CLINICAL STUDY PROTOCOL

A Phase II pilot-study to assess efficacy and safety of capecitabine and irinotecan plus bevacizumab followed by capecitabine and oxaliplatin plus bevacizumab or the reverse sequence in patients with metastatic colorectal cancer

MODIFIED XELIRI + AVASTIN FOLLOWED BY XELOX + AVASTIN OR THE REVERSE SEQUENCE IN MCRC

Protocol Version/Approval Date: VERSION 1.0 – ML25153

EudraCT number: 2011-002191-16

Representant of the Sponsor:

Date: _____ Signature: _____

Coordinating-Investigator:

Date: _____ Signature: _____

Principal Investigator at site: _____

Date: _____ Signature: _____

Head of Biometrics:

Date: _____ Signature: _____

Confidentiality Statement: The information contained in this document, especially unpublished data, is the property of the „Medizinische Universität Wien“ (or under its control), and therefore provided to you in confidence as an Investigator, potential Investigator or consultant, for review by you, your staff and an applicable Independent Ethics Committee / Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the Sponsor except tothe extent necessary to obtain informed consent from those persons to whom the drug may be administered.

SYNOPSIS MODIFIED XELIRI + AVASTIN FOLLOWED BY XELOX + AVASTIN OR THE REVERSE SEQUENCE IN MCRC / VERSION 1

TITLE	A Phase II pilot-study to assess efficacy and safety of capecitabine and irinotecan plus bevacizumab followed by capecitabine and oxaliplatin plus bevacizumab or the reverse sequence in patients with metastatic colorectal cancer
SPONSOR	Medizinische Universität Wien Universitätsklini für Innere Medizin I
INDICATION	Metastatic colorectal carcinoma

OBJECTIVES	Primary objective
	• to determine the efficacy of modified XELIRI (Capecitabine and Irinotecan) in combination with bevacizumab followed by XELOX (Capecitabine and Oxaliplatin) in combination with bevacizumab at progression in comparison with the reverse sequence based on duration of disease control (DDC) .
	
	Secondary objectives
	• to determine
	  • first line progression free survival (PFS)
	  • second line PFS
	  • overall response rate
	  • time to response
	  • duration of response
	  • overall survival of XELIRI plus bevacizumab and XELOX plus bevacizumab
	• tumour assessments (based on RECIST criteria) using CT scans, MRI scans, X ray, bone scan, clinical examination

TRIAL DESIGN	Multicenter, open label, two-armed, randomized pilot study, Phase II
	• Arm A (= group A):
	  XELIRI plus bevacizumab followed by XELOX plus bevacizumab
	• Arm B (= group B):
	  XELOX plus bevacizumab followed by XELIRI plus bevacizumab

NUMBER OF SUBJECTS	120
TARGET POPULATION	Patients with metastatic colorectal cancer who did not receive systemic treatment for their metastatic disease Inclusion Criteria 1) Written informed consent 2) Age ≥ 18 years

3) Patient must be able to comply with the protocol

4) Histologically or cytologically confirmed carcinoma of the colon and/or rectum with evidence of metastases.

5)Diagnosis of metastatic disease according to RECIST not more than 3 months prior to enrolment.

6) Life Expectancy of at least 3 months

7) At least one measurable metastatic lesion (as per RECIST criteria)

8) Prior adjuvant or neo-adjuvant chemotherapy/radiotherapy allowed if completed more than 6 months before inclusion.

9) ECOG performance score of 0 or 1

0) Adequate haematological function: ANC $\geq$ 1.5 x 10^9/L; platelets $\geq$ 100 x 10^9/L, Hb $\geq$ 9 g/dL

11) INR $\leq$ 1.5 and aPTT $\leq$ 1.5 x ULN within 7 days prior to starting study treatment

12) Adequate liver function: Serum bilirubin $\leq$ 1.5 x ULN; alkaline phosphatase and transaminases $\leq$ 2.5 x ULN (in case of liver metastases < 5 x ULN)

13) Serum Creatinine $\leq$ 1.5 x ULN

14) Urine dipstick for proteinuria < 2+. If urine dipstick is $\geq$ 2+, 24- hour urine must demonstrate $\leq$ 1 of protein in 24 hours

15) Negative serum pregnancy test within 7 days of starting study treatment in pre- menopausal women and women < 2 years after the onset of menopause. This test has to be reconfirmed by a urine test, should the 7 days window be exceeded. Fertile women (<2 years after last menstruation and men must use effective means of contraception (oral contraceptives, intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly or surgically sterile).

Exclusion Criteria

1) Prior chemotherapeutic treatment for metastatic CRC

2) Symptomatic CNS metastases

3) Significant vascular disease (e.g. aortic aneurysm potentially requiring surgical intervention, pulmonary embolism or recent peripheral arterial thrombosis) within 6 months prior start of study treatment.

4) History of haemoptysis = ½ teaspoon of bright red blood per episode)

within 1 month prior start of study treatment

5) Past or current history (within the last 2 years prior to treatment start) of other malignancies (Patients with curatively treated basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible).

6) Clinically significant cardiovascular disease, for example CVA (6 months before treatment start), myocardial infarction (6 months before treatment start), unstable angina, NYHA ≥ grade 2 CHF, arrhythmia requiring medication, or uncontrolled hypertension.

7) Prior history of hypertensive crisis or hypertensive encephalopathy

8) Treatment with any other investigational agent or any other biological agent (e.g.cetuximab), or participation in another clinical trial within 30 days prior to entering this study.

9) Known hypersensitivity to any of the study drugs

10) Current or recent (within 10 days of first dose of study treatment) chronic use of aspirin (> 325 mg/day)

11) Current or recent (within 10 days prior to study treatment start) use of full-dose oral or parenteral anticoagulants or thrombolytic agent for therapeutic (as opposed to prophylactic) purposes.

12) Evidence of bleeding diathesis or coagulopathy.

13) Serious, non healing wound, ulcer, or bone fracture.

14) Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to treatment, or anticipation of the need for major surgery during the course of the study. If CVAD is required for chemotherapy administration, it should be inserted within 2 days prior to study treatment cycle.

15) Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior start of study therapy

16) History of abdominal fistula, tracheo-oesophageal fistula or any grade 4 non gastrointestinal fistula, gastrointestinal perforation or intraabdominal abscess before 1st line therapy.

17) History or evidence upon physical/neurological examination of CNS disease (unrelated to cancer) (unless adequately treated with standard medical therapy) e.g. uncontrolled seizures

18) Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment-related complications

	19) Patients with contraindication for cross over chemotherapy (e.g. patients treated with irinotecan based first line therapy and serious polyneuropathy > grade 1, not feasible for oxaliplatin based cross over second line therapy, or patients treated with oxaliplatin based first line therapy and hereditary fructose intolerance not feasible for Irinotecan based cross over second line therapy) 20) Pregnancy or lactation 21) Fertile women (<2 years after last menstruation) and men not willing to use effective means of contraception.
LENGTH OF STUDY	3 years from first patient entered (accrual time will be years from 1st patient entered, projected analysis of the primary endpoint will be years from first patient entered).
INVESTIGATIONAL PRODUCT(S) DOSE/ ROUTE/ REGIMEN	Arm A: Capecitabine : 800mg/m^2 bid d1-14, bevacizumab 7,5 mg/kg given on day 1 q3w combined with irinotecan 200mg/m^2 iv. d q3w . Bevacizumab (7.5 mg/kg q3w) ± Capecitabine (1000 mg/m^2 bid, days 1 14 q3w) maintenance Arm B: Capecitabine: 1000mg/m2 bid d1-14, bevacizumab 7,5 mg/kg given on q3w combined with oxaliplatin 130mg/m^2 iv. d w Bevacizumab (7.5 mg/kg q3w) ± Capecitabine (1000 mg/m^2 bid, days 1 14 q3w) maintenance At disease progression irinotecan will be replaced by oxalipaltin (armA), or oxaliplatin by irinotecan (arm B). Bevacizumab will be continued. <u>First line treatment:</u> Protocol treatment with XELOX or XELIRI will be given for 6 months unless prior disease progression, unacceptable toxicity or patient refusal. Capecitabine can be given in addition to Bevacizumab as maintenance treatment at the investigators' discretion (until disease progression, unacceptable toxicity or patient refusal) Bevacizumab will be given until disease progression, unacceptable toxicity or patient refusal. <u>Second line treatment:</u> Protocol treatment with XELOX or XELIRI will be given for 4 months unless prior disease progression, unacceptable toxicity or patient refusal. Capecitabine can be given in addition to Bevacizumab as

	maintenance treatment at the investigators' discretion (until disease progression, unacceptable toxicity or patient refusal). Bevacizumab will be given until disease progression, able toxicity or patient refusal. In case of irinotecan or oxalipaltin - related discontinuation the fluoropyrimidine and bevacizumab will be continued. In case of bevacizumab related discontinuation the fluoropyrimidine and irinotecan or oxaliplatin will be continued.
COMPARATOR "DRUG" DOSE/ ROUTE/ REGIMEN	Not applicable
ASSESSMENTS OF:	
EFFICAC	• DDC of modified XELIRI in combination with bevacizumab followed by XELOX in combination with bevacizumab at progression in comparison with the reverse sequence • first line PFS • second line PFS • overall response rate • time to response • duration of response • overall survival of XELIRI plus bevacizumab and XELOX plus bevacizumab • tumour assessments (based on RECIST criteria) using CT scans, MRI scans, X ray, bone scan, clinical examination
SAFETY	• physical exam • vital signs • ECG (at baseline) • ECOG Performance score • concomitant disease and medication • adverse events • aboratory data: **Haematology** Haemoglobin, platelet count, RBC, WBC including differential (neutrophiles, lymphocytes, monocytes, eosinophiles, basophiles), INR, aPTT **Serum Chemistry** Na^+, K , Ca^{++}, Cl^-, urea (BUN), total Protein, Albumin, Alkaline Phosphatase, ALT, AST, GGT, LDH, total Bilirubin (direct Bilirubin in case of abnormal total Bilirubin), Serum creatinine and Glucose, CEA, total albumin (calculated according to Cockroft Gault, see section 7.2.6. of the protocol)

Urinalysis - Dipstick urinalysis is sufficient as long as the protein result is < 2+. If urine dipstickshows protein = 2+, 24- our urine must demonstrate = 1 of protein in 24 hours for eligibility. For further specifications refer to Section 7.1.3.

PROCEDURES (summary):
After a screening/baseline period, the patients will be allocated by randomization to a XELIRI or XELOX based regimen in combination with bevacizumab in first line treatment and the reverse sequence in second line treatment. Based on the schedule patients are planned to receive chemotherapy for 6 months in the first-line setting and 4 months in the second-line setting unless prior progression, unacceptable toxicity or patient refusal.
In first and second line treatment capecitabine can be maintained on investigators decision until disease progression, unacceptable toxicity or patient refusal.

STATISTICAL ANALYSES:

All analyses of efficacy and safety endpoints will be of exploratory nature.

Primary efficacy analysis

The primary efficacy analysis will investigate DDC between arm A and arm B.
DDC will be calculated by the Kaplan-Meier estimator and compared by using the Mantel-Haenszel-Log-Rank-Test. Power calculation will be made too.

Secondary efficacy variables, Safety Analysis

Secondary efficacy variables, AEs, safety variables and all other variables will be analyzed using descriptive statistics and appropriate statistical methods.

Study populations

All patients having got an ID will be included in the full analysis set (FAS). The population of all patients who have received at least one dose of study medication after randomization is the intent-to-treat (ITT) population. The per-protocol (PP) population excludes severe protocol violators. The efficacy analyses use the ITT and the PP population (ITT and PP analysis). Safety analysis will be performed in the FAS (inclusion condition: patient must have received at least one dose study medication) as well as in the ITT population.

Sample Size Estimation

No formal sample size calculation has been performed because of the lack of sufficient information. A sample size of 60 patients per group is planned to obtain a more reliable estimate of the treatment effect. This sample size should be adequate to get preliminary information about the magnitude of a potential difference between the DCC of both treatments (arm A and arm B). The data resulting from this pilot study can be used for the sample size estimation of a confirmatory trial which is designed either towards superiority or towards non-inferiority.

Randomization

The Randomization procedure will be performed by the computer software BLOCKRAND based on computer-generated permutated blocks. Randomization will be stratified by center.

SCHEDULE OF ASSESSMENTS

	Before Treatment		Study treatment period		End of treatment	Post Treatment
	Screening (= 21 days to random)	Baseline	Before each cycle	Every 8 - weeks	28 days Safety Follow-up (+/- 3d)	3 Mo Safety FU (± 1 week)
Consent form	x					
Demographics and medical history	x					
Cancer and treatment history	x					
ECG[1]						
Physical examinations and vital signs[2]						
Weight and Height[3]						
ECOG performance status		x				
Tumour assessment (CT or MRI (RECIST) (abdominal/pelvic CT; where applicable)[4]						
Chest X ray (if suspicion of lung lesions)	Only if clinically indicated					
Radionuclide bone scan/skeletal X ray for suspected bone metastases[9]	Only if clinically indicated					
Cranial CT for suspected CNS metastases	Only if clinically indicated					
Blood count[5]						

	Screening (= 21 days to random)	Baseline	Before each cycle	Every 8 - weeks	28 days Safety Follow-up (+/- 3d)	3 Mo Safety FU (± 1 week)
Clinical chemistry 2: INR, aPTT or PTT, PT, total protein, CEA, Cl, BUN, albumin, GGT, Glucose		x				
Creatinine clearance (calculated)[6]						
Serum Pregnancy test[7]						
K Ras status (if available)[10]		x				
Adverse events and concomitant medication		x				Target events
Survival and tumor status/ other anticancer treatment						x

1: Repeat during treatment phase if clinically relevant
2: Includes neurological examination, vital signs include body temp., pulse and blood pressure
3: Height at baseline only
4: =28 days before treatment start; also chest CT if lung metastases are suspected
5: Haemoglobin, platelet count, RBC, WBC including differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
6: For Capecitabine - creatinine clearance according Cockcroft-Gault formula (see section 7.2.6 of protocol)
7: women of child-bearing age
8: If CR/PR, confirmation of response after 4 weeks
9: Bone lesions identified at screening should be confirmed and followed by plain X ray
10: In case no status is available, K Ras testing will be retrieved and noted in the CRF whenever feasible

Table of Contents

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	(SGPT) Alanine Aminotransferase
ANC	Absolute neutrophil count
AST	(SGOT) Aspartate aminotransferase
aPTT	Activated partial thromboplastin time
BBP	Bevacizumab beyond first progression
BP	Blood pressure
BUN	Blood Urea Nitrogen
Ca++	Calcium
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CNS	Central Nervous System
COX	Cyclooxygenase type II
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CVAD	Central venous access device
DDC	Duration of disease control
DPD	Dihydropyrimidine dehydrogenase
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Collaborative Oncology Group
ECT	emission computed tomography

EDTA	Ethylene Diaminotetracyclicamino acetate
EU-CTD	European Union Clinical Trial Directive
FA	Folinic acid (leucovorin)
FAS	Full analysis set
5 FU	5 Fluorouracil
5 FU/LV	5 Fluorouracil with leucovorin
GGT	γ Glutamyltransferase
GI	Gastrointestinal
Hb	Haemoglobin
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification number
IHC	Immunohistochemistry
INR	International normalized ratio (prothrombin ratio)
IRB/EC	Institutional Review Board / Ethics Committee
ITT	Intent treat
IV	Intravenous
K+	Potassium
LD	Longest diameter
LDH	Lactate dehydrogenase
LV	Leucovorin (folinic acid)
MI	Myocardial infarction
MRI	Magnetic resonance imaging
mRNA	Messenger Ribonucleic acid
Na+	Sodium
NCI	National Cancer Institute
NSAIDs	Nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free survival
PP	Per protocol
PR	Partial response
PTT	Partial thromboplastin time
Q3W	Every three weeks
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Recombinant nuclear antibody
RT-PCR	Real-time polymerase chain reaction
SAE	Serious adverse event
SAR	Serious adverse reaction
SD	Stable disease
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient ischemic attack
ULN	Upper limit of normal
US	Ultrasound
USP	U.S. pharmacopeiaVEGF Vascular endothelial growth factor
WBC	White blood cell

1 Background

Colorectal cancer is one of the most common malignancies in Austria with an estimated incidence between 30 – 35 per 100.000. Between 4.400 and 5.000 patients are newly diagnosed with colorectal cancer per year. Colorectal cancer is the second most common cancer in Austrian women and the third most common cancer in Austrian men, and is the cause of death in over 2.200 patients each year in Austria[Statistik Austria]. Although early-stage disease is associated with favourable survival outcomes, the majority of patients present with advanced disease, either at the time of initial diagnosis or upon recurrence despite potential curative surgery. Prognosis for these patients is poor.

