A randomized multicenter clinical trial for patients with multi-organ, colorectal cancer metastases comparing the combination of chemotherapy and maximal tumor debulking versus chemotherapy alone
### PROTOCOL TITLE

A randomized multicenter clinical trial for patients with multi-organ, colorectal cancer metastases comparing the combination of chemotherapy and maximal tumor debulking *versus* chemotherapy alone

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Chemotherapy and maximal tumor debulking of multi-organ CRC metastases

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

5-FU  5-fluorouracil
ABR  ABR form (General Assessment and Registration form) is the application form that is required for submission to the accredited Ethics Committee (ABR = Algemene Beoordeling en Registratie)
AE  Adverse Event
AR  Adverse Reaction
CA  Competent Authority
CCMO  Central Committee on Research Involving Human Subjects
CV  Curriculum Vitae
DEBIRI-TACE  Transarterial chemo-embolization using irinotecan drug-eluted beads
DSMB  Data Safety Monitoring Board
EU  European Union
EudraCT  European drug regulatory affairs Clinical Trials GCP Good Clinical Practice
FOLFOX  Combination of 5-fluorouracil, leucovorin and oxaliplatin
IB  Investigator’s Brochure
IC  Informed Consent
IMP  Investigational Medicinal Product
IMPD  Investigational Medicinal Product Dossier
LV  leucovorin
mCRC  Metastatic colorectal cancer
METC  Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
MFI  Multidimensional fatigue inventory
OS  Overall survival
PFS  Progression free survival
RFA  Radiofrequency ablation
RT  Radiation therapy
SABR  Stereotactic ablative radiotherapy
(S)AE  Serious Adverse Event
SPC  Summary of Product Characteristics (in Dutch: officiële productinformatie IB1-tekst)
Sponsor  The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study
but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.

**SUSAR**  Suspected Unexpected Serious Adverse Reaction

**Wbp**  Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)

**WMO**  Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen)

**XELOX**  Combination of capecitabine and oxaliplatin
SUMMARY

Rationale: Colorectal cancer (CRC) is one of the leading causes of cancer death world-wide mostly as a consequence of metastatic disease. Combination chemotherapy strategies are currently available that improve survival time of patients with metastatic colorectal cancer (mCRC). New developments in local treatments, including surgical procedures, radiofrequency ablation (RFA), transarterial chemo-embolization using irinotecan drug-eluted beads ((DEBIRI-)TACE) and stereotactic ablative radiotherapy (SABR), have been suggested to further improve survival time when used for individual selected patients. It is unknown to what extent these strategies improve survival compared to systemic chemotherapy because comparison studies of these treatment modalities have not been performed. Surgical resection of liver and lung metastases may improve 5-year survival rates up to 35-60% in selected patients. Currently, CRC patients with unresectable liver or extrahepatic metastases are primarily eligible to systemic treatment using chemotherapy with or without monoclonal antibodies resulting in an overall survival (OS) of approximately 22 months.

To date, the combination of chemotherapy and maximal tumor debulking has not been compared to chemotherapy alone in patients with multi-organ mCRC in a randomized controlled trial. In order to study whether adding maximal tumor debulking to chemotherapy will benefit survival of multi-organ mCRC patients we designed a multicenter randomized controlled trial. Our hypothesis is that maximal tumor debulking in addition to systemic treatment with chemotherapy and biologicals will provide an improvement in progression free and overall survival in this patient group.

Objective: The primary objective of this study is to compare overall survival rates of CRC patients with multi-organ metastases with an indication for first line systemic treatment randomized for treatment with combination chemotherapy or treatment with combination chemotherapy and additional maximal tumor debulking including surgical tumor resection, RFA, (DEBIRI-)TACE and SABR, depending on best clinical judgment by a multidisciplinary team.

Study design: Randomized controlled multicenter intervention study.

Study population: Patients with multi-organ mCRC, who are not amenable for HIPEC and aged ≥ 18 years, with an indication for first line palliative systemic treatment.

Intervention: After study inclusion, diagnostic biopsies or study biopsies will be obtained from a metastatic site. All patients will receive 3 cycles of capecitabine and oxaliplatin (XELOX) or comparable intravenous regimen consisting of 4 cycles of 5-Fluorouracil (5-FU) and oxaliplatin (FOLFOX), bevacizumab may be added to both regimens. After radiological evaluation, patients with stable disease or response will be randomized to either continuation of XELOX/FOLFOX alone or to additional local treatment including surgery, RFA, (DEBIRI-)TACE and SABR depending on best clinical judgment by a multidisciplinary team.
**Main study parameters/endpoints:** The primary objective is OS counting from the date of study inclusion to the date of death. Secondary objectives include: 1) Progression free survival (PFS), 2) To determine the safety and efficacy of the additional local treatment, 3) To determine quality of life in the two study arms, 4) To study whether CEA can predict for treatment response and survival, 5) To determine the relation of genomic (instability) profiles and response to therapy, 6) To study the relation of microRNA (miRNA) profiles and response to therapy, 7) To study (phospho)proteomic profiles in relation to response to therapy, 8) To study circulating endothelial cells (CECs) and immune cells in relation to response to therapy.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** After enrolment in this study a tumor biopsy of a metastatic site prior to treatment with XELOX/FOLFOX with or without bevacizumab will be obtained. The biopsy and its preparations as appropriate may cause physical discomfort and adverse effects of XELOX/FOLFOX and bevacizumab, currently considered as standard treatment in mCRC patients, may occur. Patients randomized for additional local treatment may experience physical discomfort or adverse effects from the additional local treatment including surgery, RFA, (DEBIRI-)TACE and SABR. Response to therapy will be measured by (18F-FDG-PET)-CT or by MRI when required. In addition, patients will be asked to complete quality of life questionnaires and the multidimensional fatigue inventory (MFI). Follow-up during therapy will include laboratory analysis on regularly visits to the outpatient clinic. In addition, blood samples will be obtained for research purposes. This study aims to show benefit for adding maximal tumor debulking to chemotherapy by increasing PFS and OS rates of mCRC patients. In addition, results of this study will be used to eventually obtain personalized treatment regimens on the basis of molecular characteristics of the tumor.
1. INTRODUCTION AND RATIONALE

1.1 Treatment of metastatic colorectal cancer (mCRC)

Colorectal cancer (CRC) is one of the leading causes of cancer death affecting 11,000 patients each year in the Netherlands (Siesling et al. 2003). In approximately 20% of patients distant metastases are already present at time of diagnosis (van der Pool et al. 2010a). The liver is the most common metastatic site. Other frequent sites of disease involvement include lungs, regional lymph nodes and peritoneum (de Haas et al. 2008). Approximately 50% of CRC patients with early-stage disease will eventually develop liver metastases. When metastases of CRC patients are restricted to the liver, possible curative treatment can be obtained by surgical resection of the metastases. Also patients with (an) oligo metastasis(es) restricted to the lungs may be candidates for surgical resection. Complete surgical resection of metastatic lesions substantially improves survival rates to around 35-60% in selected patients (Dols et al. 2009; Pfannschmidt et al. 2010; Rees et al. 2008; van der Pool et al. 2010b). However in only 5-20% of patients surgical resection of liver and/or lung metastases is feasible. At present, CRC patients with unresectable liver and/or extrahepatic metastases are treated with systemic combination chemotherapy. Most common combinations are oxaliplatin or irinotecan plus capecitabine or 5-Fluorouracil (5-FU) with or without the combination of bevacizumab. In case of K-RAS wild-type tumors, anti-epidermal growth factor receptor (EGFR) antibodies panitumumab and cetuximab are being used mostly as single agents in third line. These systemic chemotherapeutic combinations have response rates of 40-70% resulting in a median overall survival (OS) rate of approximately 22 months (Emmanouilides et al. 2007; Van Cutsem et al. 2009b; Ychou et al. 2008).

1.2 Systemic therapy of mCRC

For a long time, treatment with the antimetabolite 5-FU and leucovorin (LV) was the standard chemotherapeutic treatment regimen of mCRC improving OS rates from approximately 6 months to 10-12 months (Advanced Colorectal Cancer Meta-Analysis Project 1992). In the last decade development of new chemotherapeutic agents such as oxaliplatin, a cytotoxic agent from the diaminocyclohexane platinum family, and irinotecan, a topoisomerase I inhibitor, have significantly improved OS of these patients. Combining 5-FU and LV with irinotecan or oxaliplatin have increased median survival rates to 14-16 months (de Gramont A. et al. 2000; Douillard et al. 2000; Saltz et al. 2000). Several large randomized controlled trials have been performed to study the best chemotherapeutic combination, but no differences were observed in progression free survival (PFS) in mCRC patients between a combination of 5-FU and oxaliplatin (FOLFOX) or 5-FU and irinotecan (FOLFIRI). In addition similar survival rates have been observed in patients
Chemotherapy and maximal tumor debulking of multi-organ CRC metastases

treated with sequential or combined administration of 5-FU and oxaliplatin or irinotecan (Koopman et al. 2007; Seymour et al. 2007; Tourignand et al. 2004). Treatment of mCRC patients with a combination of the three chemotherapeutic agents (FOLFOXIRI), showed no definite improved response rates and median OS, compared to FOLFIRI alone (Souglakos et al. 2006; Masi et al. 2011).

Since the year 2004 several studies have been performed to optimize systemic treatment in mCRC patients by addition of monoclonal antibodies, such as bevacizumab (monoclonal antibody against vascular endothelial growth factor (VEGF)), cetuximab and panitumumab (both monoclonal antibodies against EGFR), to chemotherapy. The addition of biologicals has improved median survival to > 20 months.

Hurwitz et al. showed a significant improvement in median survival between patients treated with bevacizumab in combination with irinotecan and 5-FU with an OS of 20.3 months compared to 15.6 months in patients treated with irinotecan, 5-FU and a placebo. Also median PFS was longer in patients treated with additional bevacizumab compared to placebo with survival rates of 10.6 and 6.2 months, respectively (Hurwitz et al. 2004). Also the study by Saltz et al. showed significant improved PFS by adding bevacizumab to mCRC patients treated with FOLFOX or XELOX (capecitabine and oxaliplatin). OS was similar between the two treatment arms, with survival rates of 21 and 20 months in patients treated with and without bevacizumab respectively (Saltz et al. 2008).

Van Cutsem et al. compared FOLFIRI treatment with or without cetuximab in mCRC patients in a randomized controlled trial. Although no significant difference was observed in OS, both response rates and PFS were higher in patients treated with cetuximab and FOLFIRI compared to patients treated with FOLFIRI alone, with survival rates of 8.9 and 8.0 months respectively for PFS and 19.9 and 18.6 months respectively for OS (Van Cutsem et al. 2009a). Recently, no improvements in PFS and OS were observed with the addition of cetuximab to oxaliplatin-based first-line treatment (Maughan et al. 2011). Douillard et al. showed that adding panitumumab to FOLFOX significantly improved PFS. Median OS was not significantly different between patients treated with or without panitumumab with survival rates of 24 and 20 months respectively (Douillard et al. 2010).

Results of combined treatment with monoclonal antibodies might be promising in mCRC, however response to these targeted agents has only been shown in a subset of mCRC. Treatment with anti-EGFR antibodies was found to be only effective in patients with K-RAS wild-type tumors (Amado et al. 2008; Lievre et al. 2008). Still, not all K-RAS wild-type tumors respond to anti-EGFR treatment indicating that other, yet unknown, biological factors or pharmacokinetics may affect tumor response. Further studies are needed to explore the relation between the biology of the tumor and response to therapy and to develop diagnostic tests for response prediction of targeted agents in patients with mCRC.
1.3 Surgery of mCRC

Currently, mCRC patients with liver metastases can only be cured by surgical resection of these lesions. Surgical resection can be performed if there is sufficient residual liver after resection to enable survival of the patient, corresponding to 20-25% of the total functioning liver volume. Patients with pre-existent liver disease such as steatosis, cirrhosis or chemotherapy associated steatohepatitis need at least 30-40% of the liver remnant to survive. In addition, one of the three main hepatic veins must be left in place and the liver remnant has to comprise a portal vein, hepatic artery and a bile duct. Of all patients with liver metastases, only about 10-20% of the patients are eligible for this surgical treatment. Resection of liver metastases can substantially improve 5-year survival rates to around 35-60% (Dols et al. 2009;Primrose 2010;Rees et al. 2008;van der Pool et al. 2010b).

In a subgroup of patients with mCRC, surgical resection of pulmonary metastases can be performed. The surgical procedures include wedge resection, segmentectomy, lobectomy or pneumonectomy. In general, only patients who can undergo a potentially curative operation are eligible for surgery, which usually includes patients with isolated pulmonary metastases (oligo metastases) and good pulmonary function. After complete resection of pulmonary metastatic sites 5-year survival rates of 40-68% can be achieved (Pfannschmidt et al. 2007;Pfannschmidt et al. 2010;Riquet et al. 2010). Approximately 5-10% of mCRC patients will have metastases in both liver and lungs. In selected patients combined resection of lung and liver metastasis is feasible and 5-year survival rates of 30-60% have been reported (de Haas et al. 2008;Pfannschmidt et al. 2007;Pfannschmidt et al. 2010). One has to realize that these reports concern a specifically selected group of patients and 5-year survival rates are therefore highly biased.

For patients with extrahepatic and non-isolated lung metastases surgical tumor resection is usually considered as a contraindication. Nevertheless, extensive surgical treatment has resulted in long term survival in patients after a combination of complete resection of all metastatic sites and perioperative chemotherapy (de Haas et al. 2008). The possibility of curative resection after downsizing initially unresectable metastatic lesions is reported by Adam et al. They showed that 16% of the patients with primarily unresectable metastases could be cured by chemotherapy treatment followed by surgical resection of the metastatic lesions. Having extrahepatic metastases was not a contraindication for liver resection and when located in the abdomen, extrahepatic metastases were resected concurrently with hepatectomy. Also, extrahepatic metastases outside the abdomen were surgically removed, but after a delay of 2-3 months due to meanwhile given chemotherapeutic treatment (Adam et al. 2009).

