, Emil-Barell-Str. 1, 79639 Grenzach-Wyhlen, Germany.

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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