1.1 Chemotherapy in metastatic colorectal cancer (mCRC)

Since its introduction, 5 fluorouracil (5-FU) has been the cornerstone of treatment for metastatic colorectal cancer (mCRC). Early studies demonstrated that 5 FU in combination with leucovorin (LV) improved survival for patients with mCRC compared with best supportive care (BSC) [Simmonds et al 2000]. Subsequently irinotecan and oxaliplatin were approved for first line treatment of mCRC and combinations such as FOLFIRI and FOLFOX are widely used. The introduction of these compounds led to improved survival. In a meta analysis of 7 phase III trials median overall survival correlated significantly with the percentage of patients who received all 3 agents, which points to the importance of exposure to all active drugs during treatment [Grothey et al 2004]. Meanwhile the oral 5FU prodrug capecitabine (Xeloda®) proved equivalence to 5 FU and is a well tolerated alternative combination partner for Irinotecan or oxaliplatin (see table 1)

Data from a randomised, controlled phase III study **(CAIRO**) [Koopman et al., Lancet 2007] support the use of Xeloda at a starting dose 1000 mg/m^2 for 2 weeks every 3 weeks in combination with irinotecan for the first-line treatment of patients with metastatic colorectal cancer. Sequential treatment consisted of first-line treatment with Xeloda (1250 mg/m^2 twice daily for 14 days), second-line irinotecan (350 mg/m^2 on day 1), and third-line combination of capecitabine (1000 mg/m^2 twice daily for 14 days) with oxaliplatin (130 mg/m^2 on day 1). Combination treatment consisted of first-line treatment of Xeloda (1000 mg/m^2 twice daily for 14 days) combined with irinotecan (250 mg /m^2 on day 1) (XELIRI) and second-line capecitabine (1000 mg/m^2 twice daily for 14 days) plus oxaliplatin (130 mg/m^2 on day 1). In first-line treatment the median progression-free survival in the intent-to-treat population was 5.8 months (95%CI 5.1 - 6.2 months) for Xeloda monotherapy and 7.8 months (95%CI 7.0 - 8.3 months; p=0.0002) for XELIRI.

Data from an interim analysis of a multicentre, randomised, controlled phase II study (**AIO KRK 0604**) [Reinacher-Schick et al., ASCO 2008] support the use of Xeloda at a starting dose of 800 mg/m for 2 weeks every 3 weeks in combination with irinotecan and bevacizumab for the first-line treatment of patients with metastatic colorectal cancer. 115 Patients were randomised to treatment with Xeloda combined with irinotecan (XELIRI) and bevacizumab: Xeloda (800 mg/m^2 twice daily for two weeks followed by a 7 day rest period), irinotecan (200 mg/m^2 as a 30 minute infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg as a to 90 minute infusion on day 1 every 3 weeks); a total of 118 patients were randomised to treatment with Xeloda combined with oxaliplatin plus bevacizumab: Xeloda (1000 mg/m^2 twice daily for two weeks followed by a 7 day rest period), oxaliplatin (130 mg/m^2 as a 2 hour infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg as a 30 to 90 minute infusion on day 1 every 3 weeks). Progression-free survival at 6 months in the intent-to-treat population was 80% (XELIRI plus bevacizumab) versus 74% (XELOX plus bevacizumab). Overall response rate (complete response plus partial response) was 45% (XELOX plus bevacizumab) versus 47% (XELIRI plus bevacizumab).

The **AIO KRK-0104** randomized phase II trial investigated the efficacy and safety of cetuximab combined with capecitabine and irinotecan (CAPIRI) or capecitabine and oxaliplatin (CAPOX) in the first-line treatment of metastatic colorectal cancer (mCRC).[Moosmann etal., JCO 2011]
A total of 185 patients with mCRC were randomly assigned to cetuximab (400 mg/m^2 day 1, followed by 250 mg/m^2 weekly) plus CAPIRI (irinotecan 200 mg/m^2, day 1; capecitabine 800 mg/m^2 twice daily days 1 through 14, every 3 weeks; or cetuximab plus CAPOX (oxaliplatin 130 mg/m^2 day 1; capecitabine 1,000 mg/m^2 twice daily day 1 through 14, every 3 weeks). The primary study end point was objective response rate (ORR).
In the intention-to-treat patient population (n _ 177), ORR was 46% (95% CI, 35 to 57) for CAPIRI plus cetuximab versus 48% (95% CI, 37 to 59) for CAPOX plus cetuximab. Analysis of the *KRAS* gene mutation status was performed in 81.4% of the intention to treat population. Patients with *KRAS* wild-type in the CAPIRI plus cetuximab arm showed an ORR of 50.0%, a PFS of 6.2 months and an OS of 21.1 months. In the CAPOX plus cetuximab arm, an ORR of 44.9%, a PFS of 7.1 months and an OS of 23.5 months were observed. While ORR and PFS were comparable in *KRAS* wild-type and mutant subgroups, a trend toward longer survival was associated with *KRAS* wild-type. Both regimens had manageable toxicity profiles and were safe.

Data from a multicentre, randomised, controlled phase III clinical study (**NO16967)** [Rothenberg et al., Ann Onc 2008] support the use of Xeloda in combination with oxaliplatin for the second-line treatment of metastastic colorectal cancer. In this trial, 627 patients with metastatic colorectal carcinoma who had received prior treatment with irinotecan in

combination with a fluoropyrimidine regimen as first line therapy were randomised to treatment with XELOX or FOLFOX-4.
FOLFOX-4 in terms of progression-free survival in the per-protocol population and intent-to-treat population are shown in Table 2. The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival (see Table 2). The median follow up at the time of the primary analyses in the intent to-treat population was 2.1 years; data from analyses following an additional 6 months of follow up are also included in the Table 2

Table 2 Key efficacy results for the non inferiority analysis of Study **NO16967**

PRIMARY ANALYSIS			
XELOX (PPP*: N=251; ITT: N=313)**		**FOLFOX-4 (PPP*: N = 252; ITT**: N= 314)**	
Population	**Median Time to Event (Days)**		**HR (95% CI)**
Parameter: Progression-free Survival			
PPP ITT	154		1.03 (0.87; 1.24) 0.97 (0.83; 1.14)
Parameter: Overall Survival			
PPP ITT	388		1.07 (0.88; 1.31) 1.03 (0.87; 1.23)
ADDITIONAL 6 MONTHS OF FOLLOW UP			
Population	**Median Time to Event (Days)**		**HR (95% CI)**
Parameter: Progression-free Survival			
PPP ITT	154		1.04 (0.87; 1.24) 0.97 (0.83; 1.14)
Parameter: Overall Survival			
PPP ITT	393		1.05 (0,88; 1,27) 1,02 (0,86; 1,21)

*PPP= Per Protocol Population; **ITT=Intent to treat Population.

The trial by Tournigand et al., 2004 showed that when disease progression occurs after combining a fluoropyrimidine with either oxaliplatin or irinotecan, crossover to the other agent in second-line therapy can still produce satisfactory response rates and stable disease over several months. Both the FOLFIRI regimen and the FOLFOX6 regimen were analysed in first-line and – following crossover on progression – in second-line therapy. The two arms showed similar response rates (first-line therapy: FOLFIRI 56% vs. FOLFOX 54% and second-line therapy: FOLFIRI 4% vs. FOLFOX 15%). There were no significant differences in PFS (first-line therapy: FOLFIRI 8.5 months vs. FOLFOX 8.0 months and second-line therapy: FOLFIRI 2.5 months vs. FOLFOX 4.2 months) or OS (FOLFIRI-FOLFOX: 21.5 months vs. FOLFOX-FOLFIRI 20.6 months) (see table 2).

1.2 Bevacizumab in metastatic colorectal cancer

Recent advances in molecular biology have resulted in an improved understanding of the cell signalling processes involved in tumour growth and proliferation and provided a rationale for the development of targeted agents for the treatment of solid tumours. These agents have been designed to interfere in processes that are essential for tumour function. The most successful approaches examined to date involve the inhibition of the vascular endothelial growth factor (VEGF). VEGF is a powerful stimulator of new vessel proliferation and a potent survival and permeability factor for existing tumour vasculature [Gerber and Ferrara 2005]. VEGF is a key survival factor for tumour vasculature – without VEGF, recently formed microvasculature disintegrates and endothelial cells undergo apoptosis [Hicklin and Ellis 2005; Ferrara 2004; Erber et al 2004]. Agents that interfere with VEGF function have been shown in preclinical models to normalize tumour vasculature, suppressing the growth of established tumours [Jain 2001; Jain 2005] and improving the delivery of anticancer drugs. In addition, anti-VEGF therapy has been shown to have late effects, suppressing new vessel growth and the regrowth of vessel scaffolds [Inai et al 2004; Gerber and Ferrara 2005; Hicklin and Ellis 2005].

Many approaches have been developed to inhibit the VEGF pathway. The most successful of these is the development of the monoclonal humanized antibody bevacizumab (Avastin®), which targets circulating VEGF and prevents angiogenesis of tumour cells. Bevacizumab binds VEGF, preventing it from interacting with its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors in angiogenesis models leads to endothelial cell growth and new blood vessel formation.

1.2.1 Preclinical studies with bevacizumab

Anti-VEGF therapy in preclinical models of colon cancer showed tumour growth inhibition compared with control animals [Gerber and Ferrara 2005; Kim et al 1993; Melnyk et al 1999; Mesiano et al 1998]. Other studies have shown a reduction in the number and size of tumour metastases compared with controls [Melnyk et al 1999; Warren et al 1995]. Preclinical studies have also demonstrated the efficacy of combining bevacizumab with cytotoxic agents, including cyclophosphamide [Browder et al 2000], paclitaxel [Griffon-Etienne et al 1999], and epirubicin [Benbow et al 1999].

1.2.2 Clinical studies with bevacizumab

In a three-arm phase II study by Kabbinavar and colleagues, 104 patients with mCRC were randomized to one of the following: 5 FU 500 mg/m^2 plus LV 500 mg/m weekly for 4 weeks, repeated every 6 weeks (Roswell Park regimen); 5 FU/LV plus bevacizumab 10 mg/kg every 2 weeks (high-dose bevacizumab); or 5 FU/LV plus bevacizumab 5 mg/kg every 2 weeks (low-dose bevacizumab) [Kabbinavar et al 2003]. Efficacy and survival outcomes are shown in Table 3.
After crossover, two of 22 patients had a partial response to bevacizumab alone. Adverse events included thrombosis, which was the most significant adverse event and was fatal in one patient, hypertension, proteinuria, and transient epistaxis (lasting <5 minutes).

Table 3. Efficacy and safety outcomes in a phase II study of 5 FU/LV with or without bevacizumab
[Kabbinavar et al., 2003]

This study showed that the addition of bevacizumab to 5 FU/LV markedly improved outcomes compared to 5 FU/LV alone.
Similar results were seen in a second randomized phase II study in which bevacizumab plus 5 FU/LV was compared with placebo plus FU/LV as first-line therapy in patients with mCRC who were not considered optimal candidates for first-line irinotecan [Kabbinavar et al 2005]. The median survival was 16.6 months for patients in the bevacizumab + 5 FU/LV group and 12.9 months for those in the 5 FU/LV + placebo group (P=0.16). Patients in the bevacizumab group had significantly prolonged median PFS (9.2 months) compared with the 5 FU/LV + placebo group (5.5 months; P=0.0002) and a trend towards improved response rate (26.0% vs. 15.2% for placebo; P=0.055). Grade 3 hypertension was more common in patients treated with bevacizumab (16% vs. 3% for placebo) but was manageable. The authors concluded that firstline therapy with bevacizumab + 5 FU/LV provided a clinically significant benefit for mCRC patients who were not considered optimal candidates for first-line irinotecan treatment.

1.2.3 Phase III studies with bevacizumab: first-line mCRC

A phase III program has since demonstrated the efficacy and tolerability of bevacizumab in combination with 5 FU-based regimens, as summarized in Table 4.

In the first phase III study (study AVF2107g), performed in 815 previously untreated patients with mCRC, the efficacy of the IFL regimen (irinotecan 125 mg/m^2 90-minute infusion, followed by LV 20 mg/m^2 iv bolus, followed by 5 FU 500 mg/m^2 iv bolus; once weekly for 4 weeks, repeated every 6 weeks) was compared with that IFL plus bevacizumab (5 mg/kg iv every 2 weeks) [Hurwitz et al., 2004].

The addition of bevacizumab significantly prolonged OS and PFS, as shown in Table 4, while the response rate was markedly higher (45% vs. 35% for IFL + placebo; p=0.0029) and duration of response significantly longer (10.4 months vs. 7.1 months for IFL + placebo; p=0.0014) in patients in the bevacizumab group. Grade 3 hypertension was reported in 11% of patients in the bevacizumab group and 2% of those in the IFL group (p<0.01) but was easily manageable. Thrombotic events occurred in 19% of patients in the bevacizumab plus IFL group and 16% of those in the IFL group. Based on these findings, the US Food and Drug Administration (FDA) approved the combination of 5 FU-based chemotherapy plus bevacizumab for first-line treatment of patients with mCRC in 2004.

Hurwitz and colleagues also reported that the combination of bevacizumab plus 5 FU/LV was an active treatment for patients with mCRC, with similar activity and tolerability to of IFL [Hurwitz et al 2005]. In this study, patients were randomized to treatment with one of three regimens: IFL plus placebo; IFL plus bevacizumab 5 mg, or bevacizumab 5 mg plus 5 FU/LV (5-FU 500 mg/m^2 plus LV 500 mg/m^2 weekly for 4 weeks, repeated every 6 weeks; Roswell Park regimen). After a planned interim analysis confirmed the safety of the bevacizumab + IFL arm, recruitment of patients to the bevacizumab plus 5 FU/LV arm was discontinued.

Results from the comparison of bevacizumab plus 5 FU/LV and IFL are shown in Table 4. Similar response and survival rates were observed in the two groups. Toxicities were as expected for 5 FU/LV and IFL, with modest increases in the bevacizumab arm in hypertension (grade 3 in 18% and 3% for bevacizumab + 5 FU/LV and IFL, respectively) and bleeding (grade 1/2 epistaxis in 32% and 10%, respectively). This study demonstrates that the combination of bevacizumab and 5 FU/LV is an attractive treatment for patients with previously untreated mCRC.

Results from the XELOX-1/NO16966 study have shown that bevacizumab can also be combined with oxaliplatin-containing regimens [Saltz et al 2008]. This study was initially designed to prove non-inferiority of the XELOX regimen compared with FOLFOX-4. However, when it was shown that the addition of bevacizumab to the IFL regimen significantly improved OS and PFS, this study was amended to assess the potential effect of adding bevacizumab to XELOX or FOLFOX-4. the resulting 2x2 placebo-controlled study, patients

were randomized to treatment with bevacizumab or placebo plus either XELOX or FOLFOX4, as shown in Figure 1.

Results from this large study demonstrate that the addition of bevacizumab to oxaliplatin-based chemotherapy regimens significantly improves PFS compared with the oxaliplatin regimen alone. Patients treated with bevacizumab had a PFS of 9.4 months compared with 8.0 months in the placebo group (HR 0.83 [95% CI 0.72–0.95]; p=0.0023). A trend towards a significant difference in OS was observed (21.3 vs. 19.9 months, respectively; HR 0.89 [95% CI 0.76–1.03]; p=0.77).

Analysis of on-treatment PFS vs. general PFS suggested that continuation of bevacizumab until disease progression might be necessary to optimize the effect of bevacizumab on PFS. Only 29% of bevacizumab patients and 44–50% of placebo patients were treated until disease progression, with many patients who had not progressed completing treatment at the end of the primary treatment phase (Week 48).The rate of discontinuations related to adverse events was higher in bevacizumab patients (30% vs. 21% for placebo), although most were related to chemotherapy rather than bevacizumab. The incidence of adverse events of special interest to bevacizumab was low. Grade 3/4 hypertension occurred in 4% of patients in the bevacizumab group and 1% in the placebo group; grade 3/4
bleeding and arterial thrombotic events occurred in 2% each of bevacizumab patients and 1% of placebo patients.