Incomplete, but maximal resection of tumor lesions gives a survival benefit for patients with ovarian cancer (Tangjitgamol et al. 2009). As a consequence, some suggest that maximal tumor
debulking for metastatic disease may also benefit colorectal cancer patients (Primrose 2010), although this hypothesis is yet unproven.

Taken together, these results indicate existing opportunities for improving survival rates by combining chemotherapy with surgical resection of metastases in potentially non-curative mCRC patients with multiple metastases.

1.4 Local treatment modalities in mCRC

To further improve survival rates of mCRC patients several local therapies have been applied for the treatment of unresectable liver metastases in the past few years including radiofrequency ablation (RFA), transarterial chemo-embolization using irinotecan drug-eluted beads ((DEBIRI-)TACE) and stereotactic ablative radiotherapy (SABR). A recent study suggested that RFA may improve survival in patients with unresectable liver metastases, with relatively low complication rates (van Tilborg et al. 2010). In addition, interim analysis of a randomized phase II trial showed an improved progression free survival in patients with unresectable liver metastases treated with RFA and chemotherapy compared to chemotherapy alone (Ruers et al. 2008;Ruers et al. 2010). RFA has also been successfully used for treatment of pulmonary metastases. Lencioni et al. reported RFA treatment in 53 patients with pulmonary metastases. Of these patients, 19 had metastatic disease isolated to the lungs, including 4 patients who had undergone surgical resection of pulmonary metastases before. The other 34 patients were previously treated for hepatic metastases by surgical resection and/or RFA. One and two year OS rates in this selected group of patients were 89% and 66%, respectively (Lencioni et al. 2008). In the study by Yan et al., 30 patients were treated with RFA for their pulmonary metastases after initial hepatectomy for treatment of liver metastases. In this again highly selected group of patients, the median survival rate after lung RFA was 32 months with a 3 year survival rate of 45% (Yan et al. 2007). Besides RFA, the use of (DEBIRI-)TACE has shown promising results in the treatment of mCRC liver metastases, with response rates of up to 75% (Aliberti et al. 2006;Fiorentini et al. 2007;Martin et al. 2009b). The combination of (DEBIRI-)TACE and RFA suggested an improved local disease control in hepatocellular carcinoma lesions larger than 3 cm (Veltri et al. 2006), indicating that these two local therapeutic options could have an important role in improving survival rates of patients with mCRC. For patients who are not eligible for surgery or RFA, or who are refractory to RFA, SABR can safely be used in a selected population to achieve adequate local control, thereby suggesting improved survival rates of patients with mCRC(van der Pool et al. 2010c).

Recently, Cui et al. compared treatment of mCRC patients with non-curative resectable liver metastases using chemotherapy, surgery and RFA with or without additional hepatic artery infusion with oxaliplatin. They found an improved overall survival and a decreased recurrence rate of liver metastases in patients treated with additional hepatic arterial infusion with oxaliplatin (Cui
et al. 2010), indicating that more aggressive local treatment of metastases can improve long-term survival in mCRC patients and that combining different therapeutic options is feasible and effective.

1.5 Prognostic and predictive markers in CRC

Despite improvement of mCRC therapy resulting in better survival rates, knowledge on treatment response and risks of relapse or progression is still largely unknown. More insights in biological tumor behavior may result in better understanding of treatment failure and may yield biological markers for prediction of response to therapy or risks of relapse. This could help in identifying patients who will not benefit from certain treatment and thereby avoiding unnecessary treatment associated toxicity. In addition, patients with high relapse risk profiles can be subjected to more aggressive treatment to improve survival rates.

Currently, the only marker routinely used in clinical practice of individualized mCRC treatment is K-RAS, since treatment with anti-EGFR antibodies was found to be only effective in patients with K-RAS wild-type tumors as mentioned in section 1.2. Another prognostic and response predictive marker extensively studied in relation to prognosis and treatment response, but not yet used in routine clinical practice, is microsatellite instability status. CRC patients with microsatellite instable stage II and III tumors have a better prognosis compared to patients with microsatellite stable CRC. For patients with mCRC this relationship could not be proven, mainly due to the low incidence of microsatellite instable mCRC tumors (Koopman et al. 2009). Also a functioning mismatch repair system is needed for inducing cytotoxicity upon 5-FU incorporation into the DNA, indicating that microsatellite instable tumors are less sensitive to 5-FU treatment (Sargent et al. 2010; Walther et al. 2009).

Several genome-wide DNA- and RNA-based profiling methods have been performed in an attempt to discover new prognostic and predictive markers for mCRC. Thus far, these studies have not resulted in markers which can be used in the clinic to predict for response to therapy or patient outcome mostly due to lack of reproducibility and small sample sizes.

1.6 Study rationale

CRC is one of the leading causes of cancer death world-wide mostly as a consequence of metastatic disease. Combination chemotherapy strategies are currently available that improve survival times of patients with mCRC. Surgery, RFA, (DEBIRI-)TACE and SABR have been suggested to further improve survival time when used for individual selected patients. It is unknown to what extent these treatment modalities improve survival compared to standard systemic combination therapy alone since comparative studies have not been performed. Studies in which patients with mCRC have received the newest combinations of systemic treatment,
Chemotherapy and maximal tumor debulking of multi-organ CRC metastases

consisting of combined chemotherapy and monoclonal antibodies, median OS was approximately 22 months. In these studies patients with a significantly worse prognosis have been included compared to the previous studies in which local treatments were applied to highly selected patient. Therefore, data showing that surgical resection of liver and lung metastases may improve 5-year survival rates up to 35-60%, which seems significantly higher than the results of optimal systemic therapy, should be considered with caution. To date, a combination of chemotherapy and maximal tumor debulking has not been compared to chemotherapy alone in patients with multi-organ mCRC with an indication for first line palliative systemic treatment in a randomized controlled trial. In order to study the effect of adding maximal tumor debulking to chemotherapy on survival of multi-organ mCRC patients we designed a multicenter randomized controlled trial. The primary aim of this study is to compare OS rates of patients with multi-organ metastases randomized for treatment with chemotherapy consisting of capecitabine and oxaliplatin (XELOX) or comparable intravenous regimen consisting of 5-Fluorouracil (5-FU) and oxaliplatin (FOLFOX) or treatment with XELOX/FOLFOX and additional maximal tumor debulking, including surgical tumor resection and other local therapies such as RFA, (DEBIRI-)TACE and SABR. Our hypothesis is that local treatment will provide an improvement in PFS and OS in this patient group. Patients with only intra-abdominal metastases eligible for treatment with hyperthermic intraperitoneal chemotherapy (HIPEC) or patients with metastases limited to one organ will not be included in this study. Only multi-organ mCRC patients with >1 extrahepatic metastases or >5 hepatic metastases located in more than one lobe will be included in this study. In our opinion, these patients have too extensively metastatic disease to be applicable for primary curative local treatment. Furthermore, patients with ≥1 hepatic metastases and para-aortal or celiac lymph node metastases or adrenal metastases will be included in this study, because of poor survival rates with local treatment only (Adam et al. 2008; de Haas et al. 2009).

As secondary objectives we will study PFS of patients, safety and feasibility of combined treatment and quality of life. We will also study whether the tumor marker CEA and circulating endothelial cells can predict response to therapy and survival. In addition, genomic (instability) profiling, miRNA profiling and (phospho)proteomic profiling will be performed in an exploratory setting to unravel biological markers for response to therapy and prognosis of patients in order to ultimately aim for tailored based treatment of mCRC patients.
2 OBJECTIVES

2.1 Study parameters/endpoints

Primary Objective:
Primary endpoint of the study will be overall survival (OS), counting from the date of study inclusion to the date of death of the patient.

Secondary Objectives:
1. Progression free survival, counting from the date of study inclusion to the date of either progressive or recurrent disease
2. To determine safety and efficacy of additional local treatment in combination with chemotherapy
3. To determine quality of life in the two study arms
4. To study whether CEA can predict for treatment response and progression free survival
5. To determine the relation of genomic (instability) profiles and response to therapy
6. To study the relation of miRNA profiles and response to therapy
7. To study (phospho)proteomic profiles in relation to response to therapy
8. To study circulating endothelial cells (CECs) and immune cells in relation to response to therapy

2.2 Main study parameter/endpoint (primary objective)

We will compare OS rates of patients included in both study arms. OS will be defined counting from the date of study inclusion to the date of death due to CRC (event) or to the last day of follow-up (censored).

Follow-up information will be obtained from hospital case records in up to a mandated 10 years follow-up regimen or from general practitioners.

2.3 Secondary parameters endpoints (secondary objectives)

2.3.1 Progression free survival rates (PFS)
Besides OS, we will evaluate PFS of the patients included in the study. PFS will be defined counting from the date of study inclusion to the first event defined as local recurrence or progression, distant recurrence or death from any cause.
We will compare PFS rates between patients included in the two different study arms.

2.3.2 Safety and efficacy of combined treatment strategies and (18F-FDG-PET-)CT response evaluation

In this study several therapeutic strategies will be combined in an attempt to improve survival of mCRC patients. All therapeutic strategies that will be used in this study, i.e. surgery, RFA, (DEBIRI-)TACE and SABR, have been safely used in mCRC patients. Cui et al. have shown that a combination of chemotherapy, surgery, RFA and hepatic artery infusion can be safely and successfully combined (Cui et al. 2010) and Mima et al. have shown that the combination of hepatic surgery and RFA after chemotherapy is safe (Mima et al. 2012). Since (DEBIRI-)TACE and SABR are only minimally invasive techniques we expect that the combined treatment strategies in this study will be safe.

For assessing response rates we will use CT or 18F-FDG-PET-CT and when required MRI. 18F-FDG-PET-CT will be used as a tool for response prediction in solid tumors and has been included in the latest edition of the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) to detect progressive disease (Eisenhauer et al. 2009). Several studies have demonstrated the role of 18F-FDG-PET-CT in initial staging, restaging, and neoadjuvant chemotherapy response assessment in CRC patients. Recently, 18F-FDG-PET has been successfully used for response evaluation in patients with recurrent CRC (Shamim et al. 2011).

We will evaluate the efficacy of the local treatment strategies by reporting time and location of disease recurrence. Responses after local treatment will be determined by an expert panel. Furthermore, we will evaluate the feasibility of baseline FDG uptake values as a prognostic tool in an exploratory design.

2.3.3 Quality of life

An important factor in treatment of patients with mCRC is their quality of life. Anticancer treatment can influence quality of life both positively and negatively due to benefits and risks of treatment. As a secondary objective we aim to study the difference in quality of life between two treatment arms. To more accurately evaluate the well-being of patients the European Organisation for Research and treatment of Cancer Quality of Life questionnaires (EORTC QoL) will be used. Two questionnaires will be included, the EORTC QLQ-C30 (appendix I) generally used to assess QoL of the cancer patients and the module EORTC-QLQ-CR29 (appendix II) specifically for QoL evaluation in CRC patients. As fatigue is the most common side-effect of anticancer treatment and a factor with a huge impact on patients quality of life, we will independently assess fatigue using the multidimensional fatigue inventory (MFI) (Smets et al. 1995) (appendix III).
2.3.4 To study whether CEA can predict for treatment response and PFS
As one of the secondary objectives we will evaluate the correlation of tumor markers to treatment response. In CRC carcinoembryonic antigen (CEA) is commonly used to evaluate response of chemotherapy in CRC patients. This tumor marker has shown good correlation to radiological response to therapy as measured by CT scan in patients with liver metastases (de Haas et al. 2010).

2.3.5 To study the relation of genomic (instability) profiles and response to therapy
Collected tumor samples will be analyzed by massively parallel sequencing (MPS). This recently developed technique enables analysis of genome-wide copy number alterations and genomic variations including substitutions, point-deletions and insertions (Wheeler et al. 2008). Patterns of DNA copy number aberrations and single nucleotide polymorphisms have been shown to correlate with clinicopathological variables, including survival of patients, risk of relapse, radiotherapy induced toxicity and response to chemotherapy (Brosens et al. 2010; Buffart et al. 2007; Kong et al. 2008; Postma et al. 2009; Weiss et al. 2003). These results indicate that tumor behavior is reflected by underlying genetic tumor profiles.

MPS has also been successfully applied on archival material for analysis of DNA copy number aberrations and mutations (Schweiger et al. 2009). Using this technique Leary et al. demonstrated that rearranged DNA sequences could serve as potential biomarkers. These rearranged sequences could be detected in the presence of large amounts of normal DNA, including patient plasma (Leary et al. 2010). Jones et al. showed that high-throughput sequencing in combination with DNA copy number aberrations lead to selection of drug therapy which resulted in good anti-tumor response in the patient (Jones et al. 2010).

Nilssen et al. showed that platelets contain tumor-derived RNA biomarkers and that platelets from glioma patients contain a distinct RNA signature compared to healthy control subjects. Platelets will be isolated from an EDTA tube to determine RNA profiles of platelets using gene-expression arrays as previously described (Nilsson et al. 2011). We will correlate changes in these profiles in therapy response to identify new possible biomarkers.

Furthermore plasma derived from the platelet isolation process will be snap frozen at -80°C and will be used for miRNA profiling as described below in paragraph 2.3.6.