Results from the randomized Phase III PACCE trial show that bevacizumab and chemotherapy (oxaliplatin- and irinotecan-based) as first-line treatment for mCRC are highly active in terms of PFS and OS, whereas the addition of panitumumab to bevacizumab and oxaliplatin- or irinotecan-based chemotherapy results in increased toxicity and decreased PFS.
In the final analysis, median PFS was 11,4 months for the chemotherapy and bevacizumab
median survival was 24.5 months for the chemotherapy and bevacizumab arm.
Increased toxicity without evidence of improved efficacy was observed in the panitumumab arm of the irinotecan cohort. Grade 3/4 adverse events in the oxaliplatin cohort (panitumumab *vs* chemotherapy and bevacizumab) included skin toxicity (36% *v* 1%), diarrhea (24% *v* 13%), infections (19% *v* 10%), and pulmonary embolism (6% *v* 4%).

1.2.4 Phase III studies of bevacizumab: second-line mCRC

The efficacy and tolerability of bevacizumab in the second-line treatment of patients with mCRC has also been examined. Giantonio and colleagues randomized patients who had failed treatment with irinotecan and 5 FU for advanced disease to one of three arms: FOLFOX4 + bevacizumab (n=286), FOLFOX4 (n=291), or bevacizumab alone (n=243) [Giantonio et al 2007]. Efficacy results are summarized in Table 5. The addition of bevacizumab to the FOLFOX4 regimen resulted in a statistically significant increase in OS: patients in the bevacizumab + FOLFOX4 group had a median OS of 12.9 months, compared with 10.8 months in the FOLFOX4 group (HR 0.75; p=0.0011). The median OS in the bevacizumab alone group was 10.2 months. PFS was also significantly prolonged by bevacizumab (7.3 vs. 4.7 months for bevacizumab + FOLFOX4 vs. FOLFOX4, respectively; HR 0.61; p<0.0001). In addition, more patients treated with bevacizumab + FOLFOX4 had a response to treatment (22.7% vs. 8.6% in the FOLFOX4 group (p<0.0001).

Grade 3/4 adverse events are summarized in Table 6. There was no significant difference between the bevacizumab + FOLFOX4 and FOLFOX4 groups in the incidence of adverse events leading to treatment discontinuation or in -cause 60-day mortality.

Based on these findings, the authors concluded that the addition of bevacizumab to

combination of 5 FU/LV and oxaliplatin improved survival duration in patients with previously treated mCRC.

Based on the above trials, bevacizumab is approved for treatment of metastatic colorectal cancer in combination with fluoropyrimidine based CTx.

1.3. Optimizing outcomes in mCRC: Treatment duration of bevacizumab

Preclinical studies have shown that VEGF is expressed throughout the life cycle of the tumour. Studies have also shown that anti-VEGF agents have activity throughout this process and that withdrawal of anti-VEGF agents results in vessel regrowth [Mancuso et al 2006]. In this setting, sustained VEGF inhibition has been shown to achieve and maintain tumour regression [Klement et al 2000; Klement et al 2002]. A key, and as yet unanswered, question in mCRC therapy is how long bevacizumab treatment should be continued.

Results from bevacizumab studies in patients with mCRC appear to support preclinical data, as indicated in Figure 2. Longer treatment duration in the bevacizumab arm of study AVF2107g translated into a significant improvement in PFS compared with the placebo arm. In -1/NO16966, patients in the placebo and bevacizumab arms received treatment for a similar duration (approximately 6 months). The addition of bevacizumab resulted in a superior PFS, but of lesser magnitude than in AVF2107g, believed to be due to the lack of treatment continuation.

A further cross-study comparison of 'general' and 'on-treatment' PFS demonstrated that 'general' and 'on-treatment' PFS was similar in study AVF2107g. There was, however, a considerable difference between these analyses in XELOX-1/NO16966. The HR for the general PFS analysis was lower in AVF2107g than in XELOX-1/NO16966 (HR=0.58 vs. 0.83, respectively). In contrast, the 'on-treatment' analyses were not different between the two trials (HR=0.54 vs. 0.63). These observations suggest that there was a difference in the use of treatment between the two studies. As the majority of patients in study AVF2107g were treated until progression, this comparison reflects the superior efficacy of regimens in which bevacizumab is given until disease progression.

Insight into the effect of treatment with bevacizumab beyond progression has been provided by the non randomized, prospective bevacizumab treatment register known as the BRITE Study. In this prospective study, the impact of treatment with bevacizumab beyond first progression was examined [Grothey et al 2008]. A total of 1445 patients (74% of the BRiTE study population) had disease progression, and received further treatment after progression with bevacizumab (n=642,44%), treatment other than bevacizumab (n=531; 37%), or no treatment (n=253; 18%).

In a multivariate analysis that included pre- and post-treatment variables, performed to adjust for possible confounding factors within this nonrandomized trial, bevacizumab treatment after progression was independently associated with prolonged survival after first progression ($p<0.001$). (Table 7).
Survival outcomes are summarized in Table 8.

Bevacizumab was well tolerated in this study and treatment with this agent after first progression did not result in an increase in adverse events compared with bevacizumab before progression only (Table 9).

In a Phase III study of first-line XELOX plus bevacizumab (BEV) for 6 cycles followed by XELOX plus BEV or single-agent (s/a) BEV as maintenance therapy in patients (pts) with metastatic colorectal cancer (mCRC): **The *MACRO* Trial** (Spanish Cooperative Group for the Treatment of Digestive Tumors [TTD])[Tabernero et al., J Clin Oncol 28:7s, 2010 (suppl; abstr 3501)] it could be shown that BEV as a maintenance therapy following induction

XELOX-BEV was not inferior to continuation XELOX-BEV. This study suggests that maintenance therapy with s/a BEV is an appropriate option following induction XELOX-BEV in pts with mCRC.

Previously untreated mCRC pts were randomized to receive BEV (7.5 mg/kg) + XELOX (capecitabine 1,000 mg/m^2 bid d1-14 + oxaliplatin 130 mg/m^2 d1) q3w x6 cycles continued by maintenance therapy with XELOX-BEV (Arm A) or s/a BEV (Arm B) until progression. The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), objective response rate (ORR), and safety. The statistical design was based on a noninferiority hypothesis; a mPFS of 10 months in Arm A; unilateral a of 0.025 and ß of 0.8; and a sample size of 470 pts for a hazard ratio (HR) of 1.2. **Results:** 480 pts (median age 64 years, range 30-82) were randomized: 239 Arm A, 241 Arm B; no significant differences in demographic characteristics. Median follow-up was 16 months (range: 0.7-35.7). There were not statistically significant differences in ORR, PFS, and OS between the 2 arms. (Table 9a) Preliminary analysis of safety shows that tolerability was acceptable in the 2 arms, with grade 3/4 diarrhea in 11% and 13%, HFS in 12% and 6%, and neuropathy in 24% and 7% in Arms A and B, respectively.

Table 9a:

Efficacy	Arm A	Arm B	p value	HR/OR (95% CI)
mPFS, months	11.0	10.3	0.59	HR: 1.07 (0.84-1.36)
mOS, months	25.3	20.7	0.63	HR: 1.07 (0.81-1.41)
ORR, %			0.51	OR: 1.13 (0.79-1.63)
M1 resection, %		8.3	0.51	OR: 1.23 (0.66- 2.32)

In a randomized, multicenter phase III trial, bevacizumab plus capecitabine were given as maintenance treatment after initial treatment with bevacizumab plus XELOX in previously untreated metastatic colorectal cancer. [Yalcin et al., J Clin Oncol 29: 2011 (suppl 4; abstr 474)]
It could be shown that BEV + capecitabine as maintenance therapy following induction BEV + XELOX is non-inferior to continuous BEV + XELOX until progression. While this study is ongoing, these interim findings suggest that maintenance therapy with BEV + capecitabine is an appropriate option following induction BEV + XELOX in pts with mCRC.

BEV (7.5 mg/kg) + XELOX (capecitabine 1,000 mg/m^2 bid d1-14 + oxaliplatin 130 mg/m^2 d1 q3w) administered until progression (Arm A) or 6 cycles of BEV + XELOX followed by BEV + capecitabine were administered until progression (Arm B). PFS was the primary endpoint; secondary endpoints included overall survival (OS), objective response rate (ORR), and safety. A sample size of 118 patients (pts) was calculated to achieve 80% power to detect an increase of 1.5 months in median PFS between Arm A (9.5 months) and Arm B (11.0 months) with a standard deviation of 3.9 months and significance level of 0.05 using a 10% drop-out rate. **Results:** A total of 122 pts were randomized. No significant differences were found in demographic characteristics between the two arms. Median treatment period was 6.1 (range 0.7-13.4) and 6.8 (range 0.7-12.4) months in Arms A and B, respectively. Interim analysis showed no statistically significant differences in median PFS

and ORR (Table 9b). Tolerability was also acceptable in both arms with grade 3/4 diarrhoea in 7.7% vs. 8.2%, weakness in 15.2% vs. 8.4%, hand-foot syndrome in 6.3% vs. 9.4%, and neuropathy in 2.8% vs. 4.6% of pts in Arms A and B, respectively.

Table 9b:

Efficacy	**Arm A (n=61)**	**Arm B (n=61)**	**P value**
Median PFS, months	8.3	9.9	0.064
ORR, %	57.4	69.2	0.207

Results from a large German community-based cohort study. [Patterns of maintenance treatment (Tx) following first-line bevacizumab (bev) plus chemotherapy (CT) for metastatic colorectal cancer (mCRC)] [Arnold et al., J Clin Oncol 29: 2011 (suppl 4; abstr 502)] showed that a trend towards better PFS was observed in pts receiving bev + CT maintenance vs. single-agent bev.

Induction and maintenance Tx in a large observational cohort study of bev + various first-line CT regimens were analysed. Results of the entire cohort were reported earlier [Arnold et al. ASCO GI 2010].

From Jan 05 to Jun 08, 1620 patients (pts) were enrolled at 261 sites. 1,307 pts (81% of total) received bev + fluoropyrimidine-oxaliplatin (n=306, 23.5%) or fluoropyrimidine-irinotecan (n=1,001, 76.5%). While Tx reduction was not predefined, after induction 271 pts (21%) received de-escalated maintenance Tx: bev alone (n=106; 8%), or bev + CT (n=165; 13%). Median Tx duration for pts receiving bev alone was 8.7 mo for induction and 3.2 mo for maintenance. Pts receiving bev + CT maintenance had shorter induction (5.1 mo) but longer maintenance (4.4 mo). Median PFS (after induction) with bev maintenance was 10.8 mo vs. 13.5 mo for bev + CT maintenance. Data are available from 161 pts with bev + CT maintenance after induction with oxaliplatin (n=97) or irinotecan (n=64). Median total Tx duration was 9.6 mo for oxaliplatin-based induction and 10.9 mo for irinotecan-based induction; median induction duration was 4.1 and 5.5 mo, and maintenance duration was 4.3 and 4.4 mo, respectively. Median PFS (after induction) was 12.8 and 14.1 mo, respectively. Progressive disease (PD) has not yet occurred in 165 pts (62% of maintenance cohort). A higher proportion of pts received Tx until PD (74% and 79%, respectively).

2 Aim and Rationale of Study

Several phase II studies evaluated the safety and efficacy of adding bevacizumab to XELOX and XELIRI regimen in metastatic colorectal cancer (Ducreux et al., FNLCC ACCORD 13/ 0503 study – ASCO 2009, Reinacher Schick et al, ASCO 2008).
Results have shown that these combinations are highly activ and tolerable.

Of special interest is the therapeutic index of the dose modified XELIRI regimen investigated in the AIO trial (Reinacher Schick et al., ASCO 2008)

Tournigand et al investigated if sequential replacement of oxaliplatin and irinotecan as combination partners to infusional 5FU are safe and effective. XELOX or XELIRI + bevacizumab have been investigated in several trials, but in an approach with clearly defined cross-wise XELIRI-XELOX change criteria.

In this trial we also like to follow the concept of maintenance therapy, which was investigated in the MACRO trial [Trabernero et al., J Clin Oncol 28:7s, 2010(suppl; abstr 3501)]
The addition of Capecitabine to a Bevacizumab maintenance therapy is also a strategy of high interest and was studied by Yalcin et al[Yalcin et al., J Clin Oncol 29: 2011 (suppl 4; abstr 474)].
Therefore investigators in this trial have the option to add Capecitabine to Bebacizumab in terms of maintenance therapy.

Based on these trials the addition of bevacizumab to an approach with clearly defined cross-wise XELIRI-XELOX change criteria combined with the concept of maintenance therapy seems to be attractive option to improve the results for patients with metastatic colorectal cancer.

In the ongoing TML study (Treatment in Multiple Lines, ML18147) patients are randomized to flouropyrimidine based chemotherapy plus oxaliplatin/ irinotecan + bevacizumab for 2nd line treatment, depending on the first line treatment.

This trial investigates two different sequential treatment optiones with XELIRI/ XELOX in first and second line with the addition of bevacizumab and tries to give answer to the question if there is an optimal sequence for the benefit of the patient.

3 Objectives of the Study

3.1 Primary objective

- Duration of Disease Control (DDC)

3.2 Secondary objectives

- first line PFS
- second line PFS
- overall response rate
- time to response
- duration of response
- overall survival
- tumour assessments (based on RECIST criteria) using CT scans, MRI scans, X ray, bone scan, clinical examination

4 Study Design

4.1 Overview of Study Design

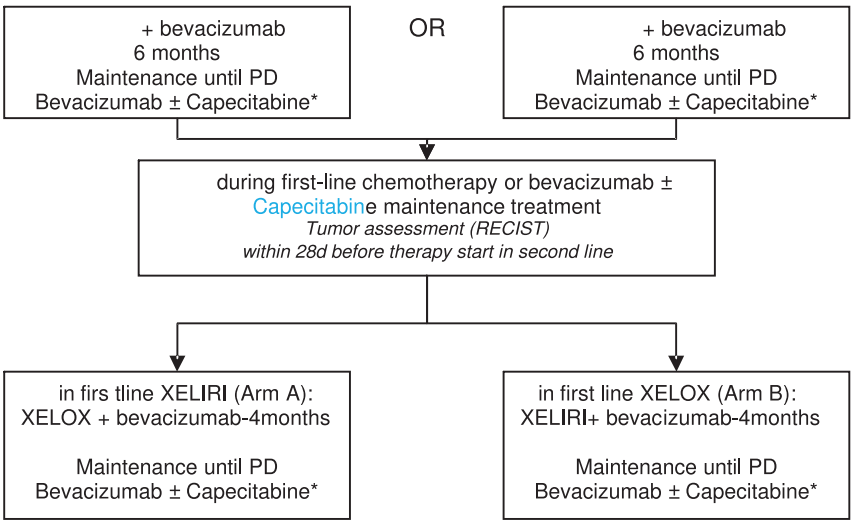
This study is designed as a prospective, randomized, open-label, 2 arm pilot trial of chemotherapy + Bevacizumab therapies in a cross wise design for second-line metastatic colorectal cancer and disease progression under first-line chemotherapy + Bevacizumab combination. The study is designed to evaluate the efficacy of XELIRI followed by XELOX and XELOX followed by XELIRI + Bevacizumab in terms of DDC.

Targeted patient population: Patient with metastatic colorectal cancer who did not receive systemic treatment for their metastatic disease

Patients will be treated with an established first line therapy consisting of either XELOX or XELIRI plus bevacizumab. The chemotherapy treatment will be given for 6 months except prior disease progression, unacceptable toxicity or patient refusal.
Bevacizumab will be given until disease progression, unacceptable toxicity or patient refusal.
Capecitabine can be given in addition at the investigators' discretion until disease progression, unacceptable toxicity or patient refusal.

If serious side effects occur despite adequate dose reduction, oxaliplatin or irinotecan should be discontinued. In case of oxaliplatin or irinotecan-related discontinuation capecitabi e and bevacizumab should be continued.
If capecitabine also has to be discontinued in first line treatment bevacizumab should be continued.
In case of permanent discontinuation of bevacizumab for toxicities as specified in Section 7.1, chemotherapy should be continued according to the study protocol.

Upon completation of first line chemotherapy, in both treatment arms, patients with disease control (CR, PR, stable disease) will receive bevacizumab maintenance treatment (7,5 mg/kg every 3 weeks). On investigators decision patients can receive capecitabine as additional maitenance treatment. (1000 mg/m^2 oral bid, days 1 14 q3w)
Patient with documented tumour progression based on RECIST criteria using CT scan or MRI scan during a bevacizumab treatment break = 3 months (longer break possible for other treatment components) or in the course of first-line receive therapies as indicated in the flow chart:



*On investigators decision, in addition to Bevacizumab (7.5 mg/kg q3w), patients can receive capecitabine as maitenance treatment. (1000 mg/m^2 oral bid, days 1 14 q3w)
Essentially at the time of progression irinotecan will be replaced by oxaliplatin (ARM A) or oxaliplatin will be replaced by irinotecan (ARM B). The second line treatment will be given for a duration of 4 months unless prior disease progression, unacceptable toxicity or patient refusal. If serious side effects occur despite adequate dose reduction, oxaliplatin or irinotecan should be discontinued. In case of oxaliplatin or irinotecan-related discontinuation capecitabine and bevacizumab should be continued.
If capecitabine also has to be discontinued within the 4 months of chemotherapy treatment in second line bevacizumab should be continued.
In case of permanent discontinuation of bevacizumab for toxicities as specified in Section 7.1, chemotherapy should be continued according to the study protocol.

If a patient withdraws consent for further participation in the study, follow up assessments will be discontinued, however, the patient should still be followed for survival.

In patients with metastases confined to the liver and a good-quality response, the possibility of surgical resectability of liver metastases should be re-evaluated, irrespective of study arm.

4.2 Number of Subjects

It is planned that 120 patients will be enrolled in this study to receive first and second line treatment in approximately 16 centers. It is assumed that relevant study protocol violations will happen at about 20% of the included patients (definition as drop outs with exclusion from PP population). Eligible patients will be allocated to treatment arm A or treatment arm B by randomization. The patient ID number will be allocated to the patient via the eCRF.

5 Study Population

Patients with metastatic colorectal cancer (according to RECIST criteria) who did not receive systemic treatment for their metastatic disease.

All patients must satisfy the following criteria in order to be eligible for the study:

5.1 Inclusion Criteria

1)Written informed consent

2) Age ≥ 18 years

3) Patient must be able to comply with the protocol

4) Histologically or cytologically confirmed carcinoma of the colon and/or rectum with evidence of metastases.

5 Diagnosis of metastatic disease according to RECIST not more than 3 months prior to enrolment.

6) Life Expectancy of at least 3 months

7) At least one measurable metastatic lesion (as per RECIST criteria)

8) Prior adjuvant or neo-adjuvant chemotherapy/radiotherapy allowed if completed more than 6 months before inclusion.

9) ECOG performance score of 0 or 1

0) Adequate haematological function: ANC $\geq 1.5 \times 10^9$/L; platelets $\geq 100 \times 10^9$/L, Hb ≥ 9 g/dL

11) INR ≤ 1.5 and aPTT ≤ 1.5 x ULN within 7 days prior to starting study treatment

12) Adequate liver function: Serum bilirubin ≤ 1.5 x ULN; alkaline phosphatase and transaminases ≤ 2.5 x ULN (in case of liver metastases < 5 x ULN)

13) Serum Creatinine ≤ 1.5 x ULN

14) Urine dipstick for proteinuria < 2+. If urine dipstick is $\geq 2+$, 24- hour urine must demonstrate $\leq$ 1 g of protein in 24 hours

15) Negative serum pregnancy test within 7 days of starting study treatment in pre-menopausal women and women < 2 years after the onset of menopause. This test has to be reconfirmed by a urine test, should the 7 days window be exceeded. Fertile women (<2 years after last menstruation and men must use effective means of contraception (oral contraceptives, intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly or surgically sterile).

5.2 Exclusion Criteria

1) Prior chemotherapeutic treatment for metastatic CRC

2) Symptomatic CNS metastases

3) Significant vascular disease (e.g. aortic aneurysm potentially requiring surgical intervention, pulmonary embolism or recent peripheral arterial thrombosis) within 6 months prior start of study treatment.

4) History of haemoptysis (= ½ teaspoon of bright red blood per episode) within 1 month prior start of study treatment

5) Past or current history (within the last 2 years prior to treatment start) of other malignancies (Patients with curatively treated basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible).

6) Clinically significant cardiovascular disease, for example CVA (6 months before treatment start), myocardial infarction (6 months before treatment start), unstable angina, NYHA ≥ grade 2 CHF, arrhythmia requiring medication, or uncontrolled hypertension.

7) Prior history of hypertensive crisis or hypertensive encephalopathy

8) Treatment with any other investigational agent or any other biological agent (e.g.cetuximab), or participation in another clinical trial within 30 days prior to entering this study.

9) Known hypersensitivity to any of the study drugs

10) Current or recent (within 10 days of first dose of study treatment) chronic use of aspirin (> 325 mg/day)

11) Current or recent (within 10 days prior to study treatment start) use of full-dose oral or parenteral anticoagulants or thrombolytic agent for therapeutic (as opposed to prophylactic) purposes.

12) Evidence of bleeding diathesis or coagulopathy.

13) Serious, non healing wound, ulcer, or bone fracture.

14) Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to treatment, or anticipation of the need for major surgery during the course of the study. If CVAD is required for chemotherapy administration, it should be inserted within 2 days prior to study treatment cycle.

15) Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior start of study therapy

16) History of abdominal fistula, tracheo-oesophageal fistula or any grade 4 non gastrointestinal fistula, gastrointestinal perforation or intraabdominal abscess before 1st line therapy.

17) History or evidence upon physical/neurological examination of CNS disease (unrelated to cancer) (unless adequately treated with standard medical therapy) e.g. uncontrolled seizures

18) Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment-related complications

19) Patients with contraindication for cross over chemotherapy (e.g. patients treated with irinotecan based first line therapy and serious polyneuropathy > grade 1, not feasible for oxaliplatin based cross over second line therapy, or patients treated with oxaliplatin based first line therapy and hereditary fructose intolerance not feasible for Irinotecan based cross over second line therapy)

20) Pregnancy or lactation

21) Fertile women (<2 years after last menstruation) and men not willing to use effective means of contraception.

6 Assessments and Procedures

Please refer to the Schedule of Assessments for an overview.

Data will be collected via the completion of an electronic case report form CRF) for each eligible patient.

The investigator should confirm eligibility of the patient according to the inclusion and exclusion criteria of the study.

6.1 Screening Examination and Eligibility Screening Form

All patients will provide written Informed Consent before any study specific assessment is performed.

Screening assessments should occur within 28 days of first study treatment.

Patients not meeting the eligibility criteria will not be enrolled into the study. Once the patient's eligibility has been confirmed, the enrolment will occur and a patient ID number will be allocated to the patient via the eCRF.

Patients should receive their first dose of study treatment on the day of randomization, but not later than 7 days after randomization.

6.2 Study Assessments

6.2.1 Tumour Measurements

For patients with multiple measurable lesions, up to 5 lesions per organ should be identified, recorded and measured within 28 days before start of treatment. Tumour measurements / assessments will be performed based on RECIST criteria using CT scan or MRI scan.

- Brain metastases should be excluded by clinical examination. In case of neurological symptoms, CT or MRI scan of the brain will be performed.

- If suspicion of lung lesions, chest CT should be performed.

- If suspicion of bone metastasis, radiologic/scintigraphic assessment should be performed

The exact technique used for measurement of lesions (i.e. either CT or MRI scan) will be left to the discretion of the investigator, however, for each patient the same technique must be used throughout the study, assessed whenever possible by the same individual. All lesions identified at screening have to be assessed at each scheduled tumour measurement.

To be evaluable for response, patients must have at least one measurable lesion. The measurable lesion(s) will be the main indicator of response.
Measurable lesions must have at least one diameter of 20 mm with conventional techniques and at least 10 mm with spiral CT scan. Where there are several lesions, assessment is based on the sum of the longest diameters of the individual target lesions.

In cases where there is suspicion of progression before the next scheduled assessment, an unscheduled tumour assessment should be performed.
If a ient inadvertently misses a prescribed tumour evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessment, unless signs of disease progression are present clinically.

In case a detected increase in tumour size is below the resolution limit of the CT/MRI scanner, it is accepted to continue with treatment until a second assessment at a later time point unequivocally confirms progressive disease.

The following are defined as non-target lesions: bone lesions, leptomeningeal disease, pleural/pericardial effusion, ascites, inflammatory breast disease, lymphangitis, cystic lesions and lesions not measurable by computed tomography (CT) or magnetic resonance imaging (MRI). All non-target lesions are described over time and need not be measured.

6.2.2 Other Clinical Assessments (excluding laboratory tests)

Clinical assessments at baseline include:

- Demographic Information (including stratification information) and medical history
- Cancer and treatment history (including K Ras status if available)
  Current diseases and Concomitant medications
- Physical examination, height and weight measurements and vital signs
- ECOG performance status
- ECG.

6.2.3 Laboratory Assessments

The local laboratories will perform the analyses and provide their respective reference ranges.

Laboratory assessments will include the following:

Haematology - Haemoglobin, platelet count, RBC, WBC including differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)

Coagulation tests: INR and aPTT

Serum Chemistry Na+, K+, Ca++, Cl–, urea (BUN), total protein, albumin, alkaline phosphatase, ALT, AST, GGT, LDH, total bilirubin (direct bilirubin in case of abnormal total bilirubin), serum creatinine, glucose, CEA, total albumin [if capecitabine is used - creatinine clearance will be calculated according Cockroft-Gault, see section 7.2.6]

Urinalysis - Dipstick urinalysis is sufficient as long as the protein result is < 2+. If urine dipstickshows protein = 2+, 24-hour urine must demonstrate = 1 g of protein in 24 hours for eligibility. For further specifications refer to Section 7.1.3.

Serum Pregnancy test (if applicable) within 7 days of starting study treatment in pre-menopausal women and women < 2 years after the onset of menopause. Note: a negative test has to be reconfirmed by a urine test, should the 7 day window be exceeded.

6.3 Study Procedures

6.3.1 Screening procedures (days -28 to -1)

All patients will be screened and baseline procedures performed from 4 weeks to 24 hours prior to the start of study treatment. These includes the following:

Table 10 – Screening Procedures (days -28 to -1)

Signed informed consent	Obtained prior to enrolment
Demographics and medical history	Includes age, gender, race and previous and current diseases
Cancer and treatment history	Including K Ras status if available
Physical examination and vital signs	Physical examination will include height (at screening only), weight, and neurological examination. Vital signs measurements will include body temperature, pulse and blood pressure. In case of neurological symptoms, a CT or MRI of the brain will be performed
ECOG performance status	See Appendix 5
Bone scan	Bone scan will be performed only if clinically indicated at screening. Bone lesions noted on screening scan should be confirmed and followed by plain X ray (bone lesions are not target lesions).
ECG	
Tumour measurement (CT or MRI) of the chest and abdomen/ pelvic region	

6.3.2 Baseline procedures (days -7 to -1)

Table 11 - Baseline Procedures (days -7 to -1)

Serum pregnancy test	A serum pregnancy test will be performed in pre-menopausal women and women who are menopausal for < 2 years. In case the sampling date for serum pregnancy testing exceeds 7 days before treatment start, a urine test is required for confirmation of the absence of pregnancy.
Haematology / blood chemistry	
Urinalysis	If urine dipstick is $\geq$ 2+, 24-hour urine must demonstrate $\leq$ 1 g
aPTT, INR	

Note: the insertion of a central venous access device (CVAD) must occur at least 2 days prior to the initiation of bevacizumab treatment.

Randomization will occur after patient eligibility has been established.

6.3.3 Treatment phase

During the treatment phase the following assessments and procedures will be performed:

Table 12 – Assessments during Treatment Phase

Concomitant medications Adverse events	Assessed on ongoing basis
Physical examinations and vital signs	Before each cycle of therapy and at end of therapy, includes body weight and blood pressure. In case of hypertension the guidelines as specified in Section 7.1.2 should be followed.
ECOG Performance Status	Before each cycle of therapy. See
Chest X ray, Chest CT	In patients with lung metastases at baseline every 8 9 weeks
Bone scan	Only if clinically indicated
ECG	if clinically indicated
Serum pregnancy test	In premenopausal women once a month/ before each cycle
Haematology / Na, K, Ca, creatinine, bilirubin, ALT, AST, ALP, LDH	Prior to every chemotherapy cycle
aPTT / INR or PTT, PT, total protein, CEA, Cl^-, BUN, albumin, GGT, Glucose	Every 8 – 9 weeks
Urinalysis	Must be assessed prior to each bevacizumab infusion. In case of a $\geq$ 2+ protein dipstick result, a 24-hour urine collection is required. Further treatment should be in line with the recommendations as defined in Section 7.1.3.
Tumour measurements	(CT or MRI) Every 8 – 9 weeks disease progression.

Table 13 – Assessments at End of treatment

Concomitant medications and Adverse events	Any SAEs or AEs of special interest should be followed until return to baseline status, the condition has stabilised or until the patient's death.

Physical examinations and vital signs	Before each cycle of therapy and at end of therapy, includes body weight and blood pressure. In case of hypertension the guidelines as specified in Section 7.1.2 should be followed.
ECOG Performance Status	Before each cycle of therapy. See Appendix 5.
ECG	
Serum pregnancy test	In premenopausal women once a month/ before each cycle
Haematology / Na, K, Ca, creatinine, bilirubin, ALT, AST, ALP, LDH	
Survival	After end of therapy follow up every 3 months

Patients who discontinued therapy for any reason should have a safety follow-up completed 28 days after last dose of any study treatment. This assessment should include ECOG performance status, physical examination, vital signs, concomitant treatments and adverse events.

6.3.4 Post-treatment follow-up

Patients will have a follow-up assessment every 3 months post treatment over a period of 24 months. The following information will be collected during the follow-up visits:

- Tumour status
- Survival data
- Subsequent anti-cancer therapy
- Study drug related serious adverse events will be monitored until the event has resolved.

6.4 Study Drugs

Clinical use and administration of all drugs used in the study should follow the respective product/prescribing information.
In case of permanent discontinuation of chemotherapy for toxicities as specified in Section 7.2, bevacizumab should be continued in the absence of progressive disease. In case of permanent discontinuation of bevacizumab for toxicities as specified in Section 7.1, chemotherapy should be continued according to the study protocol.

Bevacizumab used in the study for 2nd line treatment is labelled for treatment of metastatic colorectal cancer.

6.4.1 Oxaliplatin

Mode of action: DNA cross-linkage

Administration: intravenous. Oxaliplatin is first reconstituted in the original vial with water for injection or 5% glucose solution (10 mL for the 50 mg dosage or 20 mL for the 100 mg dosage), then diluted for infusion in 250–500 mL of 5% glucose solution. Stability: The reconstituted solution is microbiologically stable for 24 hours at 3 8°C, and chemically and

physically stable for 48 hours at 2 8°C and 30°C. The prepared infusion is intended for immediate use. Never mix with 0.9% sodium chloride solution. The intravenous infusion is given over 2 hours.

Common side effects: Blood dyscrasias, neurotoxic effects in the form of peripheral sensory neurotoxicity (predominantly reversible), cold-induced dysesthesia (reversible), cramps, pharyngolaryngeal sensory disturbances, paresthesia, nausea, vomiting, diarrhea, allergic reactions.

6.4.2 Irinotecan

Mode of action: topoisomerase I inhibitor. Inhibition of DNA topoisomerase I by irinotecan induces single-strand DNA lesions which block the DNA replication fork and are responsible for the cytotoxicity. This cytotoxic activity was found to be time-dependent and was specific to the S phase.

Administration: intravenous. The required amount of irinotecan solution is aseptically withdrawn from the vial with a calibrated syringe and injected into a 250 ml infusion bag or bottle containing either 0.9% sodium chloride solution or 5% glucose solution. The solution is then thoroughly mixed by manual rotation.
The shelf-life of unopened vials is 36 months. If the solution is prepared under aseptic conditions, it should be used (infusion completed) within 12 hours at room temperature or 24 hours if stored at 2 8°C. Vials of irinotecan concentrate should be stored protected from light. The prepared infusion solution is administered intravenously over 30 to 90 minutes.

Common Side effects: Neutropenia, diarrhea and “late diarrhea”. Nausea and vomiting may also occur, as well as an acute cholinergic syndrome.

6.4.3 Capecitabine

Administration: oral. After oral ingestion, capecitabine crosses the intestinal mucosa as the intact drug and is metabolised in the liver to 5'-deoxy- fluorocytidine (5'-DFCR) by the enzyme carboxylesterase. 5'-DFCR is metabolised by the enzyme cytidine deaminase to 5'-deoxy- fluorouridine (5'-DFUR), which in turn is converted to 5 FU by thymidine phosphorylase, an enzyme found in particularly high concentrations in tumours. The drug is administered in the morning and evening, in each case half an hour after a meal, starting on the evening of day 1 and ending on the morning of day 15.