In addition microsatellite instability (MSI) analysis will be performed using the MSI Analysis System consisting of five nearly monomorphic mononucleotide markers (BAT-25, BAT-26, NR-21, NR-24, MONO-27) according to the manufacturer’s instructions, since MSI status is known to influence response to chemotherapeutic agents used in this study (Sargent et al. 2010). As one of the secondary aims the obtained genomic (instability) patterns will be correlated to survival of patients and response to therapy, including (radiotherapy induced) toxicity, in order to
unravel new predictive biomarkers, markers contributing to therapy selection and knowledge on mechanisms of resistance to anti-cancer drugs.

2.3.6 To study the relation between miRNA profiles and response to therapy

MiRNA expression analysis will be performed to analyze the relation between miRNA expression profiles and response to therapy. MiRNAs have been shown to play a role in initiation and progression of cancer including regulation of angiogenesis. In addition, miRNA expression profiles have been shown to correlate with disease progression and prognosis of patients. Different miRNA expression profiles have been observed between patients who responded to chemotherapy treatment compared to non-responders. The pharmacodynamic mechanism of 5-FU and oxaliplatin might be partly based on their influence on miRNA expression, as treatment with these agents alter miRNA expression profiles in CRC cell lines (Hummel et al. 2010; Zhou et al. 2010).

Besides correlation between clinical parameters and miRNA expression profiles of tumor tissue, profiles of miRNAs circulating in plasma can distinguish patients and healthy individuals. Moreover, these profiles of circulating miRNAs seem to correlate with clinical stage of the disease and outcome of the patients (Hummel et al. 2010; Taylor and Gercel-Taylor 2008). Therefore we aim to obtain miRNA profiles from blood samples of patients and to compare them with miRNA expression profiles of tumor tissue. In addition we aim to correlate the obtained profiles to prognosis of patients.

Treatment with chemotherapy can alter miRNA expression profiles (Rossi et al. 2007). Therefore, we will also perform miRNA expression profiling during chemotherapeutic treatment to study these changes in order to obtain putative markers to predict for response to therapy.

2.3.7 To study (phospho)proteomic profiles and response to therapy

Serum peptide profiling will be performed according to standard procedures as previously described (Voortman et al. 2009). Serum peptide abundances will be quantified and generated data will be used to study peptide signatures with clinical value including response to therapy, radiotherapy induced toxicity and outcome of patients. Collected serum samples will be analyzed by Mass Spectrometry using the Matrix Assisted Laser Desorption Ionized-tandem Time of Flight (MALDI-TOF-TOF) analyzer currently present at our institution. The read-out of the MALDI-TOF Mass Spectrometry will be analyzed using an in-house developed pipe-line that allows for data preprocessing, multivariate statistic analysis and pattern recognition (OPL Analyzer) (Pham et al. 2010; Voortman et al. 2009). Using this method Voortman et al. showed different peptide profiles between patients with non-small cell lung cancer (NSCLC) who responded to combination therapy consisting of cisplatin, gemcitabine and bortezomib, compared to non-responders. In addition, serum peptide signatures of patients with long PFS differed from patients with short PFS.
(Voortman et al. 2009) and differed between mice with high and low rates of radiation induced lung toxicity (Kong et al. 2008). Besides serum peptide profiles, proteomic profiles of blood derived cells will be studied in an exploratory analysis.

Kinome profiling will be performed on tumor tissue samples before and during treatment with XELOX/FOLFOX, as previously described (Piersma et al. 2010). Kinase activity profiles have been shown to correlate to tumor response upon cancer treatment. Folkford et al. showed higher substrate signal levels in tumor biopsies of rectal cancer patients in poor responders to chemoradiotherapy treatment, including 5-FU and oxaliplatin, compared to good responders. Also basal phosphorylation levels were found to be significantly higher in poor responders compared to good responders. Generally, this high kinase activity was inhibited in the presence of sunitinib, a tyrosine kinase inhibitor, indicating that these poor responders might benefit from treatment with kinase inhibitors (Folkvord et al. 2010).

2.3.8 To study circulating endothelial cells (CECs) and immune cells in relation to response to therapy

Of all patients we will obtain one CellSave® tube of blood for the analysis of circulating endothelial cells (CECs) before and after treatment. CECs have been shown to be correlated to time to progression and tumor response in metastatic breast cancer patients (Bidard et al. 2010). Also in prostate cancer a prognostic value of CECs was observed and levels of these circulating cells changed during treatment with docetaxel (Strijbos et al. 2010).

In this study the amount of CECs will be correlated to response to therapy and survival time in order to investigate if they can be used as predictive markers.

The immune status of patients with colorectal cancer has been related to clinical outcome and holds prognostic significance. Specifically, the infiltration of tumor fields by memory CD8⁺ T cells has been related to prognosis. Remarkably, this so-called immunoscore has been shown to more accurately predict survival of patients with colorectal cancer than the classical TNM staging system(Galon et al. 2012; Mlecnik et al. 2011; Galon et al. 2006). In previous immunotherapy trials conducted in patients with castration resistant prostate cancer at the VU University medical center a pre-treatment immune profile was identified based on flowcytometric analysis of T cell and myeloid subsets in peripheral blood that was predictive for overall survival (Santegoets et al. 2012; van den Eertwegh et al. 2012) In this study we will try to validate this panel of immune cells in patients with advanced colorectal cancer by flowcytometric analysis of the leucocyte pellet derived in the process of platelet isolation. The obtained immune profiles will be related to survival. These data may provide evidence for an immune involvement in the outcome of conventional therapies in patients with advanced colorectal cancer and may yield useful blood-based immune biomarkers for outcome prediction of treatment or general prognosis.
3. STUDY DESIGN

3.1 Summary of study design

This randomized controlled trial (RCT) is intended to improve survival rates of CRC patients with multi-organ metastases. We hypothesize that a combination of chemotherapy and maximal tumor debulking is superior in overall survival time compared to chemotherapy alone in these patients. Patients with multi-organ mCRC with an indication for palliative systemic treatment, who are not candidates for hyperthermic intraperitoneal chemotherapy (HIPEC), will receive study information. After acquiring informed consent these patients will be screened by a medical oncologist and evaluated by an expert panel. Patients are eligible for inclusion if they meet the inclusion and exclusion criteria, including the opinion of the expert panel that macroscopic radical tumor debulking can be achieved with local treatment modalities in at least 80% of metastatic lesions and taking into account the following:

<table>
<thead>
<tr>
<th>Patients with CRC metastases in</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2 different organs if at least &gt;1 extrahepatic metastases or</td>
</tr>
<tr>
<td>≥ 2 different organs including &gt;5 hepatic metastases not located to one lobe or</td>
</tr>
<tr>
<td>≥ 2 different organs and including either a positive para-aortal or celiac lymph nodes or adrenal metastases or peritoneal carcinomatosis or pleural carcinomatosis</td>
</tr>
</tbody>
</table>

*The primary tumor is excluded as metastatic site*

Drainage of pleural fluid with chemical pleurodesis is considered macroscopic radical treatment. After study inclusion diagnostic biopsies or study biopsies of one metastatic lesion will be obtained. All patients will receive 3 cycles of chemotherapy with the current XELOX (capecitabine and oxaliplatin; 3-week cycle) or 4 cycles of current FOLFOX (5-FU and oxaliplatin; 2-week cycle) regimen with or without bevacizumab. A baseline CT or ¹⁸F-FDG-PET-CT will be performed no more than 28 days prior to the first dose of chemotherapeutic treatment. After 3 or 4 cycles of XELOX or FOLFOX, respectively, a second CT or ¹⁸F-FDG-PET-CT will be made and response rates will be evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). When required for assessing response rates, a MRI scan will be performed. Patients who show clinical benefit, defined as stable disease or response to therapy, will be randomized in one of the two study arms, arm A and arm B (Figure 1). Patients with progressive disease will be treated according to best clinical practice, including all treatment modalities.
Chemotherapy and maximal tumor debulking of multi-organ CRC metastases

Patients included in study arm A will continue to receive XELOX or FOLFOX therapy with or without bevacizumab until disease progression or unacceptable therapy related toxicity. After 6 cycles of XELOX or FOLFOX, capecitabine monotherapy is also allowed. In case of unacceptable toxicity of oxaliplatin, capecitabine monotherapy may be considered before 6 cycles of XELOX or FOLFOX. When patients show progressive disease, they will be treated with second line therapy according to best clinical practice. Palliative local treatment options are accepted for a single progressive metastasis or for symptomatic metastases.

Patients in study arm B will be treated with 1 additional cycle of XELOX or FOLFOX without bevacizumab and additional local treatment, according to the treatment plan of the expert panel, in case of >30% response rates. Preferred local treatment will be surgical resection of the tumor lesions. Tumor lesions that were not resected will be treated by any form of other local treatment i.e. RFA, (DEBIRI-)TACE, SABR, depending on best clinical judgment and depending on the metastatic site (Appendix IV). After local treatment, patients will continue systemic therapy until they completed in total at least 8 cycles of XELOX or corresponding 12 cycles of FOLFOX therapy with or without bevacizumab from study inclusion. After a total of 6 cycles of XELOX or FOLFOX, monotherapy with capecitabine is allowed, with or without bevacizumab. In case of unacceptable toxicity XELOX or FOLFOX therapy will be withheld. In case of unacceptable toxicity of oxaliplatin, monotherapy with capecitabine may be considered.

Local treatment procedures should be completed within 3 months. When three different local treatment procedures have to be performed within one patient, the last local treatment may be performed after systemic therapy otherwise systemic treatment will be too much delayed.

Patients with progressive disease will be treated according to best clinical practice, including all treatment modalities. Patients in study arm B with stable disease according to RECIST 1.1 will receive 3 additional cycles of XELOX or 4 cycles of FOLFOX with or without bevacizumab, whereafter response rates will be reevaluated. When these patients show a response or stable disease at this reevaluation they will be subjected to 1 additional cycle of XELOX or FOLFOX without bevacizumab and local treatment as described above. After local treatment patients will continue systemic therapy until they completed in total at least 8 cycles of XELOX or corresponding 12 cycles of FOLFOX therapy with or without bevacizumab from study inclusion. After a total of 6 cycles of XELOX or FOLFOX, monotherapy with capecitabine is allowed, with or without bevacizumab. In case of unacceptable toxicity XELOX or FOLFOX therapy will be withheld. In case of unacceptable toxicity of oxaliplatin, capecitabine monotherapy may be considered. Patients with progressive disease will be treated according to best clinical practice, including all treatment modalities.
It is recommended to continue treatment until disease progression or unacceptable toxicity. However, continuation of any treatment schedule after 6 months in absence of disease progression or unacceptable toxicity is at the discretion of the investigator.

In total we aim to include 478 patients. This number is based on the assumption that in our patient group 20% of the patients will not show clinical benefit, defined as response or stable disease, when treated with XELOX or FOLFOX (de Gramont A. et al. 2000;Emmanouilides et al. 2007;Giacchetti et al. 2000) (see also Table1) and including 191 patients in each study arm.

### Tabel 1. Disease response and overall survival with first-line XELOX or FOLFOX ± Bevacizumab treatment

<table>
<thead>
<tr>
<th>Study (number of patients)</th>
<th>≥2 involved organs (n, %)</th>
<th>CR+PR (%)</th>
<th>SD (%)</th>
<th>PD (%)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comba 2001 (n=35)</td>
<td>19 (54%)</td>
<td>45.2</td>
<td>19.4</td>
<td>35.5</td>
<td>N.A.</td>
</tr>
<tr>
<td>Delaunoit 2005 (n=267)</td>
<td>175 (58.8%)</td>
<td>53.9</td>
<td>11.6</td>
<td>34.5</td>
<td>21.0**</td>
</tr>
<tr>
<td>Douillard 2010 (N=331)*</td>
<td>263 (79.5%)</td>
<td>48.0</td>
<td>N.A.</td>
<td>N.A.</td>
<td>19.7</td>
</tr>
<tr>
<td>Emmanouilides 2007 (n=53)</td>
<td>39 (73.6%)</td>
<td>67.9</td>
<td>20.8</td>
<td>11.4</td>
<td>N.A.</td>
</tr>
<tr>
<td>Giachetti (n=100)</td>
<td>50 (50%)</td>
<td>53.0</td>
<td>24.0</td>
<td>11.0</td>
<td>19.4</td>
</tr>
<tr>
<td>de Gramont 2000 (n=210)</td>
<td>120 (60%)</td>
<td>50.0</td>
<td>31.9</td>
<td>18.1</td>
<td>16.2</td>
</tr>
<tr>
<td>Maughan 2011 (n=367)*</td>
<td>223 (60.8%)</td>
<td>57.0</td>
<td>N.A.</td>
<td>N.A.</td>
<td>17.9</td>
</tr>
<tr>
<td>Sakar 2007 (n=121)</td>
<td>32 (26.4%)</td>
<td>48.0</td>
<td>N.A.</td>
<td>N.A.</td>
<td>15.0***</td>
</tr>
<tr>
<td>Saltz 2008 (n=1400)</td>
<td>817 (58.4%)</td>
<td>48.0</td>
<td>N.A.</td>
<td>N.A.</td>
<td>20.6</td>
</tr>
<tr>
<td>Tol 2009 (n=378)</td>
<td>201 (54.6%)</td>
<td>50.0</td>
<td>44.0</td>
<td>6.0</td>
<td>20.3****</td>
</tr>
<tr>
<td>Waddell 2010 (n=45)</td>
<td>N = 77 metas</td>
<td>46.7</td>
<td>28.9</td>
<td>24.4</td>
<td>20.5</td>
</tr>
</tbody>
</table>

* WT-KRAS only  
** Patients with PR without subsequent metastatic resection  
*** Patients with ≥ 2 involved organs  
**** OS for ≥3 involved organs = 16.2 (data not published)  
Abbreviations: CR = Complete response, PR = Partial response, SD = Stable disease, PD = Progressive disease, OS = Overall survival, mo = Months
Figure 1: Study design

Patients with multiorgan metastasized CRC

Informed consent

Review by expert panel – debulking feasible?
Screening
Study biopsy

Inclusion

3 Cycles XELOX or 4 cycles FOLFOX ± bevacizumab

Progressive disease

2nd line treatment

Response or stable disease

Randomization

ARM A
Continue systemic therapy

ARM B
Stable disease
Response

3 Cycles of XELOX or 4 Cycles of FOLFOX ± bevacizumab

Progressive disease

2nd line treatment

Response or stable disease

1 cycle chemotherapy, Tumor Debulking

Continue systemic therapy
3.2 Collection of tumor tissue

Blood samples for miRNA profiling, peptide profiling, tumor marker, CECs and immune cells will be drawn simultaneously with regular blood samples during outpatient visits as much as possible. Of all patients included in the study a biopsy specimen will be obtained from a metastatic tumor site prior to start of XELOX/FOLFOX treatment. If a snap frozen biopsy of a metastatic site obtained no longer than two months before study inclusion is available for study analyses, no additional biopsy needs to be taken. If any uncertainties exist regarding the diagnosis of the metastatic disease a diagnostic biopsy is required. If diagnosis is not possible on fresh frozen tumor biopsy, this biopsy will be formalin-fixed and paraffin-embedded according to routine diagnostic procedures. All (other) biopsies will be snap frozen in liquid nitrogen upon collection and stored at -80°C until use. If possible, snap frozen or formalin-fixed paraffin-embedded (FFPE) tissue will be collected from the primary tumors. Biopsies will be considered representative if 4 µM cryosections contain more than 50% tumor cells based on ‘sandwich’ H&E-staining.