Common side effects: Hand-foot syndrome, diarrhea, cardiotoxicity, stomatitis, mild myelotoxicity (leucopenia, thrombocytopenia).

6.4.4 Bevacizumab

Bevacizumab used in the study for 2nd line treatment is labelled for treatment of metastatic colorectal cancer.

Mode of action: Bevacizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, 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 regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

Administration: Section 8.2

Common side effects: hypertension, fatigue or asthenia, diarrhoea and abdominal pain.

6.5 End of study

The clinical cut- ff date for the final analysis of progression free survival is the date at which the last data point from the last patient was captured to reach the 100% information.
After the primary analysis the patients will continue to be followed every 3 months for evaluation of treatment response and status of disease progression over a period of 24 months. At this time, the trial will end no further data will be collected on the clinical database for this study. The end of the ML25153 is defined as the last patient last visit at the end of the follow up period.

7 DOSE MODIFICATIONS

7.1 Dose modifications for bevacizumab

Bevacizumab should only be initiated under the supervision of a physician experienced in the treatment of cancer patients. Please refer to the summary of product characteristics as the primary source of safety information.

Bevacizumab is contraindicated in patients with known hypersensitivity to bevacizumab or any component of this drug product.

No dose reduction of bevacizumab is foreseen for an individual patient. Skipped doses or termination of treatment will be based on the observed toxicities as specified below. No dose adjustments are allowed except for body weight changes of more than 10%. Missed doses will not be made up for.

A rounding up or down of the dose is acceptable to allow practical ease of administration (± 10%)

Specific instructions on the grading and management of hypertension, proteinuria, thrombosis/embolism, haemorrhage and other events attributable to bevacizumab, are provided below from section 7.1.2 to 7.1.7.

Grade 3 4 bevacizumab-related AEs, should be managed as below:

- First occurrence: hold bevacizumab until toxicity has improved to grade $\leq$1
  Second occurrence: permanently discontinue treatment

In addition any patient who experiences the following events should permanently discontinue bevacizumab:

- Gastrointestinal perforation, abscesses and fistulae
- Arterial or venous thromboembolic events
- Grade 3/4 haemorrhagic events other than pulmonary or CNS haemorrhage
- Symptomatic grade 4 thrombosis
- Grade 4 hypertension (hypertensive crisis) or Grade 3 hypertension not appropriately manageable by medication
- Grade 4 proteinuria (nephrotic syndrome)
- Reversible posterior leucencephalopathy syndrome
- Any grade of pulmonary haemorrhage/haemoptysis
- Grade $\geq$2 CNS haemorrhage
- Any grade of hypersensitivity/allergic reactions in response to bevacizumab infusion
- Grade =3 bowel obstruction
- Any grade of wound dehiscence requiring medical or surgical intervention (if the wound is from an incision that entered a body cavity)

- Grade =3 left ventricular systolic dysfunction

Note that bevacizumab should be temporarily interrupted in the event of febrile grade 4 neutropenia and/or grade 4 thrombocytopenia, since these conditions are predisposing factors for an increased bleeding tendency.

In case bevacizumab is discontinued, chemotherapy should be continued according to protocol.

7.1.1 Surgical procedures / wound healing complications

Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed.

Bevacizumab should be withheld for at least 5 weeks before conducting elective surgery.
Emergency surgery should be performed as appropriate without delay.

7.1.2 Hypertension

Blood pressure needs to be assessed before each bevacizumab administration.
The following table indicates the clinical action to be taken in the event of an AE/SAE of hypertension.
Blood pressure measurements should occur after the patient has been in a resting position for =5 minutes. Repeat measurement of BP for verification should be undertaken if the initial reading is =140 mmHg systolic and/or =90 mmHg diastolic pressures.

Table 14 – Management of Hypertension

NCI CTCAE v4.0 Grading	Description	Action
1	Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Intervention not indicated
2	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg);	medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated; patients may continue bevacizumab therapy
3	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg)	Medical intervention indicated; more than one drug or more intensive therapy than previously used indicated Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated **Bevacizumab** should be withheld for persistent or symptomatic hypertension and should be permanently discontinued if hypertension is not controlled
4	Life threatening consequence (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	urgent intervention indicated; Occurrence of grade 4 hypertension should lead to permanent discontinuation of bevacizumab

All doses of anti-hypertensive medicines should be recorded at all visits.

7.1.3 Proteinuria

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that Grade 1 proteinuria may be related to bevacizumab dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome).

All patients receiving bevacizumab will have a urinalysis performed within 48 hours prior to each bevacizumab dose. All toxicity will be graded according to NCI CTC-AE (version 4.0) guidelines. Adjustment of bevacizumab administration for proteinuria will occur according to the following guidelines:

- Proteinuria by dipstick has to be assessed before each bevacizumab administration unless proteinuria has been determined by 24-hour urine

NCI CTCAE v4.0 Grading	**Urinalysis**	**Treatment action**
Grade 1	1+ proteinuria urinary protein <1.0 g/24 hrs	No bevacizumab dose modifications
Grade 2	2+ proteinuria urinary protein 1.0 - 3.4 g/24 hrs	Suspend bevacizumab for urine protein level = 2 g/24 hrs and resume when proteinuria is < 2 g/24 hours For 2+ dipstick: may administer bevacizumab; obtain 24-hour urine to next bevacizumab dose For 3+ dipstick: obtain 24-hour urine to bevacizumab administration
Grade 3	Urinary protein >3.5 g/24 hrs	Suspend bevacizumab. Resume when proteinuria is < 2 g/24 hrs, as determined by 24-hrs urine collection <2.0 g.
Nephrotic syndrome		Discontinue bevacizumab.

7.1.4 Thrombosis / embolism

For patients who develop grade or 4 thrombosis / embolism the following action is recommended:

- Bevacizumab should be permanently discontinued in patients who develop arterial thromboembolic events.
- Grade 3 or 4 venous thrombosis: Hold study drug treatment for 2 weeks. Bevacizumab may be resumed after initiation of therapeutic-dose anticoagulant therapy as soon as all of the following criteria are met:

    - The patient must be a stable dose of anticoagulant and, if on warfarin, have an INR within the target range prior to restarting study drug treatment
    - The patient must not have had a grade 3 or 4 haemorrhagic event since entering the study
    - The patient must not have had any evidence of tumour invading or abutting major blood vessels on any prior disease assessment.

- Symptomatic grade thrombosis: Discontinue the patient from the study.

7.1.5 Haemorrhage

All toxicity will be graded according to NCI CTC-AE guidelines (version 4.0). Dose modification of bevacizumab in patients who develop Grade 3 or 4 toxicity for haemorrhage attributable to bevacizumab is as follows:

Patients who develop grade 3 or 4 haemorrhage should discontinue bevacizumab treatment.

7.1.6 Congestive Heart Failure

Prior anthracyclines exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

No significant increased incidence of CHF in patients treated with bevacizumab was observed in NSCLC or CRC trials.

Bevacizumab should be permanently discontinued in Grade =3 left ventricular systolic dysfunction.

7.1.7 Tracheo-oesophageal fistula

Patients should be monitored closely on an ongoing basis for emergent oesophagitis, oesophageal pain and/or dysphagia. Treatment with bevacizumab should be interrupted if patients develop severe or persistent oesophagitis and should not be re-introduced until the oesophagitis recovers to least CTC Grade 1 and after discussion with the study medical monitor.

Patients receiving concurrent chemotherapy and radiation plus bevacizumab for the treatment of disease including the trachea, bronchi and/or oesophagus structures may be at particular risk for the development of tracheo-oesophageal fistula. For patients who are to receive non-urgent palliative radiotherapy to the mediastinal region, it is recommended to allow at least six weeks between the administration of the last dose bevacizumab and the start of radiotherapy.

Investigators should assess and consider the benefit of palliative radiotherapy versus the risk of the potential development of tracheo-oesophageal fistula.
Bevacizumab should be permanently discontinued in patients with TE fistula or any grade 4 fistulae. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract (< grade 4), discontinuation of bevacizumab/placebo should be considered.

7.2 Dose modifications for chemotherapy

Systematic toxicity evaluation using the National Cancer Institute Common Toxicity Criteria (NCICTC) Version 4.0 (see Appendix) begins with the first treatment cycle, and is repeated before each further cycle and at the end of treatment.

Local standard practice will drive dose reduction or schedule modifications of chemotherapeutic regimens. In case of toxicity related chemotherapy dose reduction no dose re-escalation is allowed.

Additional guidelines are given in Appendices 8 and 9. In case a patient experiences severe chemotherapy-related toxicity or progressive disease, Investigators will be allowed to modify or change chemotherapy regimen as appropriate.

7.2.1 General notes regarding dose modifications for chemotherapy-related toxicity

- For adverse events which are considered by the Investigator unlikely to develop into serious or life-threatening events and which do not result in a delay or interruption of therapy (e.g. alopecia, altered taste etc.), treatment will be continued at the same dose without reduction or interruption.

- No dose reductions or interruptions will be required for anaemia if it can be satisfactorily managed by transfusions.

- If any grade 1 toxicity (except for diarrhoea or abdominal cramps) occurs, treatment will be continued at the original dose without interruption.

- If the same toxicity persists in spite of reductions, the treatment should be stopped unless a clear patient benefit is evident in which case further dose reductions may be required.

- In case of angina or myocardial infarction, study treatment will be stopped.

- If toxicity requires a dosing delay or interruption of any drug for more than one cycle, that chemotherapeutic drug should be discontinued. The patient can remain on study with the remaining chemotherapeutic drugs and will continue to be evaluated according to study procedures.

- If all chemotherapy must be discontinued permanently due to related toxicity, the patient may continue with bevacizumab.

- If chemotherapy is withheld due to toxicity, bevacizumab might also be withheld in order to maintain the synchronisation of both treatment regimens. However, treatment with bevacizumab may continue at the Investigator's discretion if no specific bevacizumab related toxicity is present (see Section 6.1).

7.2.2 Toxicities within a cycle

Patients developing

grade 4 (NCI-CTC Version 4.0) thrombocytopenia

grade 4 (NCI-CTC Version 4.0) neutropenia

grade 3 (NCI-CTC Version 4.0) non-hematological toxicity

receive the anticancer drugs capecitabine, irinotecan or oxaliplatin at 75% of the starting dose in the following cycles, while the bevacizumab dose remains unchanged. The occurrence of grade 4 non-haematological toxicity other than nausea/vomiting necessitates withdrawal from the study.

7.2.3 Toxicity at the start of the following cycle

Patients must meet the following criteria before each new cycle:

Absolute neutrophil count = 1500/mm^3 and platelet count = 100,000/mm^3

Treatment-related diarrhea and/or abdominal cramps are fully resolved to baseline or grade 0 and no loperamide has been administered during the last 24 hours.

Any bilirubin elevation has resolved to least grade 1

Recovery from any treatment-related grade 3/4 non-hematological toxicity (except alopecia) to baseline or = grade 1.

hand-foot syndrome <1 (NCI-CTC Version 4.0)

adequate renal function (creatinine clearance =30 mL/min)

Patients not meeting the above criteria on the date scheduled for the new cycle must suspend treatment with the anticancer drugs capecitabine, irinotecan or oxaliplatin until they meet the above criteria.

Bevacizumab is continued without dose reduction except in the case of bevacizumab-related toxicity (see “Dose modification: bevacizumab”).

Following a delay of up to 2 weeks, patients take the starting dose; following a delay of more than 2 weeks, all drugs (apart from bevacizumab) are reduced to 75% of the starting dose.

Dose adjustments are at the investigator’s discretion in so far as they must take account of the patient’s clinical situation and the suspected causal relationship between the toxicities and administration of the anticancer drugs. Dose re-escalation is not permitted. If the above criteria necessitate postponement for more than 3 weeks, the patient should be withdrawn from the study.

7.2.4 Toxicity and dose modification: oxaliplatin

Neurotoxic side effects occurring treatment with **oxaliplatin** require the following response (see Table 15):

A small proportion of patients (1–2%) experience a syndrome of pharyngolaryngeal dysesthesia, a special form of acute neuropathy characterised by a subjective feeling of dysphagia and dyspnea with no objective evidence of airway obstruction. This unpleasant sensation is non-lifethreatening and rapidly reversible without treatment. The duration of oxaliplatin infusions should be increased to 6 hours in the following cycles.

Table 15: Dose modification for oxaliplatin-induced neuropathy

	Duration of toxicity		
	1 7 days	**>7 days**	**Persisting between cycles**
Cold-induced dysesthesia	No change	No change	No change
Paresthesia	No change	No change	Reduce oxaliplatin by 25%
Paresthesia with pain	No change	Reduce oxaliplatin by 25%	Stop oxaliplatin Continue capecitabine
Paresthesia with functional impairment	No change	Reduce oxaliplatin by 50%	Stop oxaliplatin Continue capecitabine

If oxaliplatin is withdrawn because of specific neurotoxicity, treatment should be continued with capecitabine and bevacizumab until progression (study end).

Grade 3 or 4 allergic reactions require cessation of treatment with oxaliplatin. Where there is clinical evidence of pulmonary fibrosis, further treatment should be given only after excluding the disease and discontinued if fibrosis is confirmed.

7.2.5 Toxicity and dose modification: irinotecan

The side effects of irinotecan are neutropenia, diarrhea and “late diarrhea”. Nausea and vomiting may also occur, as well as an acute cholinergic syndrome. Nausea and vomiting can be treated prophylactically with 5 HT_3 antagonists or other antiemetics.

7.2.5.1 Acute cholinergic syndrome

This syndrome appears within the first 24 hours (3-weekly) irinotecan infusion and comprises early diarrhea, abdominal cramps, sweating, salivation, lacrimation and miosis. If these symptoms occur, 0.25 mg atropine should be given subcutaneously before each further infusion, if not contraindicated.

7.2.5.2 Late-onset diarrhea

This diarrhea, which occurs more than 24 hours after irinotecan administration in up to 35% of patients, must be treated with loperamide. Loperamide is not given prophylactically, but may be prescribed if needed.

7.2.5.3 Loperamide dosage:

1 capsule (2 mg) every 2 hours

Start immediately after first loose stool (initial dose 4 mg)

Maximum dose 8 capsules/tablets daily

Maximum (uninterrupted) duration of administration 48 hours

As soon as the first loose stool appears, the patient should start to drink large amounts of electrolyte solution. If late diarrhea is accompanied by fever with grade 3/4 neutropenia, a broadspectrum antibiotic must be given prophylactically. Hospital admission is necessary:

if severe diarrhea (>6 bowel movements per day) lasts for longer than 48 hours

if diarrhea and vomiting occur

if diarrhea is accompanied by fever >38°C

in febrile neutropenia

7.2.5.4 Irinotecan dose modification (see Appendix 8)

The side effect profile of irinotecan is dominated by diarrhea. The precondition of <grade 2 diarrhea must be met before the start of the next cycle. Otherwise a treatment break is ordered until the above criteria are met. Following a delay of up to 2 weeks, patients take the starting dose; following a delay of more than 2 weeks, irinotecan is reduced to 75% of the starting dose.
When diarrhea occurs, it is necessary to wait for a week after symptoms have resolved. If the above criteria necessitate postponement for more than 3 weeks, the patient should be withdrawn from the study.

7.2.6 Toxicity and dose modification: capecitabine (see Table 16)

Capecitabine dose modifications in the study (see Appendix 8). Dose-limiting side effects of capecitabine therapy include diarrhea, abdominal pain, nausea, stomatitis and -foot syndrome. Most adverse events are reversible and do not require permanent treatment withdrawal, although it may be necessary to interrupt treatment or reduce the dose, depending on the severity:

Table 16: Recommended dose modification scheme for capecitabine :

	Grade 2	**Grade 3**	**Grade 4**
Single occurrence of symptoms	Interrupt treatment until symptoms resolve to grade 0 1, then continue at **100%** of starting dose	Interrupt treatment until symptoms resolve to grade 0 1, then continue at **75%** of starting dose	Interrupt treatment until symptoms resolve to grade 0 1; further treatment, if favoured by the physician, should be given at **50%** of the starting dose

If grade 4 toxicities occur for a second time during treatment, treatment must be discontinued; with grade 3 toxicities the dose must be reduced to 50%, and with grade 2 toxicities to 75%. If a grade 2 toxicity occurs for a third time during treatment, the dose must be reduced to 50%; with grade 3 toxicity, treatment must be discontinued.