Patients included in study arm B may be treated by surgical resection of metastatic lesions after the first 4 or 5 cycles of chemotherapy. This surgical resected material will also be collected for analysis of response to chemotherapy. Patients included in study arm A and patients included in study arm B in whom surgical resection of metastatic lesions is not indicated will be asked permission for an additional biopsy of a metastatic tumor lesion after 3 cycles XELOX or 4 cycles of FOLFOX treatment for analysis of treatment response and molecular profiling technologies.
4 STUDY POPULATION

4.1 Study population
Patients with multi-organ mCRC with an indication for first line palliative systemic treatment, who are not applicable for HIPEC, may participate in this randomized controlled clinical trial when they are eligible according to the inclusion and exclusion criteria as described below.

4.2 Inclusion criteria
Screening must be performed no longer than 14 days prior to study inclusion. Subjects are eligible if they meet the following criteria:

- Histological or cytological documentation of cancer is required.
- Indication for first line palliative systemic treatment for metastatic colorectal cancer
- Patients with CRC metastases in
  - ≥ 2 different organs if at least >1 extrahepatic metastases or
  - ≥ 2 different organs including >5 hepatic metastases not located to one lobe or
  - ≥ 2 different organs including either a positive para-aortal lymph nodes or celiac lymph nodes or adrenal metastases or pleural carcinomatosis or peritoneal carcinomatosis
  - The primary tumor is excluded as metastatic site
- Feasible radical tumor debulking. Incomplete tumor debulking is allowed only if at least 80% of metastases can be treated.
- To meet the inclusion criteria a cytological analysis should be performed in case of any uncertainty about the presence of a lesion e.g. a false positive or false negative result on imaging.
- Age ≥ 18 years.
- WHO performance status 0 – 1.
- Life expectancy of at least 12 weeks.
- Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to screening:
  - Hemoglobin ≥ 5.6 mmol/L;
  - Absolute neutrophil count (ANC) ≥ 1,500/mm³;
  - Platelet count ≥ 100*10⁹/l;
  - Total bilirubin ≤ 1.5 times the upper limit of normal;
  - ALT and AST ≤ 2.5 x upper limit of normal (≤ 5 x upper limit of normal for subjects with liver involvement of their cancer);
  - Albumine > 30 g/l;
4.3 Exclusion criteria

Subjects who meet the following criteria at the time of screening will be excluded:

- Prior (neo-)adjuvant chemotherapy for < 6 months after last treatment and first detection of extrahepatic metastases, except for neoadjuvant capecitabine in the context of chemoradiation for rectal carcinoma.
- Candidates for HIPEC.
- Patients with liver metastases only
- Evidence of brain metastases.
- History of other prior malignancy except for adequately treated basal cell or squamous cell skin cancer or in-situ cervical cancer. Patients with other malignancies are eligible if they have remained disease free for at least 5 years.
- History of cardiac disease:
  - Congestive heart failure > NYHA class 2;
  - Active Coronary Artery Disease (defined as myocardial infarction within 6 months prior to screening);
  - Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).
- Uncontrolled hypertension. Blood pressure must be ≤160/95 mmHg at the time of screening on a stable antihypertensive regimen. Blood pressure must be stable on at least 3 separate measurements on at least 2 separate days.
- Uncontrolled infections (> grade 2 NCI-CTC version 4.0).
- Pregnant or breast-feeding women. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment. Both men and women enrolled in this trial must agree to use adequate barrier birth control measures (e.g., cervical cap, condom, and diaphragm) or intrauterine device during the course of the trial. Oral birth control methods alone will not be considered adequate on this study, because of
the potential pharmacokinetic interaction between study drug and oral contraceptives. Concomitant use of oral and barrier contraceptives is advised.

- Concurrent anticancer chemotherapy, immunotherapy or investigational drug therapy during the study or within 4 weeks of the start of study drug.
- Concomitant chronic use of dexamethasone, anti-convulsants and anti-arrhythmic drugs other than digoxin or beta blockers.
- Severe allergy for contrast media not controlled with premedication.
- Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results.
- Any condition that is unstable or could jeopardize the safety of the subject and their compliance in the study.

4.4 Sample size calculation and interim analyses

In total we aim to include 478 patients, taking into account that in our patient group 20% of the patients will not show clinical benefit, defined as response or stable disease, when treated with XELOX or FOLFOX (de Gramont A. et al. 2000; Emmanouilides et al. 2007; Giacchetti et al. 2000) and including 191 patients in both study arms A and B. This number is based on the assumption that in our patient group the OS time will be 24.8 and 18 months in patients treated with combined chemotherapy and additional maximal tumor debulking (experimental arm) versus in the patient group treated with combined chemotherapy only (control arm), respectively (de Gramont A. et al. 2000; Sakar et al. 2007; Tol et al. 2009). In this randomized controlled trial the ratio of experimental versus control arm is 1:1. The accrual time of the patients is expected to be approximately 60 months. Using the log-rank test this trial will have 80% power to show this difference in OS with a 5% type I error rate (two-sided) when a minimum of 382 patients are enrolled with a follow-up time of 24 months.

Based on the interim report after inclusion of the first 100 patients a decision for study continuation will be made.

We will perform an interim analysis when 30% of the patients are included in the study for 12 months. The study will be stopped for futility if at the time of the interim analysis the number of observed events (deaths) in arm B is larger than that in arm A. If the true median OS time of patients in study arm B is 24.8 months, while the true median OS survival time of patients included in study arm A is 18 months, the study will be incorrectly ended in 8.4% of the cases by including this stopping criterion. If median OS in both arms is 18 months the study will be correctly stopped.
at interim analysis in 46.5% of the cases. The power of the study will be 75.8% by including the stopping criteria compared to a power of 80% without including a stopping rule.

If more than 10% of patients withdraw from the study after 20% of patients have been randomized, the study will be terminated for being unfeasible (see also 7.2-7.3).

We define local treatments feasible when they can be performed within 3 months time period (see also 6.6). Otherwise systemic therapy will be too much delayed. If, after 20% of patients have been included, maximal debulking is not performed within 3 months in > 20% of the patients randomized to maximal debulking in arm B, the study will be terminated for being unfeasible.

5. SYSTEMIC TREATMENT OF SUBJECTS

5.1 Chemotherapy

All patients will receive 3 cycles of capecitabine and oxaliplatin (XELOX) or comparable 4 cycles of 5-FU and oxaliplatin (FOLFOX) with or without bevacizumab. Patients with > 30% response rates and randomized to study arm B will receive an additional chemotherapy while waiting for their local treatment schedule. This cycle will be without bevacizumab because of subsequent local treatment.

XELOX regimen

Oxaliplatin Dosing Instructions

Oxaliplatin will be administered at the dose of 130 mg/m² given as a 2 hour intravenous infusion on day 1 of a three week cycle prior to the first dose of capecitabine. The investigator must calculate the dose using the body surface area (BSA) of the patient at baseline. The dose of oxaliplatin administered should be as close as possible to the calculated dose of 130 mg per m². Oxaliplatin should always be administered before fluoropyrimidines.

Capecitabine Dosing Instructions

Capecitabine will be administered at the dose of 1000 mg/m² orally twice daily within 30 minutes after the end of a meal (breakfast, dinner). The dose to be used can be found in the capecitabine dosing tables in Appendix V. Tablets should be swallowed with approximately 200 mL water (not fruit juices). The first dose of each cycle will be administered as the evening dose on day 1 and the last dose of each cycle is scheduled the morning of day 15, followed by a 7 day rest period. This provides for a total of 28 single doses per cycle over 15 calendar days.
Co-medication
During chemotherapeutic treatment patients will receive co-medication as proposed below or according to standard procedures of local site:
Day 1: 8 mg ondansetron and 10 mg dexamethasone disodium phosphate in 100 ml glucose 5% prior to administration of cytostatic agents in ± 10 minutes. After 12 hours 8 mg ondansetron orally or 16 mg ondansetron suppository.
Day 2 and 3: 2 times 8 mg ondansetron orally (or once daily 16 mg ondansetron suppository)
Day 4 and 5: 3-4 times daily 10 mg metoclopramide orally or 3-4 times daily 20 mg metoclopramide suppository.

FOLFOX regimen
Dosing instructions
FOLFOX will be administered as follows by oxaliplatin, administered as a 85 mg/m² intravenous infusion over 2 hours on day 1, concomitantly with leucovorin (LV) as a 400 mg/m² infusion over 2 hours, followed by 5-FU, given as a 400 mg/m² bolus injection, and then as a 2400 mg/m² continuous infusion over 46 hours. Cycle length is 2 weeks composing of approximately 49 hours of infusion and 12 days of rest.

Co-medication during FOLFOX treatment is similar to co-medication described for XELOX.

Bevacizumab
Bevacizumab may be added to chemotherapy regimens, either in the XELOX regimen (7.5 mg/kg every three weeks) or in the FOLFOX regimen (5 mg/kg every two weeks), according to the standard procedures.

5.2 Use of co-medication
At study initiation, patients should report their concomitant medications to the physician. Due to interactions with capecitabine patients on coumarin derivates will be treated with LMWH instead for the length of the study. The maximal tolerated dose of capecitabine is reduced by concomitant use of folic acid or interferon-α, therefore dose reduction should be considered in patients using this medication.

5.3 Escape medication
Supportive care for treatment-related symptoms will be offered as needed to all patients in this study.

6 ON-STUDY PROCEDURES

6.1 Expert panel
Several multi-disciplinary expert panels will be appointed consisting of a medical oncologist, a surgical oncologist, a radiotherapist and a radiologist in hospitals able to perform all local treatments. At least one expert of each discipline has to be present at the expert panel discussions. Patients are eligible for inclusion if the expert panel agrees that macroscopic radical tumor debulking can be achieved using local treatment modalities. Incomplete tumor debulking is allowed only if at least 80% of metastases can be treated. In this respect, drainage of pleural fluid with chemical pleurodesis is considered macroscopic radical treatment. The treatment plan will be recorded and judged on feasibility by an independent expert panel.

6.2 Randomization
After informed consent and study inclusion, patients will be treated with 3 or 4 cycles of XELOX or FOLFOX with or without bevacizumab. Patients who show clinical benefit, defined as stable disease or response, will be randomly assigned to one of the two study arms, arm A and arm B (Figure 1). Randomization will be performed by a minimization technique with stratification according to treatment response (stable disease versus partial or complete response according to RECIST 1.1), gender, location of the metastases and number of organs involved (metastatic disease with liver and lung involvement only versus metastatic disease with involvement of any 2 other organs versus more than 2 organs involved), baseline serum lactate dehydrogenase (LDH) concentration (normal versus abnormal) and previous local treatment for metastatic disease. A randomization form is available in OpenClinica and a notification will be sent to the trial coordinators when this form is filled out. Patients will then be randomized centrally by the trial coordinators in order of notification.

6.3 Physical examination
Physical examination of the patients will be performed before start of treatment and after 3 cycles of treatment with XELOX or 4 cycles of treatment with FOLFOX. Furthermore physical examination will be performed at every visit to the (outpatient) clinic. An overview of the study evaluation is given in Table 2.
6.4 Laboratory analysis

Laboratory analysis will consist of routine hematology and chemistry analyses. This will be performed before study inclusion (for meeting inclusion criteria) and before each cycle of chemotherapy (except cycle one, when screening lab is available). Tumor markers will be evaluated at least every 3 months simultaneously with hematology and chemistry analysis and with response evaluation by CT or $^{18}$F-FDG-PET-CT (Table 2).

In addition to routine laboratory analysis blood samples will be obtained for serum miRNA and peptide profiling and for profiling of other blood derived cells in an exploratory study. For these analyses we will obtain blood samples from patients at baseline and after 1 cycle of XELOX/FOLFOX and after 3 cycles in case of treatment with XELOX or after 4 cycles when treated with FOLFOX. These additional blood samples for profiling studies will consist of 17 ml each time. We will also obtain blood from patients for analyses of CECs at baseline and after 1 and 3 or 4 cycles of XELOX or FOLFOX, respectively. An additional blood sample of 10.0 ml will be obtained for this analysis. Sampling of blood from patients will be repeated at least every three months simultaneously with routine laboratory analysis (Table 2) until disease progression.

6.5 Quality of Life questionnaires

After study inclusion and every 3 months thereafter patients will be asked to complete The European Organisation for Research and treatment of Cancer Quality of Life questionnaires (EORTC QoL) and the Multidimensional Fatigue Inventory (MFI) (appendix III) (Table 2). Two EORTC QoL questionnaires will be included, the EORTC QLQ-C30 (appendix I) to assess the quality of life of the cancer patients and the module EORTC-QLQ-CR29 (appendix II) specifically for evaluation of CRC patients. After 1 year of follow-up the questionaires will be taken annually.

6.6 Chemotherapy

After study inclusion, patients of both study arms will receive chemotherapy consisting of orally administered capecitabine 1000 mg/m$^2$ twice a day for two weeks followed by one week off and once every three weeks oxaliplatin 130 mg/m$^2$ intravenous (XELOX) or comparable intravenous regimen consisting of oxaliplatin 85 mg/m$^2$ on day 1 and 400 mg/ m$^2$ LV followed by 400 mg/m$^2$ 5-FU bolus and 2400 mg/m$^2$ continuous infusion over 46 hours (modified FOLFOX6). The XELOX scheme is repeated every 3 weeks and may be combined with 7.5 mg/kg bevacizumab as intravenous infusion over 30-90 minutes on day 1. The FOLFOX scheme is repeated every 2 weeks and may be combined with 5 mg/kg bevacizumab as intravenous infusion over 30-90 minutes on day 1. After 3 or 4 cycles of chemotherapy, depending on XELOX or FOLFOX treatment, a CT or $^{18}$F-FDG-PET-CT will be performed to evaluate response rate. In case of stable disease or response to chemotherapy treatment, according to RECIST 1.1 criteria, patients
randomized for study arm A will continue with the treatment schedule consisting of XELOX or FOLFOX. Patients included in study arm B will receive additional 3 cycles of XELOX or 4 cycles of FOLFOX with or without bevacizumab in case of stable disease. In case of >30% response rates patients will receive 1 additional cycle of XELOX or FOLFOX without bevacizumab prior to local treatment. In addition, patients in study arm B will resume chemotherapy treatment after advanced local treatment if they are adequately recovered. After a total of 6 cycles of XELOX or FOLFOX or in case of unacceptable toxicity of oxaliplatin, capecitabine monotherapy is allowed.

Table 2. Standard evaluation, laboratory tests and follow-up

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline / Screening</th>
<th>After 1 cycle of XELOX/FOLFOX</th>
<th>After 3/4 cycles of XELOX/FOLFOX</th>
<th>Follow-up phase at least every 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Phys exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Laboratory analysis&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Urinalysis&lt;sup&gt;3&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td>X</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>CT or PET-CT</td>
<td>X</td>
<td>X</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Tumor marker</td>
<td>X</td>
<td>X</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Tumor biopsy&lt;sup&gt;4&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>QoL and MFI questionnaires</td>
<td>X</td>
<td>X</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Extra blood samples&lt;sup&gt;5&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> After 3 cycles of XELOX or again after additional 3 cycles of XELOX in case of stable disease for patients included in study arm B. For FOLFOX after 4 cycles or additional 4 cycles of FOLFOX in case of stable disease for patients included in study arm B.

<sup>2</sup> Laboratory analysis: Hb, Ht, WBC, ANC, Platelets, Na, K, Ca, Mg, Alb, creatinin, bilirubin, AF, γGT, ALAT, ASAT, LDH, APTT, INR and CEA. Creatinin clearance if plasma creatinin > 100 µmol/l. Baseline laboratory analysis should be obtained no longer than 2 weeks prior to registration.

<sup>3</sup> Urinalysis: sediment screening; ICON-HCG in female patients (-7 days to 0).

<sup>4</sup> Diagnostic biopsy or study (re-)biopsy.

<sup>5</sup> Extra blood will be obtained from each patient for serum miRNA and peptide profiling, for profiling of other blood derived cells in an exploratory setting and for analyses of circulating tumor cells and circulating endothelial cells.

<sup>6</sup> Optional tumor biopsy after 3 cycles of XELOX or 4 cycles of FOLFOX treatment for patients included in study arm A and patients included in study arm B in whom surgical resection of metastatic lesions is not indicated.

<sup>7</sup> The first year of follow-up, then annually.
6.7 Local treatment

Patients included in study arm B will be subjected to local treatment. The expert panel will rediscuss and confirm treatment plans. Local treatment will be applied to as much metastatic lesions as possible. Bevacizumab will be withheld during the last cycle of XELOX/FOLFOX when patients are eligible for local treatment. Surgical resection of the metastatic lesions will be the preferred local treatment and will be performed within 3 months after the last chemotherapy cycle. Unresectable tumor lesions will be treated by any other form of local treatment (ablative or embolization techniques, SABR) depending on best clinical judgment. A predefined guideline on preferable local treatment order per metastatic site is described in Appendix IV. All local treatment procedures will be evaluated by the expert panel. Subgroup analysis will be performed to compare the outcome of radically treated patients vs. patients for which radical treatment was eventually not fully accomplished. Multiple procedures can or will be performed in the same patient. We define (multiple) local treatments feasible when they can be performed within 3 months time period. Otherwise systemic therapy will be too much delayed (see also 4.4). When three different local treatment procedures have to be performed within one patient, the last local treatment may be performed after systemic therapy otherwise this will also be too much delayed.

6.7.1 Surgery

Patients randomized for study arm B with stable disease or response on first cycles of chemotherapy will undergo surgical resection of possible metastatic sites. Surgical decisions will be based on the number and location of the metastases and upon patient’s surgical history. The feasibility and the most optimal manner of surgical resection of the metastatic lesions will be judged by the liver surgeon and/or surgical oncologist.

Surgical resection of hepatic metastases may comprise wedge resections, segmentectomy or (extended)hemihepatectomy depending of the number, size and site of hepatic metastases. Recently it was demonstrated that there is no significant difference in OS between wedge resections and segmentectomy, indicating that wedge resections can be used as a safe procedure to preserve liver parenchyma (Lalmahomed et al. 2011). The liver remnant should comprise a portal vein, a hepatic artery, a bile duct, one of the three main hepatic veins and the liver remnant should have sufficient liver function. Surgical resection of pulmonary metastases may comprise wedge resections, segmentectomy, lobectomy or pneumonectomy depending on the number, size and site of the metastases and depending on the pulmonary function of the patient. Surgical resection may be performed by anterior or posterirolateral thoracotomy and may include video-assisted thoracic surgery (VATS). Resection of involved lymph nodes will depend on
the location and preferably combined with surgical treatment of hepatic and pulmonary metastases.

Surgical resection of metastases in other locations is allowed if feasible based on the judgement of the surgeon. For peritoneal metastases metastasectomy without HIPEC is allowed and will be considered radical treatment. For pleuritis carcinomatosa drainage of pleural fluid with chemical pleurodesis is considered macroscopic radical treatment.

Surgical resected tissue specimen will be snap frozen in liquid nitrogen and stored at -80°C until use.

6.7.2 Radiofrequency ablation (RFA) procedure

Based upon the number and location of the metastases and upon patient’s surgical history the procedure will be performed using either an intra-operative or percutaneous approach. This decision will be made by the interventional radiologist and surgical oncologist in consensus.

Microwave ablation according to local procedure is allowed when RFA is not feasible.

Intra-operative RFA

All patients will be admitted to participating centers at least one day before surgery. Intraoperative ultrasound (IOUS) (Prosound Alph10; 10.0 MHz linear intraoperative probe and 5.0/1.25 MHz convex probe, Aloka, Tokyo, Japan) will be performed by an interventional radiologist, who carefully notes the exact size (maximum diameter), number and location of all metastasis. Based upon the size of the lesion and on the proximity of adjacent vital structures 2.0-5.0 cm expandable-needle mono- or bipolar electrodes (monopolar LeVeen, Boston Scientific, USA; bipolar InCircle, RFMedical, Fremont, USA) will be manually placed using ultrasound guidance by interventional radiologists in close collaboration with surgical oncologists to avoid damage to surrounding organs and structures. The electrodes are connected to a commercially available RF generator (RF3000, Boston Scientific, USA). Ablations will be performed according to the protocols provided by the manufacturers. Primary endpoints for a technically successful ablation are at least two increases in tissue impedance (roll-off) with an interablation delay of 30 seconds and a fully hyperechoic ablation zone including a tumor-free margin of a least one centimeter on IOUS. If necessary, the needle electrodes will be repositioned for one or more overlapping ablations. If deemed necessary, due to the proximity of a large portal vein or hepatic artery, a so called Pringle maneuver will be performed, placing a large hemostat to temporarily interrupt the flow of blood through both the hepatic artery and the portal vein. Needle track ablation will be performed to avoid needle track hemorrhage and possible seeding of tumor cells.

Percutaneous CT and/or US guided RFA
Procedures will be performed under general anesthesia. Patients are positioned either in a supine or prone position based upon the optimal percutaneous approach of the tumor. The procedure will be planned on at least an unenhanced CT just before the procedure. If lesions are invisible on these unenhanced images, either a contrast enhanced CT scan and/or ultrasound guidance will be made for image guidance. The RFA needles will be carefully positioned using CT fluoroscopy aiming at the tumor free ablation zone of at least 1 cm. Again needle track ablation will be performed to avoid needle track hemorrhage and possible seeding of tumor cells. For tumors with a priori high probability on needle track hemorrhage (centrally located tumors or impaired haemostasis) co-axial needle systems (CoAccess, LeVeen, Boston Scientific, USA) will be used and a number of small haemostatic foam plugs will be manually placed (Willospon, Will-Pharma, Netherlands) in the needle track while retracting the co-axial needle. Primary endpoints for a technically successful ablation are at least two increases in tissue impedance (roll-off) with an interablation delay of 30 seconds. For lesions larger than 3 cm a contrast enhanced CT scan directly after the procedure will be used as secondary endpoint. The ablation zone is defined as the non-enhancing hypodense region 70 seconds after start of contrast injection. When considered necessary, additional overlapping ablations will be performed after electrode repositioning.

6.7.3 Transarterial chemoembolisation using irinotecan drug-eluting beads ((DEBIRI-TACE) procedure

Procedures will be performed with patients fully conscious. For pain relief patients will receive low-dose continuous intravenous morphine injection starting just before the procedure. For optimal treatment planning patients will receive a CT-angiography and portal venous phase CT of the upper abdomen, in the evening after RFA and before TACE in case of combined therapy. The hospital pharmacist will prepare one vial with 100-300u drug eluting beads (2ml) (Biocampatibles, Terumo) which will be loaded according to the manufacturers protocol with 100 mg irinotecan solution (5ml irinotecan solution (20mg/ml)).

After selective catheterization of the hepatic artery an angiogram will be made to visualize the hyperemic peri-ablation zones. Superselective embolization of this zone will be performed using a microcatheter (Progreat, Terumo) injecting the beads mixed with contrast material (7ml DEBIRI-TACE solution: 7ml contrast material (Ultravist 300, Bayer, Germany)) under fluoroscopy guidance. The endpoint will be the disappearance of this hyperemic zone on angiography or having dully administered the maximum dose of 100 mg irinotecan.

In hospitals where TACE is available the procedure will be performed according to standard local protocol.

6.7.4 Stereotactic ablative radiotherapy (SABR)
Patients are either treated free breathing or will be positioned in a stereotactic body frame (Elekta Oncology Systems, Stockholm, Sweden) with maximum tolerated abdominal compression to reduce respiratory tumor motion for planning and treatment purposes, depending on treatment center preferences. Patients with cervical/upper thoracic spine may be treated using a mask system for immobilization.

Imaging for treatment planning depends on the treatment site and tumor mobility. For example, in the lung all patients receive a 4D-CT scan to account for tumor motion. 4D-CT is also necessary for intra-abdominal and liver tumors. Contrast-enhanced 4D-CT imaging in the treatment position is obtained for patients with liver metastases and in selected patients with lung and other intra-abdominal metastases. In some patients, $^{18}$F-FDG-PET or MRI studies may be required (e.g. bone, spine metastases, liver).

Once the internal target volume (ITV) is defined using 4D-CT, or the gross tumor volume (GTV) is contoured on the 3D-CT scan, a 2-5mm planning target volume (PTV) margin, depending on the treatment site, is then typically added to account for uncertainty in treatment delivery.

Treatment dose is risk-adapted and dependent on the primary site and proximity of organs at risk/critical structures. Common schedules require 1 to 8 fractions and are completed in approximately 1 - 2.5 weeks. Doses are frequently prescribed to the 80% isodose and include: 1x34Gy, 3x18Gy, 5x11Gy, 8x7.5Gy. Dose and fractionation schedules will be adjusted according to standard clinical procedures depending on target volumes and organs at risk. Treatment planning is performed using heterogeneity correction. For selected lesions, radical hypofractionated radiotherapy may be preferred. In case of hypofractionated (non SABR) radiotherapy, the dose is risk adapted and dependent on the primary site and proximity of organs at risk/critical structures. A minimum (biologic effective dose) BED of > 50 Gy has to be given. The dose that is accepted to organs at risk is detailed in department protocols, or based on published guidelines/expert opinion.