Since no data are available on tolerability and efficacy in patients with liver disease, capecitabine therapy should be carefully monitored in patients with mild to moderate hepatic dysfunction, regardless of whether liver metastases are present. Treatment with capecitabine should be interrupted if bilirubin rises to more than 3 times the normal level, or GPT (ALT) to more than 5 times the upper limit of normal (ULN). Treatment may be resumed when bilirubin decreases to =3.0×ULN or GPT to =2.5×ULN.

Treatment with capecitabine should be permanently discontinued in the event of =grade 2 cardiotoxicity.

Capecitabine is contraindicated in patients with creatinine clearance <30 mL/min. Grade 3 and 4 adverse reactions have been observed with greater frequency in patients with reduced creatinine clearance (30–50 mL/min). In these patients the starting dose should be reduced to 75% of normal. Caution is required in patients with slightly reduced creatinine clearance (50–80 mL/min), but reduction of the starting dose is not recommended. As an alternative to 24-hour urine collection, creatinine clearance may be calculated using the Cockcroft-Gault formula. (Table 17)

Table 17: Cockcroft-Gault formulas :

Cockcroft-Gault formula for women
Creatinine clearance = (140–age) × weight [kg] × 0.85/(72 × serum creatinine [mg/dL])

Cockcroft-Gault formula for men
Creatinine clearance = (140–age) × weight [kg]/(72 × serum creatinine [mg/dL])

Cockcroft-Gault formula for women (SI)
Creatinine clearance = (140–age) × weight [kg] × 0.85/(0.81 × serum creatinine [mol/L])

Cockcroft Gault formula for men (SI)
Creatinine clearance = (140–age) × weight [kg]/(0.81 × serum creatinine [mol/L])

7.2.6.1 Interactions
Interactions may occur in particular with the following compounds: coumarin anticoagulants, phenytoin, antacids, allopurinol, sorivudine and analogues.

7.2.6.2 Interaction with food
In the studies performed to date, capecitabine was always taken within 30 minutes after a meal.
Since current safety and efficacy data are based on this mode of administration, it is recommended that capecitabine has to be taken within 30 minutes after a meal.

7.3 Concomitant Medication / procedures – general aspect
No non-protocol specific anti-tumour therapy may be given during adjuvant treatment courses of the protocol.

Patients who require palliative radiotherapy or initiation of bisphosphonates during therapy should be evaluated carefully for possible disease progression before starting these treatments.
Irradiated lesions will thereafter be evaluable for progression only.

All concomitant medication(s) must be reported on the CRF. Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded including the dates, description of the procedure(s) and any clinical findings.

Patients should receive full supportive care including transfusion of blood products, antibiotics, etc. where applicable. These treatment details should be recorded in the CRF.

Use of concomitant medications should follow standard medical oncology practice.

7.4 Concomitant medications and treatment of specific side effects

7.4.1 Antiemesis
Because of oxaliplatin and irinotecan administration, HT3 receptor antagonists should generally be recommended on day 1 of chemotherapy. Prophylactic antiemetic therapy should be carried out.

7.4.2 Hand-foot syndrome
Patients experiencing palmar or plantar erythema of more than grade 1 severity while receiving capecitabine should interrupt treatment until the symptoms have resolved.

7.4.3 Diarrhea
For severe diarrhea requiring treatment, timely use of loperamide, octreotide (50 – 100 µg, 3 times daily) or budesonide (3 mg, 3 times daily) is recommended. Particular care should be taken to replace fluid losses.

For neutropenic diarrhea or fever plus diarrhea, adequate antibiotic therapy is essential, plus broad systemic i.v. antibiotics (e.g. ß lactams plus aminoglycoside).

7.4.4 Cardiotoxicity
For > grade 2 cardiac toxicity which is attributable to capecitabine, patients will be permanently discontinued from capecitabine therapy.

7.5 Assessment of Compliance and Drug Accountability for bevacizumab in 2nd line treatment:
A Drug Dispensing Log must be kept current and should contain the following information:

- the identification of the subject to whom the study medication was dispensed
- the date(s), and quantity of the bevacizumab administered to the subject.

This inventory must be available for inspection by the Monitor. All supplies, including partially used or empty containers and the dispensing logs, will be destroyed according to site specific procedures upon written approval from Sponsor.

8 STANDARD TREATMENT & INVESTIGATIONAL PRODUCT - DOSE
SCHEDULE AND ADMINISTRATION

8.1 Standard Treatment: Dose Schedule and Administration
XELOX or XELIRI Regimen + Bevacizumab are permittet as listet below for first and second line treatment. Eligible patients will be randomized to treatment Arm A or treatment Arm B.

Depending on the first line treatment patients will be crossed over in second line to the other regimen

That means:
Patients who are randomized to receive first line XELOX will receive XELIRI in the second line and patients who are randomized to receive first line XELIRI will be treated with XELOX in the second line.

XELOX
Capecitabine 1000mg/m^2 twice daily p.o.(total daily dose 2000mg/ m) days 1 14 cycle repeated day 21
Oxaliplatin 130mg/m^2 i.v. over 2 hours day 1 cycle reapeated day 21
+ Bevacizumab 7,5mg/ kg i.v. over 90 minutes day 1 cycle reapeated day 21

In case of Capecitabine maintenance treatment dosage for capecitabine in first and second line is 1000mg/m^2 twice daily p.o.(total daily dose 2000mg/ m) days 1 14 cycle repeated day 21

XELIRI
Capecitabine 800mg/m^2 twice daily p.o.(total daily dose 1600mg/ m) days 1 14 cycle repeated day 21
Irinotecan 200mg/m^2 i.v. over 90 minutes day 1 cycle reapeated day 21
+ Bevacizumab 7,5mg/ kg i.v. over 90 minutes day 1 cycle reapeated day 21

In case of Capecitabine maintenance treatment dosage for capecitabine in first and second line is 1000mg/m^2 twice daily p.o.(total daily dose 2000mg/ m) days 1 14 cycle repeated day 21

8.2 Bevacizumab Dose Schedule and Administration

Bevacizumab will be administered i.v. at a dose of 7.5mg/kg/q3w in combination with capecitabine / irinotecan or capecitabine/ oxaliplatin based chemotherapy regimen (see section 7.1).

Bevacizumab (RO 487-6646) will be provided as single use 400 mg and mg vials containing a mg/mL concentrate solution for intravenous (i.v.) infusion.

Bevacizumab labeled for clinical trial will be supplied for **second line** treatement from Roche Austria to all participating centers and is a clear to slightly opalescent, colourless to pale brown, sterile liquid for intravenous infusion in single-use vials which are preservative-free.

Bevacizumab for **1st line** treatment will be prescribed.

The study drug bevacizumab dose will be delivered intravenously over 90 minutes.
The shelf life of bevacizumab is 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.
Bevacizumab should be stored in a refrigerator (2°C-8°C). Do not shake, do not freeze. Keep the vial in the outer carton in order to protect from light.
Bevacizumab does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution. Bevacizumab should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of bevacizumab for a dose 7.5 mg/kg of weight and dilute with sodium chloride 9 mg/m^2 (0.9%) solution for injection up to a total volume of 100 m. Discard any unused bevacizumab 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 bevacizumab and polyvinyl chloride or polyolefin bags or infusion sets have been observed.

Bevacizumab infusions should not be administered or mixed with glucose solutions.

Further specifications can be found in the summary of product characteristics for bevacizumab.

8.3 Packaging and Labelling
A booklet master label will be used. Coloured labels will be applied to boxes and vials as shown in Appendix 10.

9 AFETY

9.1 Adverse Events and Laboratory Abnormalities

9.1.1 Clinical adverse events

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions which worsen during a study are to be reported as adverse events.

All clinical adverse events encountered during the clinical study will be reported on the CRF. Intensity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see Appendix 8) and reported in detail. If an adverse event occurs which is not contained in the CTCAE v4.0, the five point scale below will be used.

Table 18 – Intensity of Adverse Events not included in CTCAE v4.0

Mild	asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Severe or medically significant but Immediatly life-threatening;	hospitalization or prolongation of hospitalization indicated; but disabling; limiting self care ADL**.
Life Threatening	consequences; urgent intervention indicated.
Death	related to AE

***Activities of Daily Living (ADL)**

Instrumental ADL refer to preparing meals, shopping for es or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The causality relationship of study drug to the adverse event will be assessed by the investigator as either: **Yes or No**

If there is a reasonable suspected causal relationship to the study medication, i.e. there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed a **Yes.**

The following criteria should be considered in order to assess the relationship as **Yes:**

• Reasonable temporal association with drug administration

• It may or may not have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
• Known response pattern to suspected drug
• Disappears or decreases on cessation or reduction in dose
• Reappears on rechallenge

The following criteria should be considered in order to assess the relationship as **No**:
• It does not follow a reasonable temporal sequence from administration of the drug.
• It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
• It does not follow a known pattern of response to the suspected drug.
• It does not reappear or worsen when the drug is readministered.

9.1.2 Laboratory test abnormalities

Laboratory test results will be recorded on the Case Report Form. Laboratory test value abnormalities as should not be reported on the AE CRF as adverse events, unless they are treatment-emergent and they satisfy one or more of the following conditions for clinical significance:

- accompanied by clinical symptoms
- leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

Please note: any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an adverse event in the CRF.

9.2 Project Specific Adverse Events Definition

Progression or objective / clinical progression of the malignancy under study will be part of the efficacy assessment and should NOT be reported as an AE or SAE.

Signs and symptoms of the malignancy under study should only be reported if:

- Newly emergent (i.e. not present at baseline) and the association with the underlying malignancy and old/new metastatic lesions is unclear and/or
- The Investigator attributed deterioration of malignancy associated signs and symptoms directly to the study drug

Should there be any uncertainty regarding the attribution of the malignancy under study to an AE, it should be reported as an AE or a SAE accordingly.

9.3 Handling of Safety Parameters

9.3.1 Immediately reportable Serious adverse events

Any AE that is considered SERIOUS must be reported IMMEDIATELY (within one working day) by the investigator.
An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that any dose fulfils at least one of the following criteria:

- Is fatal (results in death); NOTE: death is an outcome, not an event

- Is Life-Threatening; NOTE: the term “Life-Threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe
- Required in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- medically significant or requires intervention to prevent one or other of the outcomes listed above

All **related** SAEs or **related** serious lab abnormalities that occurred after a patient has signed informed consent and at any time following study discontinuation or completion are immediately reportable to Roche as expedited reports.

9.3.2 Not Immediately Reportable Serious Adverse Events

Progression or deterioration of the malignancy under study (including new metastatic lesions and death due to disease progression) will be t of the efficacy assessment and should NOT be reported as AE/SAE.

Signs and symptoms clearly associated with the malignancy under study should NOT be reported as AE/SAE unless:

- Newly emergent (i.e. not present at baseline) and association with the underlying malignancy and old/new metastatic lesions is unclear

- If the investigator attributed deterioration of malignancy-associated signs and symptoms directly to the study drug

Should there be any uncertainty regarding the attribution of the malignancy under study to an AE, it should be reported as an AE or SAE accordingly.

9.3.3 Reporting and follow-up of adverse events after last dose of study treatment

9.3.3.1 Adverse events in general

All new adverse events experienced up until 28 days after the last dose of study treatment should be recorded in the CRF. Additionally, non-serious, new AEs considered related to study drug (bevacizumab, capecitabine) which occur up to 6 months after the last dose study drug should also be reported. Serious adverse events considered related to study drug should be reported indefinitely.

Follow-up of adverse events considered related to study drug (bevacizumab, capecitabine) should continue until they have returned to baseline status or stabilized or the causal relationship has been changed from related to unrelated to study drug. Follow-up of adverse events considered unrelated to study drug is required for up to 28 days after the last dose the study drug.

All severe or life-threatening adverse events must be followed up until resolution or the causal relationship has been changed from related to unrelated to study drug or the patient’s death.

9.3.4 Follow-up of laboratory abnormalities

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range/baseline values and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the CRF.

9.4 Criteria for Premature Withdrawal

Patients have the right to withdraw from the study treatment at any time for any reason. The Investigator also has the right to withdraw patients from the study treatment in the event of:

- Intercurrent illness
- Adverse events
- Pregnancy
- Treatment failure (confirmed progression of disease or death)
- Patient non-compliance with study procedures
- Administrative reasons or other reasons.

An excessive rate of withdrawals can render the study un-interpretable. Therefore, unnecessary withdrawal of patients should be avoided. If a patient withdraws consent for further study treatment, the patient should still be followed for survival. If a patient withdraws consent for further participation in the study, follow-up assessments will be discontinued.

The Investigator should contact the patient either by telephone or through a personal visit or a responsible relative must be contacted to determine as completely as possible the reason for the withdrawal. A complete final evaluation of safety should be performed 28 days from the last dose of bevacizumab and a reason for the withdrawal should be obtained. If the reason for withdrawal is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the CRF.

Bevacizumab should not be withheld for more than two administrations for reasons not related to toxicity. In case of oxaliplatin- or irinotecan-related discontinuation the capecitabine and bevacizumab will be continued.

10 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

10.1 Introduction

MedCalc® and BiAS® will be used to produce all summary tables and listings. R will be used to create figures.

Categorical data will be presented using counts and percentages.

Ordinal variables will be presented using counts and percentages (where appropriate) or minimum, 25%-percentile, median, 75%-percentile maximum and number of patients (where appropriate).

Continuous variables will be presented using minimum, 25%-percentile, arithmetic mean, median, 75%-percentile, maximum, standard deviation and number of patients.

Percentages will be rounded to two decimal places.

Minimum, 25%-percentile, arithmetic mean, median, 75%-percentile, maximum and standard deviation will be quoted to the number of decimal places as recorded in the eCRF (where appropriate to two further decimal places).

P values will be presented to 3 decimal places, values less than 0.001 will be formatted to '<0.001'. Unless otherwise stated, no correction of the type I error is made, therefore all p values are only descriptive.

To determine the clinical relevance of the study findings two-sided 95% confidence intervals for chosen variables will be calculated.

All tables and listings will report data in the following order:

- Arm A: XELIRI plus bevacizumab followed by XELOX plus bevacizumab
- Arm B: XELOX plus bevacizumab followed by XELIRI plus bevacizumab
- Total

The data of the following populations will be presented in a descriptive way:

- Data of all patients who have got an ID (FAS data set)
- Data of all patients who are not included in the ITT-Analysis
- Data of all patients randomized, if at least one dose of study medication was administered/taken after randomization. (ITT data set)
- Data of a subset of the intent-to-treat population excluded because of major protocol violations (PP data set)

10.2 Primary Endpoint

The primary endpoint is to determine the efficacy of modified XELIRI (Capecitabine and Irinotecan) in combination with bevacizumab followed by XELOX (Capecitabine and Oxaliplatin) in combination with bevacizumab at progression in comparison with the reverse sequence based on DDC.

10.3 Secondary Endpoints

The secondary endpoints are:

- to determine
    - first line PFS
    - second line PFS
    - the overall response rate
    - time to response
    - duration of response
    - overall survival of Xeliri plus bevacizumab and Xelox plus bevacizumab
- tumour assessments (based on RECIST criteria) using CT scans, MRI scans, X ray, bone scan, clinical examination.

10.4 Safety

Safety of the treatment will be evaluated by physical exam, vital signs, ECG (at baseline), ECOG performance score, concomitant disease and medication, adverse events and laboratory tests (haematology, serum chemistry and urinanalysis).

All patients who received at least one dose of treatment will be included in the safety evaluation.

10.5 Statistical Model

National, multicenter, 2 arm, randomized, parallel-group pilot study of 3 years duration from first patient in

- Arm A: XELIRI plus bevacizumab followed by XELOX plus bevacizumab
- Arm B: XELOX plus bevacizumab followed by XELIRI plus bevacizumab

This study will investigate safety and efficacy parameters.

10.5.1 Primary Variable

The primary variable is DDC and is defined as the sum of progression free survival intervals during first line and second line treatment (= time from the beginning of first line treatment until onset of progression during second line treatment). Patients without progression at the last tumour assessment date during their study participation will be censored at this tumour assessment date (exception: availability of validated information about a later onset of progression or a longer progression free interval – in such a case the date of the follow-up assessment will be either defined as the onset of progression or will replace the last tumour assessment date).

Missing onset of progression data because of refusal or because of death will be replaced (see 10.7).

If several response evaluations for a patient are progressive disease (PD), the time to PD is assessed by using the first of these measurements.

The primary efficacy analysis will investigate DDC between arm A and arm B. DDC will be calculated by the Kaplan-Meier estimator and compared by using the Mantel-Haenszel-Log-Rank-Test. Power calculation will be too.