Selected patients may require additional investigations such as pulmonary function testing or a renogram, prior to SABR.
7  RESPONSE EVALUATION

A baseline CT or $^{18}$F-FDG-PET-CT will be performed no more than 28 days prior to the first dose of chemotherapeutic treatment. For detecting hepatic and extra-hepatic lesions, sensitivity is 95% and 82%, respectively. Specificity is 87% and 95% for hepatic and extra-hepatic lesions respectively (Patel et al. 2011). All patients will receive 3 cycles of chemotherapy with the current XELOX regimen, or 4 cycles of the current FOLFOX regimen, both regimens with or without bevacizumab. After 3 or 4 cycles of XELOX or FOLFOX, respectively, a second CT or $^{18}$F-FDG-PET-CT will be made and response rates will be evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Patients included in study arm A will continue to receive XELOX/FOLFOX with or without bevacizumab and CT or $^{18}$F-FDG-PET-CT response evaluation will be performed again after every 3 or 4 cycles. Patients in study arm B will be subjected to additional 3 cycles of XELOX or 4 cycles of FOLFOX again with or without bevacizumab in case of stable disease. After additional 3 or 4 cycles of chemotherapy response will be evaluated with CT or $^{18}$F-FDG-PET-CT. Patients in study arm B will be subjected to local treatment after 1 additional cycle of XELOX/FOLOX without bevacizumab in case of ≥30% response rates. After completing local treatment response will be evaluated every three months using CT or $^{18}$F-FDG-PET-CT, until progression. RECIST 1.1 is not applicable for response evaluation after local treatment, therefore response will be assessed by an expert panel. In addition response rates will be evaluated by measuring tumor markers, when available, according to the evaluation moments mentioned above. After three years of follow-up CT or $^{18}$F-FDG-PET-CT and tumor marker evaluation will be performed every 6 months. These responses will be discussed in a multi-disciplinary team. In case of progressive disease patients will be treated according to best clinical practice, including all treatment modalities. Patients included in study arm A may receive palliative local treatment options for a single progressive metastasis or for symptomatic metastases.

7.1  Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons or in the best interest of the patient.

7.2  Replacement of individual subjects after withdrawal

A patient will be discontinued from the study therapy under the following circumstances:
- Upon patient’s request for any reason
- If unacceptable toxicity is observed
If during screening or before randomization the patient becomes unfit for treatment or if patients withdraw their informed consent before randomization, the patient will be replaced.

7.3 Follow-up of subjects withdrawn from treatment
An excessive rate of withdrawals can render the study uninterpretable. If more than 10% of patients withdraw from the study after randomization after 20% of patients have been randomized, the study will be terminated for being unfeasible. Based on reasons of withdrawal the study protocol will be amended if necessary.
8 SAFETY REPORTING

8.1 Section 10 WMO event
In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

8.2 Adverse and serious adverse events
Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the treatments in this study. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose fulfills at least one of the following criteria:

- Is fatal (results in death); (note: death is an outcome, not an event);
- Is life threatening (at the time of the event); (note: the term “life-threatening” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which could hypothetically have caused death had it been more severe);
- Required unplanned inpatient hospitalization or prolongation of existing hospitalization (note: “inpatient hospitalization” refers to an unplanned, overnight hospitalization);
- Results in persistent or significant disability or incapacity.

SAEs should be reported up until disease progression, but at least 30 days after the last systemic or local treatment that is part of the study treatment. SAEs will be reported to the accredited METC that approved the protocol, according to the requirements of that METC.

8.3 Dose modifications for toxicity

8.3.1 General notes regarding dose modifications
Toxicity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. The chemotherapeutic schedules as mentioned in paragraph 5.1 are standard regimens used for metastatic colorectal cancer patients and medical oncologists have
experience using these regimens. Grade 1 and 2 toxicity of chemotherapy has to be recorded in the patient’s chart, but does not have to be reported in the eCRF.

Guidelines to be followed in the case of a deviation from treatment schedule (i.e. treatment interruption or dose modification due to an adverse event) are specific for each treatment regimen, and are described in the following subsections. Reasons for deviation from treatment schedule, the supportive measures taken and the outcome will be documented in the patient's chart and recorded in the case report form (CRF).

- For any adverse event already apparent at baseline, the dose modifications will be applied according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has grade 1 asthenia at baseline which increases to grade 2 during treatment, this will be considered a shift of one grade and treated as grade 1 toxicity for dose modification purposes.

- For toxicities which are considered by the investigator unlikely to develop into serious or life-threatening events (e.g. alopecia, altered taste etc.), treatment will be continued at the same dose without reduction or interruption. In addition, no dose reductions or interruptions will be required for anemia (non-hemolytic) as it can be satisfactorily managed by transfusions.

- Where several toxicities with different grades or severity occur at the same time, the dose modifications applied should be the greatest reduction applicable.

- If, in the opinion of the investigator, a toxicity is considered to be due solely to one drug (e.g. hand-foot syndrome secondary to capecitabine and neurotoxicity due to oxaliplatin, hypertension and proteinuria due to bevacizumab), the dose of the other drugs does not require modification.

- There will be no dose modification of bevacizumab during unless the patient's weight changes by more than 10%, in which case the dose will be recalculated. However, the dosing schedule of bevacizumab will be interrupted in the event of certain grades of haemorrhage, thromboembolic events, hypertension, proteinuria, gastro-intestinal perforations, wound healing complications, fistula or intra-abdominal abscess, and infusion-related or allergic reactions (summarized in table 8 in appendix IV).

- Dose modifications for isolated abnormal hematologic lab values will be based on hematological parameters at start of a treatment cycle. There is no scheduled sampling during a treatment cycle and thus, no scheduled collection of nadir values.

8.3.2. Drug specific treatment precautions and dose modifications for toxicities

Drug specific treatment precautions and dose modifications for toxicities are listed in appendix VI.

8.4 Adverse effects of maximal local tumor debulking
8.4.1 Adverse effects of surgical treatment

Surgical complications will be defined according to the standard classification of surgical complications (Table 3)(Dindo et al. 2004).

Table 3. Classification of surgical complications

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Any deviation from the normal postoperative course without the need for</td>
</tr>
<tr>
<td></td>
<td>pharmacological treatment or surgical, endoscopic, and radiological</td>
</tr>
<tr>
<td></td>
<td>interventions</td>
</tr>
<tr>
<td></td>
<td>Allowed therapeutic regimens are: drugs as antiemetics, antipyretics,</td>
</tr>
<tr>
<td></td>
<td>analgetics, diuretics, electrolytes, and physiotherapy. This grade also</td>
</tr>
<tr>
<td></td>
<td>includes wound infections opened at the bedside</td>
</tr>
<tr>
<td>II</td>
<td>Requiring pharmacological treatment with drugs other than such allowed for</td>
</tr>
<tr>
<td></td>
<td>grade I complications</td>
</tr>
<tr>
<td></td>
<td>Blood transfusions and total parenteral nutrition are also included</td>
</tr>
<tr>
<td>III</td>
<td>Requiring surgical, endoscopic or radiological intervention</td>
</tr>
<tr>
<td></td>
<td>Grade IIIa Intervention not under general anesthesia</td>
</tr>
<tr>
<td></td>
<td>Grade IIIb Intervention under general anesthesia</td>
</tr>
<tr>
<td>IV</td>
<td>Life-threatening complication (including CNS complications)* requiring IC/ICU</td>
</tr>
<tr>
<td></td>
<td>management</td>
</tr>
<tr>
<td></td>
<td>Grade IVa Single organ dysfunction (including dialysis)</td>
</tr>
<tr>
<td></td>
<td>Grade IVb Multiorgan dysfunction</td>
</tr>
<tr>
<td>V</td>
<td>Death of a patient</td>
</tr>
<tr>
<td>Suffix “d”</td>
<td>If the patient suffers from a complication at the time of discharge, the</td>
</tr>
<tr>
<td></td>
<td>suffix “d” (for “disability”) is added to the respective grade of</td>
</tr>
<tr>
<td></td>
<td>complication. This label indicates the need for a follow-up to fully</td>
</tr>
<tr>
<td></td>
<td>evaluate the complication.</td>
</tr>
<tr>
<td>*Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding</td>
<td></td>
</tr>
<tr>
<td>transient ischemic attacks. CNS, central nervous system; IC, intermediate</td>
<td></td>
</tr>
<tr>
<td>care; ICU, intensive care unit.</td>
<td></td>
</tr>
</tbody>
</table>

Postoperative mortality will be defined as any death during hospitalization or within 30 days from surgery. Complication and post-operative mortality rates will be securely monitored and documented.

Previous studies reported postoperative mortality rates after pulmonary resection rates of 0-2.5%. Death was caused by pulmonary embolism, pneumonia, cardiac failure or respiratory failure (Pfannschmidt et al. 2007). Severe morbidity previously described after hepatic surgery include pelvic abscesses and splenectomy owing to intractable bleeding. No postoperative mortality has been described.
8.4.2 Adverse effects radiofrequency ablation (RFA)
Complications of RFA are categorized on the basis of outcome by using the Society of Interventional Radiology (SIR) standard table (Table 4) (Sacks et al. 2003).

Table 4. SIR classification system for complications by outcome

<table>
<thead>
<tr>
<th>Minor complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. No therapy, no consequence</td>
</tr>
<tr>
<td>B. Nominal therapy, no consequence; includes overnight admission for observation only</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. Require therapy, minor hospitalization (&lt;48 hours)</td>
</tr>
<tr>
<td>D. Require major therapy, unplanned increase in level of care, prolonged hospitalization (&gt;48 hours)</td>
</tr>
<tr>
<td>E. Permanent adverse sequelae</td>
</tr>
<tr>
<td>F. Death</td>
</tr>
</tbody>
</table>

Four different types of complications have been reported related to RFA, described in a review by Wong et al. These complications include thermal damage, such as gastrointestinal perforation, biliary stenosis and grounding pad burns, mechanical complications such as injuries to bile ducts and vessels including hemorrhage, septic complications including abscess and peritonitis and other types of complications, such as myocardial infarction (Wong et al. 2010). Previous described complications of lung RFA include mainly pneumothorax, pleural effusion and alveolar haemorrhage (Gomez et al. 2009).

Postablation syndrome may also occur approximately 3 days after RFA treatment and is usually self-limiting within 10 days. This syndrome is characterized by low-grade fever, malaise, chills, myalgia, delayed pain, nausea and vomiting (Carrafiello et al. 2007; Wong et al. 2010).

For open RFA procedures, complications will be graded by the Classification of surgical complications (Table 3)(Dindo et al. 2004).

8.4.3 Adverse effects of transarterial chemoembolisation using irinotecan drug-eluting beads ((DEBIRI-)TACE)
Most common adverse events after TACE using irinotecan-loaded beads include postembolic syndrome type symptoms of nausea, vomiting and hypertension. Other adverse events include infection, gastritis, anorexia, dehydration, cholecystitis, anemia, liver dysfunction and pneumonia. Adverse events are most commonly related to irinotecan treatment. Most adverse events are grade 1 or 2 toxicity reactions. Incidentally grade 3 liver toxicity has been reported (Martin et al. 2009b; Martin et al. 2009a). All adverse effects will be securely monitored and documented.
8.4.4 Adverse effects of stereotactic ablative radiotherapy (SABR)

In general, no serious acute toxicity will be expected after SABR. Selected toxicities are described below. Treatment should be interrupted for any grade IV event and resumed on the advice of the radiation oncologist once there is recovery to grade I. For acute toxicity below grade IV, each case should be reviewed by the treating team and the treatment plan should be reviewed as necessary.

- Mild-moderate fatigue is common with radiotherapy.
- There is a small risk of radiation-induced liver damage (RILD). This is a clinical diagnosis typically made within 3 months of liver RT, characterized by elevated alkaline phosphatase (often at least 2 times more than baseline), hepatomegaly and anicteric jaundice, with no evidence of disease progression. It can usually be managed by paracentesis and diuretic medication.
- Transient thrombocytopenia may develop after liver irradiation.
- The risk of symptomatic radiation pneumonitis after lung SABR is typically low.
- Chest wall pain or discomfort can occur after treatment of peripheral lung lesions close to the chest wall. When the treatment overlaps with the chest wall there is a risk of rib fracture, which is frequently asymptomatic or causes mild-moderate symptoms.
- Within the abdomen, the risk of adverse effects to stomach, small/large intestine (e.g. late bleeding), kidneys and other organs is low. Acid-suppression may be recommended to some patients receiving abdominal SABR in order to reduce the risk of late-gastrointestinal complications such as bleeding.
- When bevacizumab is administered after abdominal-pelvic radiation treatment serious bowel toxicity has been incidentally reported and so vigilance is required when using bevacizumab (Lordick et al. 2006).

8.5 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator’s Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorized medicinal product).

The sponsor will report expedited the following SUSARs to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
Chemotherapy and maximal tumor debulking of multi-organ CRC metastases

- SUSARs that have arisen in other clinical trial of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The sponsor will report expedited all SUSARs to the competent authority, the Medicine Evaluation Board and the competent authorities in other Member States.

SUSARs that are already reported to the EMEA Eudravigilance database do not have to be once again reported to the competent authority and the MEB because they have direct access to the Eudravigilance database.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

8.6 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States.

This safety report consists of:
- A list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- A report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.7 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
8.8 Safety Monitoring

All local treatment strategies that will be performed in this study are based on clinical daily practice. As discussed in paragraph 2.3.2 combination therapy appears to be safe, also after chemotherapy. Therefore we expect that the number of SAEs will not be increased in patients subjected to local therapy in addition to combined chemotherapy (study arm B) compared to patients treated with combined chemotherapy only (study arm A). If at interim analysis, after 30% of the patients are included in the study for 12 months, the number of deaths due to treatment is significantly larger in patients included in study arm B compared to patients included in study arm A, the study will be ended prematurely.