In case of inhomogeneities of demographic or baseline variables across the arms these variables will be examined in an exploratory way for a potential confounding effect, if considered medically relevant. A proportional hazard Cox-Regression model will be used for this purpose. The assumptation of proportional hazards will be verified by Schoenfeld-residuals. If this assumptation is violated, a time dependent Cox-Regression model will be used. If appropriate, two-sided 95%-confidence-intervals will be calculated for the hazards of the Cox-Regression model.

10.5.2 Secondary Variables

First line PFS

The first line PFS is defined as the progression free survival interval during first line treatment. Patients without progression at the last tumour assessment date during their study participation will be censored at this tumour assessment date (exception: availability of validated information about a later onset of progression or a longer progression free interval – in such a case the date of the follow-up assessment will be either defined as the onset of progression or will replace the last tumour assessment date).

Missing onset of progression data because of refusal or because of death will be replaced (see 10.7).

If several response evaluations for a patient are progressive disease (PD), the time to PD is assessed by using the first of these measurements.

Second Line PFS

The second line PFS is defined as the progression free survival interval during second line treatment. Patients without progression at the last tumour assessment date during their study participation will be censored at this tumour assessment date (exception: availability of validated information about a later onset of progression or a longer progression free interval

– in such a case the date of the follow-up assessment will be either defined as the onset of progression or will replace the last tumour assessment date).

Missing onset of progression data because of refusal or because of death will be replaced (see 10.7).

If several response evaluations for a patient are progressive disease (PD), the time to PD is assessed by using the first of these measurements.

Overall response rate

The rate of overall response will be measured as the response rate from randomization until the day of documented complete response (CR) or partial response (PR) (whichever status is recorded first).

Time to Response

Time to overall response will be measured from the time of randomization until the day of documented complete response (CR) or partial response (PR) (whichever status is recorded first). Patients without response will be censored at the date of the last tumour assessment, the date of death or the date of refusal.

Duration of Response

Duration of overall response will be measured from the time that measurement criteria are met for complete response (CR) or partial response (PR) (whichever status is recorded first) until the onset of progression. Patients without progression at the last tumour assessment date during their study participation will be censored at this tumour assessment date (exception: availability of validated information about a later onset of progression or a longer progression free interval – in such a case the date of the follow-up assessment will be either defined as the onset of progression or will replace the last tumour assessment date).

Missing onset of progression data because of refusal or because of death will be replaced (see 10.7).

If several response evaluations for a patient are progressive disease (PD), the time to PD is assessed by using the first of these measurements.

Overall Survival

Survival will be measured as the time from the randomization date to the date of death. Patients without death date will be censored at the date of the last tumour assessment (exception: availability of validated information about a later exitus date or a prolonged survival – in such a case the date of the follow-up assessment will be either defined as the exitus date or will replace the last tumour assessment date) or the date of refusal.

Tumour assessments

Tumour assessments will be based on the RECIST criteria using CT scans, MRI scans, X ray, bone scan and clinical examination.

Analysis of Secondary Endpoints

Survival functions will be calculated by the Kaplan-Meier estimator and compared by using the Mantel-Haenszel-Log-Rank-Test.

For categorical data the exact Chi-Square-Test (n x m tables) or Fisher's Exact Test (2 x 2 tables) will be calculated.

For ordinal data the exact Mann-Whitney- Test will be used.

As normality-distribution-test for continuous variables, the Kolmogorov-Smirnov-Test with Lilliefors Correction will be used at a type-I error-rate of 5%. As test of variance homogeneity for continuous variables, the Levene-Test will be used at a type-I error-rate of 5%. If normality and variance homogeneity can be assumed, the t Test will be used. If normality and no variance homogeneity can be assumed, Welch's t Test will be used. If normality cannot be assumed, the exact Mann-Whitney- Test will be used.

For variables representing a proportion of patients achieving a given clinical endpoint, cumulative incidences over time will be estimated by the Kaplan-Meier method.

Ordinal variables followed over time will be modelled using statistical methods designed for repeated measures, if appropriate. In case of two repeated measures, the exact Wilcoxon Test will be used. In case of more than two repeated measures, Friedman-Rank-Variance-Analysis will be used.

Continuous variables followed over time will be modelled using statistical methods designed for repeated measures, if appropriate. In case of normality and two repeated measures, the Paired t Test will be used. In case of non-normality and two repeated measures, the exact Wilcoxon Test will be used. In case of normality and more than two repeated measures, ANOVA will be performed. The assumption of sphericity will be tested with Mauchly's Test of Sphericity and in case of violation of the assumption, repeated measures ANOVA with Greenhouse-Geisser correction will be used. In case of non-normality and more than two repeated measures, Friedman-Rank-Variance-Analysis will be used.

10.5.3 Safety Analysis

Safety of the treatment will be evaluated by physical exam, vital signs, ECG (at baseline), ECOG performance score, concomitant disease and medication, adverse events and laboratory tests (haematology, serum chemistry and urinanalysis). Detailed information about the safety parameters is given in chapter 9.

Survival functions will be calculated by the Kaplan-Meier estimator and compared by using the Mantel-Haenszel-Log-Rank-Test.

For categorical data, the exact Chi-Square-Test (n x m tables) or Fisher's Exact Test (2 x 2 tables) will be calculated.

For ordinal data the exact Mann-Whitney- Test will be used.

As normality-distribution-test for continuous variables, the Kolmogorov-Smirnov-Test with Lilliefors Correction will be used at a type-I error-rate of 5%. As test of variance homogeneity for continuous variables, the Levene-Test will be used at a type-I error-rate of 5%. If normality and variance homogeneity can be assumed, the t Test will be used. If normality and no variance homogeneity can be assumed, Welch's t Test will be used. If normality cannot be assumed, the exact Mann-Whitney- Test will be used.

For variables representing a proportion of patients achieving a given clinical endpoint, cumulative incidences over time will be estimated by the Kaplan-Meier method.

Ordinal variables followed over time will be modelled using statistical methods designed for repeated measures, if appropriate. In case of two repeated measures, the exact Wilcoxon Test will be used. In case of more than two repeated measures, Friedman-Rank-Variance-Analysis will be used.
Continuous variables followed over time will be modelled using statistical methods designed for repeated measures, if appropriate. In case of normality and two repeated measures, the Paired t Test will be used. In case of non-normality and two repeated measures, the exact Wilcoxon Test will be used. In case of normality and more than two repeated measures, ANOVA will be performed. The assumption of sphericity will be tested with Mauchly's Test of Sphericity and in case of violation of the assumption, repeated measures ANOVA with Greenhouse-Geisser correction will be used. In case of non-normality and more than two repeated measures, Friedman-Rank-Variance-Analysis will be used.

10.5.4 Sample Size

No formal sample size calculation has been performed because of the lack of sufficient information. A sample size of 60 patients per group is planned to obtain a more reliable estimate of the treatment effect. This sample size should be adequate to get preliminary information about the magnitude of a potential difference between the DCC of both treatments (arm A and arm B). The data resulting from this pilot study can be used for the sample size estimation of a confirmatory trial which is designed either towards superiority or towards non-inferiority.

10.6 Analysis Populations

The following data sets will be used for analysing this study:

- Full Analysis Set
- Intent to treat Population
- Per Protocol Population
- Safety Analysis Population

10.6.1 Full Analysis Set

All patients having got an ID for the run-in phase will be included in the FAS.

10.6.2 Intent to treat Population

All patients randomized will be included in the ITT population, if at least one dose study medication was administered/taken after randomization.

Patients will be assigned to treatment groups as randomized for analysis purposes.

10.6.3 Per Protocol Population

The PP population will be defined as the subset of the ITT population defined by the following exclusions:

- Violation of inclusion or exclusion criteria
- Exitus before onset of progression during second line treatment
- Refusal before onset of progression during second line treatment

- Violation of study medication before onset of progression during second line treatment

- Other major protocol violations (definition for cause by the coordinating investigator) before onset of progression during second line treatment

Patients will be assigned to treatment groups as treated.

10.6.4 Safety Analysis Population

The safety analysis population will include all patients who have got an ID (FAS data set) and have received at least one dose of study medication. All safety parameters will be summarized and presented in tables based on these safety populations.

10.7 Replacement of missing values:

Missing values will only be replaced for the onset of progression.

In the case of exitus or refusal before onset of progression, a worst case approach will be used for the missing value replacement. This is the shortest assessed time until onset of progression during the specific treatment, in the case of DDC shortest assessed time until onset of progression during second line treatment (Exception: If the time until exitus or refusal is longer than the shortest assessed time until onset of progression the date of exitus or refusal will be defined as onset of progression).

10.8 Randomization

The Randomization procedure will be performed by the computer software BLOCKRAND. Block randomization will be used to ensure that at the end of the study treatment arms will be nearly equal in size. Separate randomization lists (sealed envelopes containing the allocation to arm A or B of the specific trial subject to be opened after the inclusion of the trial subject into the study and after the placing of an ID number) will be prepared for each centre.Within each centre each patient will be randomly assigned to one of the two treatment arms, with equal but random distribution of the two treatment arms within each block.

10.9 Replacement Policy

10.9.1 For subjects

No subject prematurely discontinued from the study for any reason will be replaced.

10.9.2 For centres

A centre may be replaced for the following administrative reasons:

- Excessively slow recruitment.
- Poor protocol adherence.

10.10 Steering Committee

A Steering Committee will be nominated to review the safety data of the trial and the interim analysis for efficacy. The procedure will be described in the Steering Committee charta.

11 DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

To ensure quality of data, study integrity and compliance with the protocol and the various applicable regulations and guidelines, the Sponsor may conduct site visits to institutiones participating to the protocol.

The investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the Sponsor, national and/or foreign regulatory authorities or company supplying the product under investigation, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital patient charts and other study files) to these authorized individuals.

The investigator must inform the Sponsor immediatly in case a regulatory authority inspection would be scheduled.

12 ETHICAL ASPECTS

12.1 Local Regulations / Declaration of Helsinki

The Sponsor ensures that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study fully adheres to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) with local law if affords greater protection to the subject.

12.2 Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written informed consent from each subject participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For subjects not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the subject and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The Investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The Case Report Forms for this study contain a section for documenting informed subject consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

12.3 Ethical review

This protocol and any accompanying material provided to the subject (such as subject information sheets or descriptions of the study used to obtain informed consent) as well as any advertising or compensation given to the patient, will be submitted by the Sponsor to an Independent Ethics Committee. Approval from the committee must be obtained before starting the study, and should be documented in a letter to the Investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of the Independent Ethics Committee

approval will also be submitted by the Sponsor to the Committee in accordance with local procedures and regulatory requirements.

13 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only by the Sponsor.
All protocol modifications will be submitted to the appropriate Independent Ethics Committee or Institutional Review Board for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change in monitor(s), change of telephone number(s).

14 CONDITIONS FOR TERMINATING THE STUDY

The Sponsor of the study reserves the right to terminate the study at any time.
Should this be necessary, the Sponsor will arrange the procedures on individual study basis after review and consultation. terminating the study, the Sponsor will assure that adequate consideration is given to the protection of the patient's interests.

15 INVESTIGATOR'S FILES / RETENTION OF DOCUMENTS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories (1) Investigator's Study File, and (2) subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorisation forms and other appropriate documents/correspondence etc. In addition at the end of the study the Investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, in human readable format on CD which also has to be kept with the Investigator's Study File.

Subject clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, EEG, X ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and subject screening and enrolment logs. The Investigator must keep these two categories of documents on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator can not guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container(s) outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents

are required for the continued care of the patient, appropriate copies should be made for storing outside of the site.

16 MONITORING THE STUDY

It is understood that the responsible monitor (or designee) will contact and visit the Investigator and will be allowed, on request, to inspect the various records of the trial (Case Report Forms and other pertinent data) provided that patient confidentiality is maintained in accord with local requirements. It will be the monitor's responsibility to inspect the Case Report Forms at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the Case Report Form. The Investigator (or his/her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

17 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The Investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by an identification code. The Investigator should keep a subject enrolment log showing codes, names and addresses.

18 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study will be published or presented at scientific meetings.

19 Trial Insurance

Insurance policies will be made according to the Austrian law.

Appendices

Appendix 1 - ICH Guidelines for Clinical Safety Data Management

Appendix 2 - EU Clinical Directives for SARs (Serious Adverse Reactions) Management

Appendix 3 - SAE Reporting Procedure

Appendix 4 - Tumour Assessments (RECIST criteria)

Appendix 5 - ECOG Performance Status

Appendix 6 - New York Heart Association Classification of Heart Failure

Appendix 7 - Common Terminology Criteria for Adverse Events v3.0

Appendix 8 - General Guidance for Dose Modifications of Irinotecan / 5 FU

Appendix 9 Guidelines for Dose modifications for Oxaliplatin

Appendix 10 - Bevacizumab Labelling

Appendix 11 - Declaration from Helsinki

20 APPENDICES

20.1 Appendix 1 - ICH Guidelines for Clinical Safety Data Management

ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any Adverse event that at any dose fulfils at least one of the following criteria:

- is fatal; (results in death)
- (NOTE: death is an outcome, not an event)
- is Life-Threatening
- (NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).

- required in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the Sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.
Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

An unexpected Adverse Event is one, the nature or severity of which is not consistent with the applicable product information.
Causality is initially assessed by the Investigator. For Serious Adverse Events, possible causes of the event are indicated by selecting one or more options. (Check all that apply)

- existing/Underlying disease - specify
- Study treatment – specify the drug(s) related to the event
- Other treatment (concomitant or previous) – specify
- Protocol-related procedure
- ther (e.g. accident, new or intercurrent illness) – specify

The term severe is a measure of intensity, thus a severe adverse event is not necessarily serious.
For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

A serious adverse event occurring during the study or which comes to the attention of the Investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, whichever is longer, whether considered treatment related or not, must be reported. In addition, a serious adverse event that occurs after this time, if considered related to test “drug”, should be reported.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.
For serious adverse events, the following must be assessed and recorded on the adverse events form of the Case Report Form: intensity, relationship to test substance, action taken, and outcome to date.
The Investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

LOCAL COUNTRY CONTACT for SAEs: Local Monitor

CONTACT:
STUDY MANAGER:

Name:

Address:

Telephone Number :

Fax Number:

E mail:

20.2 Appendix 2 - EU Clinical Directives for SARs (Serious Adverse Reactions)

Management
Definitions and Standards for Expedited Reporting

Suspected Unexpected Serious Adverse Reactions (SUSARs) are suspected adverse reactions related to Investigational Medicinal Products (IMP) and/or comparator(s) (including the placebos), occurring in clinical trials, and are both unexpected and serious.
SUSARs associated with an IMP that does not hold a marketing authorisation and any other SUSARs associated with the IMP, in any Member State of the European Economic Area, are subject to expedited reporting to Competent Authorities and ethics committees/Institutional Review Board of the concerned Member State, according to the EU-CTD guidelines, as soon as the Sponsor becomes aware of them. This includes SUSARs which:

- Occur in another trial conducted by the same Sponsor either in the European Community or in non-European Community countries
- Are identified by spontaneous reports or a publication
- Are transmitted to the Sponsor by another regulatory authority
- Other safety issues requiring expedited reporting:
- Safety issues that might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the trial, also qualify for expedited reporting, for instance:
- Single case reports of an expected serious adverse reaction with an unexpected outcome (e.g. a fatal outcome)
- An increase in the rate and occurrence of an expected serious adverse reaction which is judged to be clinically important

Post-study SUSARs that occur after the patient has completed a clinical trial are reported by the Investigator to the Sponsor.
New events relating to the conduct of the trial or the development of the IMP likely to affect the safety of the subjects, such as:

- An SAE which could be associated with the trial procedure and which could modify the conduct of the trial
- A significant hazard to the patient population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease
- A major safety finding from a newly completed animal study (such as carcinogenicity)

Where the IMP is authorised in a Member State and the Sponsor is the marketing authorisation holder, the reporting of SUSARs should take into account national requirements intended to manage duplication of reports in the context of Directive 2001/83/EC, Regulation 2309/93/EC and the: “Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module)”.