8.9 Data Safety and Monitoring Board

A central DSMB consisting of a chairman (medical specialist), a medical and a surgical oncologist and a statistician who are not involved in the study will be installed to monitor quality and patient safety in this multicenter trial according to the standard operating procedures of VUmc. All relevant data, including a full description of local treatments which have been performed in each individual patient, all serious adverse events and patient withdrawal, all specified per participating hospital will be made available to the DSMB by the study coordinators. The DSMB will review the safety data, report their findings to the principal investigator and advise on study continuation after 25, 50 and 100 patients are included and at the interim analysis and at the end of study. The principal investigator will submit these reports to the ethics committee along with all relevant data.
9 STATISTICAL ANALYSIS

Our hypothesis is that maximal tumor debulking in addition to combined chemotherapy will improve survival of multi-organ mCRC patients. Based on this hypothesis patients will be randomized for treatment with combined chemotherapy and additional maximal tumor debulking or for treatment with combined chemotherapy alone, which is the standard treatment. OS time of patients included in this randomized controlled trial will be evaluated as primary endpoint. Calculation of the number of patients that will be needed to address our primary endpoint with a power of 80% and a 5% type I error rate is described in section 4.4.

9.1 Descriptive statistics, univariate and multivariate analysis

The primary aim of this study is OS counting from the date of study inclusion to the date of death due to CRC (event) or to the last day of follow-up (censored). One of the secondary outcomes includes PFS counting from the date of study inclusion to the date of either progressive or recurrent disease. Univariate survival analysis will be performed using the Kaplan-Meier method. Differences in survival lengths will be analyzed using the log rank test. For determining hazard ratios (HR) for multivariate analysis, Cox regression will be used. Significance of differences for continuous and categorical data will be analyzed using the Mann-Whitney U test and Chi-square test respectively. When appropriate, box plots and cross tables will be used for descriptive statistics of continuous and categorical variables, respectively. P-values below 0.05 will be considered significant. Standard statistical analysis will be performed using SPSS for Windows. Quality of life analysis of the patients included in the trial will be included as one of the secondary objectives of this study. Patients who complete the quality-of-life questionnaires at baseline and at least once during treatment and follow-up can be included in the analysis. The largest decrease in quality of life with respect to baseline will be calculated. The Wilcoxon rank sum test will be used to detect statistical differences between the two treatment arms.

The secondary aims of this study also include profiling methods. For analysis of the different tumor profiles in correlation to clinical data, the appropriate available statistical analysis programs will be used based on Wilcoxon tests.

9.2 Interim analysis (if applicable)

After inclusion of 25, 50 and 100 patients an interim report will be provided to the Medical Ethical Committee including the report of the DSMB and all relevant data as described above. Interim analysis will be performed when 30% of the total number of patients is included in the study for 12 months. The study will be prematurely ended if the number of deaths due to
Chemotherapy and maximal tumor debulking of multi-organ CRC metastases

treatment is significantly larger in patients included in study arm B compared to patients included in study arm A, as also described in section 8.8.
In addition, the study will be prematurely ended if at interim analysis the OS time of patients included in study arm B is equal to or shorter than the OS time of patients included in study arm A, as described in section 4.4.
10 ETHICAL CONSIDERATIONS

10.1 Regulation statement
The study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO).

10.2 Informed consent
The informed consent document will be used to explain risks and benefits of the study participation to the patient in simple terms before the patient is entered into the study. The investigator is responsible to see that the informed consent is obtained from each patient and to obtain the appropriate signatures and dates in the informed consent document prior to the performance of any protocol procedures and prior to start of the study treatment.

10.3 Recruitment and consent
Written and informed consent will be obtained by the physician who includes the patient in this trial.

10.4 Benefits and risks assessment, group relatedness
The use of chemotherapeutic agents, XELOX/FOLFOX in this study, may cause discomfort. Invasive examinations, such as tumor biopsies, are needed for obtaining tumor tissue to study molecular tumor characteristics in relation to therapy response.

Risks
After study inclusion, diagnostic biopsies or study biopsies will be obtained from a metastatic site prior to treatment with XELOX/FOLFOX. The biopsy and its preparations as appropriate may cause physical discomfort. All additional local treatment options (surgery, RFA, (DEBIRI-)TACE, SABR) may cause physical discomfort or adverse effects. Follow-up during therapy will include laboratory analysis on a regular basis and in general combined with a visit to the outpatient clinic. Reversible side effects from XELOX/FOLFOX treatment, maximal tumor debulking and as a consequence of the tumor biopsy may occur.

Potential benefits
Patients with multi-organ mCRC included in the study will be randomized for XELOX/FOLFOX treatment with or without the combination with additional maximal tumor debulking. We hypothesize that patients will benefit from maximal tumor debulking in addition to chemotherapy, what is currently considered standard treatment for these patients, by improvement of PFS and
OS. In addition we aim to unravel biological markers for predicting response to therapy and prognosis of patients. These markers may yield information on how patients can be most optimally treated. Ultimately, these studies will result in more personalized treatment in which patients will receive treatment which is beneficial and will not unnecessarily be treated with agents of which they do not benefit but in contrary only experience harm.

10.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.
11 ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents

Data management
Electronic case report forms (e-CRFs) for the recording of all data will be developed in OpenClinica by the data manager of the VUMC. Data will be recorded legibly in the e-CRF. SAE’s will be reported using the SAE form in ToetsingOnline. A manual of the e-CRF and the SAE form will be made available for the investigors and data managers at all sites. CT or $^{18}$F-FDG-PET-CT data will be stored at the IMS-server for at least two years after the last patient of the study has been evaluated or longer if necessary.

Use of information and publication
With the exception of personal and confidential medical records, all data generated under the trial shall be the property of the investigator. The investigator will publish or present the data generated in the study in accordance with accepted scientific practice. The principal investigator together with the co-investigators will prepare the manuscript reporting the final results. Participating centers will be offered 1 co-authorship upon inclusion of a minimum of 48 patients.

11.2 Amendments
Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.
11.3 Annual progress report
The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.4 End of study report
The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient’s last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.5 Public disclosure and publication policy
The principle investigators and study coordinators will prepare the manuscript together with those who substantially contributed to the study. Being a (co-)investigator on this trial protocol does not automatically result in a co-authorship of the manuscript reporting the study results.
12. REFERENCES


Chemotherapy and maximal tumor debulking of multi-organ CRC metastases


Chemotherapy and maximal tumor debulking of multi-organ CRC metastases


Sakar, B., et al. "XELOX followed by XELIRI or the reverse sequence in advanced colorectal cancer." Oncology 73.5-6 (2007): 298-304.


Chemotherapy and maximal tumor debulking of multi-organ CRC metastases


Appendix I: EORTC QLQ-C30 (version 3)

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

Please fill in your initials:
Your birth date (Day, Month, Year):
Today's date (Day, Month, Year):

1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? 1 2 3 4
2. Do you have any trouble taking a long walk? 1 2 3 4
3. Do you have any trouble taking a short walk outside of the house? 1 2 3 4
4. Do you need to stay in bed or a chair during the day? 1 2 3 4
5. Do you need help with eating, dressing, washing yourself or using the toilet? 1 2 3 4

During the past week
6. Were you limited in doing either your work or other daily activities? 1 2 3 4
7. Were you limited in pursuing your hobbies or other leisure time activities? 1 2 3 4
8. Were you short of breath? 1 2 3 4
9. Have you had pain? 1 2 3 4
10. Did you need to rest? 1 2 3 4
11. Have you had trouble sleeping? 1 2 3 4
12. Have you felt weak? 1 2 3 4
13. Have you lacked appetite? 1 2 3 4
14. Have you felt nauseated? 1 2 3 4
15. Have you vomited? 1 2 3 4
16. Have you been constipated? 1 2 3 4
17. Have you had diarrhea? 1 2 3 4
18. Were you tired? 1 2 3 4
19. Did pain interfere with your daily activities? 1 2 3 4
20. Have you had difficulty in concentrating on things, 1 2 3 4
like reading a newspaper or watching television?
21. Did you feel tense?  
22. Did you worry?  
23. Did you feel irritable?  
24. Did you feel depressed?  
25. Have you had difficulty remembering things?  
26. Has your physical condition or medical treatment interfered with your family life?  
27. Has your physical condition or medical treatment interfered with your social activities?  
28. Has your physical condition or medical treatment caused you financial difficulties?

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

29. How would you rate your overall health during the past week?  
   1   2   3   4   5   6   7  
   Very poor       Excellent

30. How would you rate your overall quality of life during the past week?  
   1   2   3   4   5   6   7  
   Very poor       Excellent
Appendix II: EORTC QLQ – CR29

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

**During the past week**

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A Little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. Did you urinate frequently during the day?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32. Did you urinate frequently during the night?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33. Have you had any unintentional release (leakage) of urine?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34. Did you have pain when you urinated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35. Did you have abdominal pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36. Did you have pain in your buttocks/anal area/rectum?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37. Did you have a bloated feeling in your abdomen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38. Have you had blood in your stools?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39. Have you had mucus in your stools?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40. Did you have a dry mouth?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41. Have you lost hair as a result of your treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>42. Have you had problems with your sense of taste?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43. Were you worried about your health in the future?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>44. Have you worried about your weight?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45. Have you felt physically less attractive as a result of your disease</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>or treatment?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46. Have you been feeling less feminine/masculine as a result of your</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>disease or treatment?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47. Have you been dissatisfied with your body?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>48. Do you have a stoma bag (colostomy/ileostomy)?</td>
<td>yes</td>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(please circle the correct answer)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below**

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A Little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>49. Have you had unintentional release of gas/flatulence from your stoma bag?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>50. Have you had leakage of stools from your stoma bag?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
51. Have you had sore skin around your stoma? 1 2 3 4
52. Did frequent bag changes occur during the day? 1 2 3 4
53. Did frequent bag changes occur during the night? 1 2 3 4
54. Did you feel embarrassed because of your stoma? 1 2 3 4
55. Did you have problems caring for your stoma? 1 2 3 4

Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG

49. Have you had unintentional release of gas/flatulence from your back passage? 1 2 3 4
50. Have you had leakage of stools from your back passage? 1 2 3 4
51. Have you had sore skin around your anal area? 1 2 3 4
52. Did frequent bowel movements occur during the day? 1 2 3 4
53. Did frequent bowel movements occur during the night? 1 2 3 4
54. Did you feel embarrassed because of your bowel movement? 1 2 3 4

During the past 4 weeks:

For men only:
56. To what extent were you interested in sex? 1 2 3 4
57. Did you have difficulty getting or maintaining an erection? 1 2 3 4

For women only:
58. To what extent were you interested in sex? 1 2 3 4
59. Did you have pain or discomfort during intercourse? 1 2 3 4

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Appendix III: Multidimensional Fatigue Inventory

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

<table>
<thead>
<tr>
<th></th>
<th>That is true</th>
<th>That is not true</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General fatigue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel fit</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>I feel tired</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>I feel rested</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>I tired easily</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Physical Fatigue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physically I feel I am in an excellent condition</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Physically I feel I am in a bad condition</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Physically I can take on a lot</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Physically I feel only able to do a little</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Reduced Activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I think I do very little in a day</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>I think I do a lot in a day</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>I get little done</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>I feel very active</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Reduced Motivation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have a lot of plans</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>I feel like doing all sorts of nice things</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>I dread having to do things</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>I don't feel like doing anything</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Mental Fatigue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When I am doing something, I can keep my thoughts on it</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>I can concentrate well</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>My thoughts easily wander</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>It takes a lot of effort to concentrate on things</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Appendix IV: Local treatment per metastatic site

For extensive local treatment a multidisciplinary team with at least one experienced oncological surgeon, intervention radiologist, radiotherapist and a medical oncologist will be installed in participating centers. These teams will join central videoconferences to discuss and determine treatment plans with the central multidisciplinary study team. Local treatment will be performed on as much metastatic sites as possible. For all metastatic sites, preferred local treatment will be surgical resection of the tumor lesions.

Unresectable tumor lesions will be treated within 3 months by any form of other local treatment i.e. RFA, (DEBIRI-)TACE, SABR, depending on best clinical judgment and depending on the metastatic site. The preferred local treatment of metastases differs per location, and is listed below for each organ.

Liver
I) Surgery
II) RFA in tumor lesions < 3 cm, RFA combined with (DEBIRI-)TACE in tumor lesions ≥ 3 cm
III) SABR or (DEBIRI-)TACE in tumor lesions where RFA is not feasible or contraindicated

Lung
I) Surgery
II) SABR if surgery is not possible
III) RFA in tumor lesions < 3 cm, if SABR is not feasible or contraindicated

Ovary
I) Surgery
II) SABR if surgery is not possible

Adrenal Gland
I) Surgery
II) SABR if surgery is not possible

Lymph node
I) Surgery
II) SABR if surgery is not possible

Bone
I) SABR or radiotherapy
## Appendix V: Capecitabine Dose Calculation According to Surface Area

### 100% Dose Level

- **Twice daily 1000 mg/m²**

<table>
<thead>
<tr>
<th>Surface Area (m²)</th>
<th>Total Dose per Administration (mg)*</th>
<th>Morning</th>
<th>Evening</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.22</td>
<td>1150</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1.23 – 1.40</td>
<td>1300</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1.41 - 1.57</td>
<td>1500</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>1.58 – 1.72</td>
<td>1650</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>1.73 – 1.90</td>
<td>1800</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1.91 – 2.07</td>
<td>2000</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>2.08 – 2.22</td>
<td>2150</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>≥ 2.23</td>
<td>2300</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

*Total dose calculated on mg/m² for the median value, and is rounded to the nearest value which can be conveniently dosed equally in the morning and afternoon with 150 mg and 500 mg tablets.