Expedited reporting is usually not required in the following instances:

- Reactions which are serious but expected
- Non-serious adverse reactions, whether they are expected or not
- Events considered unrelated to IMP

Fatal and life threatening SUSARs:
The Sponsor will be reported SUSARs to the competent authorities and the EC as soon as possible and not later than 7 calendar days. This reporting is based on receipt from the Investigator site of the minimum criteria for expedited reporting. Additional information should be available as soon as possible and reported within an additional 8 calendar days.
In case, relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the competent authority and the EC in the concerned Member States within an additional eight calendar days.
All other SUSARs and safety issues (requiring expedited reporting) will be reported to competent authority and EC in the concerned member states as soon as possible and no later than 15 calendar days after the Sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be made available as soon as possible.
The distribution to the EC, of the safety letter and CIOMS-I reporting form (with analysis of similar events where produced), will be performed within 15 calendar days from the Sponsors received date (in all relevant European Economic Area member states).
In case the EC only communicate via Investigators, the Investigator will forward the information within 7 calendar days from the Sponsors received date to their ethics committee

20.3 Appendix 3 - SAE Reporting Procedure:

Investigator:

- serious in Inform on the AE form
- Completes SAE report, sends faxes to the Sponsor within 1 working day of awareness.
- Subsequently, will provide answers to data queries promptly

Sponsor:

- The Sponsor will perform adaequate due diligence with regard to obtaining follow up information on incomplete AE and pregnancy reports
- Send acknowledgement receipt to site
- Contact site if SAE notifications from Inform or SAE report is missing

20.4 Appendix 4 - Tumour Assessments (modified RECIST criteria)

Presented here is the official quick reference guide provided by the National Cancer Institute.
Measurable disease - 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.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter > 20 mm using conventional techniques or >10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques;

All measurements should be taken and recorded in metric notation, using a ruler or callipers. All screening evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before treatment start.
The same method of assessment and the same technique should be used characterize each identified and reported lesion at screening and during follow up.
Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement
CT and MRI are 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 tumours of the chest, abdomen and pelvis.
Head and neck tumours and those of extremities usually require specific protocols.
Lesions on chest X ray are not acceptable as measurable lesions. Instead, CT (or MRI) is required.
When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used measure tumour lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions assessed by clinical examination.
The utilisation of endoscopy and laparoscopy for objective tumour evaluation has not yet been fully and widely validated and must not be used. Tumour markers must not be used to assess response.
Histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumour types such as germ cell tumours).

Screening documentation of "Target" and "Non-Target" lesions

All measurable lesions up to a maximum of five lesions per organ and **10** lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at screening.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated 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 screening sum LD. The screening sum LD will be used as reference by which to characterize the objective tumour.
All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at screening. Measurements of these lesions are not required, but presence or absence of each should be noted throughout follow up.

Response Criteria

	Evaluation of target lesions
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR9	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the screening sum LD

Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
	Evaluation of non-target lesions
Complete Response (CR)	Disappearance of all non-target lesions and normalisation of tumour marker level
Incomplete Response/Stable Disease (SD)	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions [A]

[A] Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from treatment start until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	**Non-Target lesions**	**New Lesions**	**Overall response**
CR	CR	No	CR
CR	Incomplete response/SD	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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, investigation of the residual lesion can be considered (biopsy) to confirm the complete response status.

Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

To be assigned a status of PR CR, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of SD, follow up measurements must have met the SD criteria at least once after study entry at a minimum interval, not less than 6 weeks.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

SD is measured from the start of the treatment, until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

20.5 Appendix 5 - ECOG Performance Status[1]

ECOG PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. 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. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

[1]Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity and Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

20.6 Appendix 6 - New York Heart Association Classification of Heart Failure

The New York Heart Association (NYHA) functional classification system[2] relates symptoms to everyday activities and the patient's quality of life:

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort

[2] The Criteria Committee of the New York Heart Association. Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis. 6th Boston, MA: Little Brown, 1964

20.7 Appendix 7 - Common Terminology Criteria for Adverse Events v4.02

Copies of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.02 (publish date Sept.15th, 2009), will be made available to all participating centres.
The NCI CTCAE v4.02 is also available on-line at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf

20.8 Appendix 8 - General Guidance for Dose Modifications of Irinotecan / Capecitabine

See table below for general guidance for dose reductions upon **first, second, third and fourth appearance** of the specified toxicities.

	Dose Modifications At the Start of Subsequent Cycles of Therapy. Change from previous starting doses, based upon maximum toxicity encountered in the previous cycle.	
Toxicity CTCAE grade	**Capecitabine**	**Irinotecan**
Haematological Toxicity		
No toxicity	Maintain Dose	Maintain Dose
1	Maintain Dose	Maintain Dose
2	**1st, 2nd, 3rd appearance**: delay of treatment until Grade 0 1 is reached **1st appearance**: maintain dose for the following cycle **2nd appearance**: decrease dose to 75% **3rd appearance**: decraese dose to 50%	Maintain Dose
3	**1st, 2nd, 3rd appearance**: delay of treatment until Grade 0 1 is reached **1st appearance**: decrease dose to 75% **2nd appearance**: decrease dose to 50% **3rd appearance**: Stop treatment	Delay until grade 0 Decrease subsequent doses to 75%
4*	**1st appearance:** stop treatment or if continued treatment is considered to be in the best interest of the patient interrupt until grade 0 1 and then decrease the dose to 50% **2nd appearance:** stop treatment	Delay until grade 0 Decrease subsequent doses to 75%

	Dose Modifications At the Start of Subsequent Cycles of Therapy. Change from previous starting doses, based upon maximum toxicity encountered in the previous cycle.	
Toxicity CTCAE grade	**Capecitabine**	**Irinotecan**
Non-Haematological Toxicity		
No toxicity	Maintain Dose	Maintain Dose
1	Maintain Dose	Maintain Dose
2	**1st, 2nd, 3rd appearance**: delay of treatment until grade 0 1 is reached **1st appearance**: maintain dose for the following cycle **2nd appearance**: decrease dose to 75% **3rd appearance**: decraese dose to 50%	Delay until grade 0 Maintain dose
3	**1st, 2nd, 3rd appearance**: delay of treatment until grade 0 1 is reached **1st appearance**: decrease dose to 75% **2nd appearance**: decrease dose to 50% **3rd appearance**: Stop treatment	Delay until grade 0 Decrease subsequent doses to 75%
4*	**1st appearance:** stop treatment or if continued treatment is considered to be in the best interest of the patient interrupt until grade 0 1 and then decrease the dose to 50% **2nd appearance:** stop treatment	Delay until grade 0 Decrease subsequent doses to 75%

* Grade 4 -Continued treatment is at the discretion of the Investigator, i.e. only if it ~ considered to be in the best interest of the patient

20.9 Appendix 9 - Guidelines for Dose modifications for Oxaliplatin

The following dose reductions should be made for neurosensory toxicity:

20.10 Appendix 10 - Bevacizumab Labelling

Avastin 400 mg	**Avastin 100 mg**
Cover page **Box** (will be in English) **ML 25153** Bevacizumab 400 mg/16 ml (1) Lot no.: XXXXXX (2) Retest date: XXXXX (3) Administration date:_____ (4) Pat.no.:_____ Cover page **vial** (will be in English) **ML 25153** Bevacizumab 400 mg/16 ml (1) Lot no.: XXXXXX (3) Administration date:_____ (4) Pat.-no.:_____ **page 2: Index**	Cover page **Box** (will be in English) **ML 25153** Bevacizumab 100 mg/4 ml (1) Lot no.: XXXXXX (2) Retest date: XXXXX (3) Administration date:_____ (4) Pat.no.:_____ Cover page **vial** (will be in English) **ML 25153** Bevacizumab 100 mg/4 ml (1) Lot no.: XXXXXX (3) Administration date:_____ (4) Pat.-no.:_____ **page 2: Index**

20.11 Appendix 11 - Declaration from Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1) The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2) It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3) The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4) Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5) In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6) The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7) In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8) Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need spezial protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9) Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10) It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11) Medical research involving human subjects must conform to generally accepted scientific

principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12) Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13) The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14) The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15) Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16) Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be licly available.
17) Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18) Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19) Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20) The subjects must be volunteers and informed participants in the research project.
21) The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22) In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail.
The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23) When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress.
In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24) For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25) When a subject deemed legally incompetent, such a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to consent of the legally authorized representative.
26) Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27) Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28) The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29) The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30) At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31) The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32) In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm. All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Note: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical

Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

21 REFERENCES

Arnold D, Petersen , Kindler M, et al. Patterns of maintenance treatment (Tx) following first-line bevacizumab (bev) plus chemotherapy (CT) for metastatic colorectal cancer (mCRC): Results from a large German community-based cohort study. J Clin Oncol 29: 2011 (suppl 4; abstr 502)

Benbow U, Maitra R, Hamilton JW, et al. Selective modulation of collagenase 1 gene expressionby the chemotherapeutic agent doxorubicin. Clin Cancer Res 1999;5:203–208.

Browder T, Butterfield CE, Kraling BM, et al. Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. Cancer Res 2000;60:1878–1886.

M. Ducreux, A. Adenis, J. Mendiboure,et al. Efficacy and safety of bevacizumab (BEV)-based combination regimens in patients with metastatic colorectal cancer (mCRC): Randomized phase II study of BEV + FOLFIRI versus BEV + XELIRI (FNCLCC ACCORD 13/0503 study). J Clin Oncol 27:15s, 2009 (suppl; abstr 4086)

Erber R, Thurnher A, Katsen AD, et al. Microtumour growth initiates angiogenic sprouting with simultaneous expression of VEGF, VEGF receptor-2, and angiopoietin-2. FASEB J. 2004;18:338–340.

Ferlay J, Autier P, Boniol M, et al. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007;18:581–92.

Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev. 2004;25:581–611.

Gerber HP, Ferrara N. Pharmacology and pharmacodynamics of bevacizumab as monotherapy or in combination with cytotoxic therapy in preclinical studies. Cancer Res. 2005;65:671–680

Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007;25:1539–1544.

Griffon-Etienne G, Boucher Y, Brekken C, et al. Taxane-induced apoptosis decompresses blood vessels and lowers interstitial fluid pressure in solid tumours: clinical implications. Cancer Res 1999;59:3776–3782.

Grothey A et al. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil – leucovorin, irinotecan and oxaliplatinin the course of treatment. J Clin Oncol 2004, 22: 1209-14

Grothey A et al. Bevacizumab Beyond First Progression is Associated With Prolonged Overall Survival in Metastatic Colorectal Cancer: Results from a Large Observational Cohort Study (BRiTE). J Clin Oncol 2008

Hecht JR et al. A Randomized Phase IIIB Trial of Chemotherapy, Bevacizumab, and Panitumumab Compared With Chemotherapy and Bevacizumab Alone for Metastatic Colorectal Cancer JCO 2009 (27): 672 - 680

Hedrick E, Kozloff M, Hainsworth J, et al. Safety of bevacizumab plus chemotherapy as first-line treatment of patients with metastatic colorectal cancer: Updated results from a large observational registry in the US (BRiTE). J Clin Oncol 2006;24:Abstract 3536.

Hicklin DJ, Ellis LM.http://www.ncbi.nlm.nih.gov/pubmed/15585754?ordinalpos=20&itool=EntrezSystem2.PEntrez.Pu bmed.Pubmed_ResultsPanel.Pubmed_RVDocSumRole of the vascular endothelial growth factor pathway in tumour growth and angiogenesis. J Clin Oncol. 2005;23:1011–1027.

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

Hurwitz HI, Fehrenbacher L, Hainsworth JD, et al: Bevacizumab in combination with fluorouracil and leucovorin: An active regimen for first-line metastatic colorectal cancer. J Clin Oncol 23:3502- , 2005

Inai T, Mancuso M, Hashizume H, et al. Inhibition of vascular endothelial growth factor (VEGF) signaling in cancer causes loss of endothelial fenestrations, regression of tumour vessels, and appearance of basement membrane ghosts. Am J Pathol 2004;165:35–52.

Jain RK. Normalization of Tumour Vasculature: An Emerging Concept in Antiangiogenic Therapy. Science 2005;307:58–62.

Jain RK. Normalizing tumour vasculature with anti angiogenic therapy: A new paradigm for combination therapy. *Nat Med* 2001;7:987–989.

Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin 2008;58:71–96.

Kabbinavar F, Hurwitz HI, Fehrenbacher L, 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;21:60–65.

Kabbinavar FF, Schulz J, McCleod M, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. J Clin Oncol 2005;23:3697–705.

Kim KJ, Li B, Winer J, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo . Nature 1993;362:841–844.

Klement G, Baruchel S, Rak J, et al: Continuous low-dose therapy with vinblastine and VEGF receptor-2 antibody induces sustained tumour regression without overt toxicity. J Clin Invest 2000;105:R15-R24.

Klement G, Huang P, Mayer B, et al: Differences in therapeutic indexes of combination metronomic chemotherapy and an anti-VEGFR-2 antibody in multidrug-resistant human breast cancer xenografts. Clin Cancer Res 2002;8:221-232.

Miriam Koopman, Ninja F Antonini, Joep Douma et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. Lancet 2007; 370: 135–42
Kozloff M, Hainsworth J, Badarinath S, et al. Efficacy of bevacizumab plus chemotherapy as firstline treatment of patients with metastatic colorectal cancer: Updated results from a large observational registry in the US (BRiTE). J Clin Oncol 2006;24:Abstract 3537.

Mabro M, Artru P, Andre T, Flesch M, Maindrault-Goebel F, Landi B, Lledo G, Plantade A, Louvet C, Gramont A, on behalf of GERCOR. A phase II study of FOLFIRI-3 (double infusion of irinotecan combined with LV5FU) after FOLFOX in advanced colorectal cancer patients. Br Cancer. 2006; 94: 1287-92.

Mancuso MR, Davis R, Norberg SM, et al. Rapid vascular regrowth in tumours after reversal of VEGF inhibition. J Clin Invest 2006;116:2610–2621.

Melnyk O, Zimmerman M, Kim KJ, et al. Neutralizing anti-vascular endothelial growth factor antibody inhibits further growth of established prostate cancer and metastases in a pre-clinical model. J Urol 1999;161:960–963.

Mesiano S, Ferrara N, Jaffe RB. Role of vascular endothelial growth factor in ovarian cancer: inhibition of ascites formation by immunoneutralization. Am J Pathol 1998;153:1249–1256.

Moosmann N, Fischer von Weikersthal L, Vehling-Kaiser U. Cetuximab Plus Capecitabine and Irinotecan Compared With Cetuximab Plus Capecitabine and Oxaliplatin As First-Line Treatment for Patients With Metastatic Colorectal Cancer: AIO KRK-0104—A Randomized Trial of the German AIO CRC Study Group. J Clin Oncol 29: 2011.

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

A. C. Reinacher-Schick, S. Kubicka, W. Freier, et al. Activity of the combination of bevacizumab (Bev) with capecitabine/irinotecan (CapIri/Bev) or capecitabine/oxaliplatin (CapOx/Bev) in advanced colorectal cancer (ACRC): A randomized phase II study of the AIO Colorectal Study Group (AIO trial 0604). J Clin Oncol 26: 2008 (May 20 suppl; abstr 4030)

M. L. Rothenberg, J. V. Cox, C. Butts et al. capecitabine plus oxaliplatin (XELOX) versus 5 fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study. Annals of Oncology 19: 1720–1726, 2008

Saltz L, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line treatment in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26(12)

Simmonds PC et al. Palliative chemotherapy for advanced colorectal cancer systematic – review and meta analysis. BMJ 2000, 321: 531-

Souglakos J, Androulakis N, Syrigos K, et al. FOLFOXIRI (folinic acid, 5 fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5 fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). Br Cancer 2006;94:798–805.

Tabernero J, Aranda E, Gomez A, et al. Phase III study of first-line XELOX plus bevacizumab (BEV) for 6 cycles followed by XELOX plus BEV or single- gent (s/a) BEV as maintenance therapy in patients (pts) with metastatic colorectal cancer (mCRC): The *MACRO* Trial (Spanish Cooperative Group for the Treatment of Digestive Tumors [TTD]). Clin Oncol 28:7s, 2010 (suppl; abstr 3501), Abstract No: 3501

The Criteria Committee of the New York Heart Association. Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis. 6th Boston, MA: Little 1964

Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229–237.

Warren RS, Yuan H, Matli MR, et al. Regulation by vascular endothelial growth factor of human colon cancer tumourigenesis in a mouse model of experimental liver metastasis. J Clin Invest 1995;95:1789–1797.

Yalcin S, Uslu R, Dane F, et al. A Randomized, multicenter phase III trial of bevacizumab plus capecitabine were given as maintenance treatment after initial treatment with bevacizumab plus XELOX in previously untreated metastatic colorectal cancer. J Clin Oncol 29: 2011 (suppl 4; abstr 474)