### 75% Dose Level

- **Twice daily 750 mg/m²**

<table>
<thead>
<tr>
<th>Surface Area (m²)</th>
<th>Total Dose per Administration (mg)*</th>
<th>Morning</th>
<th>Evening</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.22</td>
<td>800</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1.23 – 1.40</td>
<td>1000</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>1.41 - 1.57</td>
<td>1150</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1.58 – 1.90</td>
<td>1300</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1.91 – 2.07</td>
<td>1500</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>≥ 2.08</td>
<td>1650</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

### 50% Dose Level

- **Twice daily 500 mg/m²**

<table>
<thead>
<tr>
<th>Surface Area (m²)</th>
<th>Total Dose per Administration (mg)*</th>
<th>Morning</th>
<th>Evening</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.22</td>
<td>500</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>1.23 – 1.40</td>
<td>650</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1.41 - 1.90</td>
<td>800</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1.91 – 2.07</td>
<td>1000</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>≥ 2.08</td>
<td>1150</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Total dose calculated on mg/m² for the median value, and is rounded to the nearest value which can be conveniently dosed equally in the morning and afternoon with 150 mg and 500 mg tablets.
Appendix VI: Drug specific treatment precautions and dose modifications for toxicity

VI.1 Capecitabine

Capecitabine: precautions
Capecitabine is foreseen as an outpatient treatment, and in certain circumstances adverse events that could occur, such as diarrhea, can rapidly become serious. In the case where a patient experiences any toxicity in between scheduled visits, the patient should be encouraged to contact the clinic as soon as is practical, for further directions or for treatment. It is essential that the patients are informed to interrupt capecitabine treatment as soon as grade 2 toxicity occurs, therefore the patients will need specific explanations what to do in the case of the occurrence of the most frequent toxicities (diarrhea, hand-foot syndrome, and stomatitis).

Renal impairment: Capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min (Cockroft and Gault)). Treatment should not be started or continued in patients with severe renal impairment. Reduced clearance of 5-FU has been reported in moderately renally impaired patients, which correlated with an increased incidence of grade 3 or 4 adverse events in patients with moderate renal impairment (creatinine clearance 30-50 mL/min). There is no evidence of a direct nephrotoxic effect of capecitabine. However, patients with moderate renal impairment (creatinine clearance < 50 mL/min) are not eligible for this study.

Coagulopathy: Patients receiving concomitant capecitabine and oral coumarin-derived anticoagulants should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important capecitabine-warfarin drug interaction was demonstrated in a clinical pharmacology trial. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine concomitantly with coumarin-derived anticoagulants such as warfarin and phenprocoumon. Postmarketing reports have shown clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants at the time capecitabine was introduced. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. These events occurred in patients with and without liver metastases. Age greater than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy.

Diarrhea: Capecitabine can induce diarrhea. Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement. If grade 2, 3 or 4 diarrhea occurs, administration of capecitabine should be immediately interrupted until the diarrhea resolves or decreases in intensity to grade 1.
Hand-foot syndrome: Capecitabine has been shown to cause hand-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema-erythema). If grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to < grade 1. Subsequent doses of capecitabine should be administered as per Table VI.1.

Cardiotoxicity: There has been cardiotoxicity associated with fluorinated pyrimidine therapy (including capecitabine) including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiograph changes. These adverse events may be more common in patients with a prior history of coronary artery disease.

Hepatic insufficiency: In patients with mild to moderate hepatic dysfunction due to liver metastases, caution should be exercised when capecitabine is administered but no dose reduction is necessary. The effect of severe hepatic dysfunction on capecitabine is not known.

Hyperbilirubinemia: Administration of capecitabine should be interrupted if treatment related elevations in bilirubin of >3.0 x ULN (grade 3) or treatment-related elevations in hepatic aminotransferases (ALT, AST) of >2.5 x ULN occur. Treatment may be resumed when bilirubin decreases to ≤3.0 x ULN (grade 2) or hepatic aminotransferases decrease to ≤2.5 x ULN.

Geriatric patients: Patients > 80 years old may experience a greater incidence of grade 3 or 4 adverse events, in particular diarrhea, nausea, hand-foot syndrome and vomiting.

Pregnancy: Female patients must be instructed to stop taking capecitabine if they become pregnant during the study, and immediately inform the investigator. The Investigator should counsel the patient, and discuss the risk of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. The investigator should report all pregnancies in the study to the sponsor.

Contraindications: Capecitabine is contraindicated in patients with known hypersensitivity to capecitabine, 5-fluorouracil or to any of the excipients, in patients who have a history of severe and unexpected reactions to fluoropyrimidine therapy, and in patients with known DPD deficiency. Capecitabine is contraindicated in patients with severe leucopenia, neutropenia, or thrombocytopenia, severe hepatic impairment, or severe renal impairment (creatinine clearance below 30 mL/min). Use of capecitabine is contraindicated during pregnancy and lactation, and concomitantly with sorivudine or its chemically related analogues, such as brivudine.

Capecitabine: dose modifications for non-hematological toxicities

If grade 2, 3 or 4 non-hematological toxicity occurs, interrupt capecitabine immediately (see also Table VI.1) (except for toxicity solely related to oxaliplatin) then follow instructions below for further actions.

The recommendations found in this section for dose adjustments for capecitabine should be followed for those toxicities usually considered to be related to capecitabine treatment. Thus,
neurosensorial toxicities do not result in a dose reduction for capecitabine. Instead, one should follow the instructions for dose adjustments of oxaliplatin (Table VI.3). If the calculated creatinine clearance decreases during treatment to a value < 30 mL/min, treatment should be discontinued. The specific dose reductions (i.e. the number of tablets to be taken at various dose levels) can be found in Appendix V. Once the dose has been reduced it should not be increased at a later time, except if oxaliplatin is permanently discontinued. Hyperbilirubinemia will be managed as outlined in “precautions”. For treatment-related elevations in hepatic aminotransferases (ALT, AST) and alkaline phosphatase (ALP) the guidance in Table VI.1 is consistent with the management outlined in “precautions”.

Note: capecitabine treatment interruptions are regarded as lost treatment days and the planned treatment schedule should be maintained. Missed doses due to treatment interruptions must not be replaced.

Table VI.1. Non-hematologic adverse effects: dose adjustments for capecitabine

Note: Treatment must be interrupted for toxicities grade ≥2 and cannot continue unless toxicities resolve to grade ≤ 1.

<table>
<thead>
<tr>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st occurrence</td>
<td>No dose reduction; prophylaxis where possible</td>
<td>75% of original dose with prophylaxis where possible</td>
</tr>
<tr>
<td>2nd occurrence</td>
<td>75% of original dose</td>
<td>50% of original dose</td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>50% of original dose</td>
<td>Stop treatment permanently-unless it is considered to be in the best interest of the patient to stay on treatment</td>
</tr>
<tr>
<td>4th occurrence</td>
<td>Stop treatment permanently-unless it is considered to be in the best interest of the patient to stay on treatment</td>
<td></td>
</tr>
</tbody>
</table>
Grade ≥ 2 diarrhea
Capecitabine can induce diarrhea, which can sometimes be severe. Patients with severe diarrhea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement. If grade 2, 3 or 4 diarrhea occurs, administration of capecitabine should be immediately interrupted until the diarrhea resolves or decreases in intensity to grade ≤ 1. Following the second occurrence of grade 2 or higher toxicity, subsequent doses of capecitabine should be decreased (see Table VI.1). Standard antidiarrhea treatments (e.g. loperamide) should be initiated, as medically appropriate, as early as possible. capecitabine can not be re-started until diarrhea has resolved to grade 0 or 1, and no loperamide has been given for 24 hours.

Grade ≥ 2 nausea/vomiting
Capecitabine can induce nausea or vomiting. If grade 2, 3 or 4 nausea and/or vomiting occurs, administration of capecitabine should be immediately interrupted until these symptoms resolve or decrease in intensity to grade ≤ 1. Treat symptomatically. For prophylaxis, the patients must be supplied with oral anti-emetics in order to treat themselves in case nausea or vomiting occurs at home. The administration of oral metoclopramide is recommended for capecitabine-induced nausea (the use of 5-HT3 antagonists is at the discretion of the investigator). Adequate secondary therapeutic and prophylactic treatment has to be initiated once nausea or vomiting has occurred. If nausea/vomiting recur despite adequate prophylaxis, then dose modifications should also be made according to Table VI.1.

Grade ≥ 2 hand/foot syndrome
Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema) is a cutaneous toxicity with a severity range of grades 1 to 3 as shown:
Grade 1: skin changes or dermatitis without pain (e.g. erythema, peeling).
Grade 2: skin changes with pain, not interfering with function.
Grade 3: skin changes with pain, interfering with function.
If grade 2 or 3 hand-foot syndrome occurs administration of capecitabine should be immediately interrupted until the event resolves or decreases in intensity to grade ≤ 1. Subsequent doses of capecitabine should be administered as mentioned in Table VI.1. Hand-foot syndrome should be treated symptomatically (i.e. use of emollients is recommended). The use of vitamin B6 is not permitted for symptomatic or secondary prophylactic treatment of hand-foot syndrome; impaired efficacy has been reported with concomitant use of vitamin B6 and cisplatin.
Grade ≥ 2 stomatitis
If grade 2 or 3 stomatitis occurs, administration of capecitabine should be immediately interrupted until the event resolves or decreases in intensity to grade ≤1. Treat symptomatically. Subsequent doses of capecitabine should be administered as mentioned in Table VI.1.

Cardiac toxicity
For grade ≥ 2 cardiac toxicity which is attributable to capecitabine, patients will be permanently discontinued from capecitabine therapy.

VI.2 Oxaliplatin

Oxaliplatin: precautions
Anaphylactic/anaphylactoid reactions: As is the case for other platinum compounds, hypersensitivity and anaphylactic/anaphylactoid reactions have been reported. These allergic reactions were similar in nature and severity to those reported with other platinum-containing compounds, i.e., rash, urticaria, erythema, pruritis, and, rarely, bronchospasm and hypotension. These reactions occur within minutes of administration (can also occur at other than the first cycle of treatment) and should be managed with appropriate supportive therapy (e.g. standard epinephrine, corticosteroid, and antihistamine therapy). Drug-related deaths associated with platinum compounds from this reaction have been reported.

Neurological: An acute, reversible primarily peripheral sensory neuropathy of early onset, occurring within hours or one to two days of dosing, resolves within 14 days, and frequently recurs with further dosing. The symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paresthesia, dysesthesia and hypoesthesia in the hands, feet, perioral area, or throat. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed. The acute, reversible pattern of sensory neuropathy was observed in about 56% of study patients who received oxaliplatin with infusional 5-FU/LV. In any individual cycle acute neurotoxicity was observed in approximately 30% of patients. Ice (stomatitis prophylaxis) should be avoided during the infusion of oxaliplatin because cold temperature can exacerbate acute neurological symptoms. An acute syndrome of pharyngolaryngeal dysesthesia seen in 1-2% of patients is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing).

A persistent (> 14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysesthesias, hypoesthesias, but may also include deficits in proprioception that can interfere with daily activities (e.g., writing, buttoning, swallowing, and proprioception-related ambulatory impairment). These forms of neuropathy occurred in 48% of the study patients
receiving oxaliplatin with infusional 5-FU/LV. Persistent neuropathy can occur without any prior acute neuropathy event. The majority of the patients (80%) who developed grade 3 persistent neuropathy progressed from prior grade 1 or 2 events. These symptoms may improve in some patients upon discontinuation of oxaliplatin.

Elevations of biological liver function tests are commonly reported when being treated with oxaliplatin and 5-FU. Most of times these elevations are mild in severity and do not translate in any symptoms. In a few cases, clinical symptoms are associated with these liver abnormalities. When present, clinical symptoms may consist of jaundice, ascites, hepato- and/or splenomegaly. These liver abnormalities and clinical symptoms may be related to disease or, in rare cases, may reflect a direct effect of the oxaliplatin treatment on the liver tissue, which may include veno-occlusive disease (modification of the liver vasculature).

**Pulmonary:** Oxaliplatin has been associated with pulmonary fibrosis (0.7% of study patients), which may be fatal. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

**Pregnancy and lactation** To date there is no available information on safety of use in pregnant women. Based on pre-clinical findings, oxaliplatin is likely to be lethal and/or teratogenic to the human fetus at the recommended therapeutic dose, and is therefore not recommended during pregnancy. Patients becoming pregnant during the study should be withdrawn from the study treatment. Excretion in breast milk has not been studied. Breast-feeding is contraindicated during oxaliplatin therapy.

**Oxaliplatin: dose modifications for toxicities**

**Peripheral neuropathy**

Oxaliplatin is consistently associated with two types of peripheral neuropathy: paresthesias and dysesthesias of the hands and feet (chronic), and peri-oral region (early onset). Patients treated with oxaliplatin in this study will be counseled to avoid cold drinks and exposure to cold water or air, especially for 3 to 5 days following oxaliplatin administration. For peripheral neuropathy, dose adjustments will we determined according to Table VI.3.

**Dose modifications for non-hematological toxicity**

For toxicities or miscellaneous events (including, but not limited to auditory, ocular, metabolic, hepatic, central nervous system, renal, or pulmonary AEs) not listed below in Table VI.2 and VI.3, management should be symptomatic, if possible, if these are grade < 3 AEs. For grade ≥3 AEs, extended rest period to allow for recovery from toxicity to grade 1 or less until readministration of chemotherapy should not exceed 3 weeks from the schedule. Then oxaliplatin treatment should be reinstituted at a lower dose, if medically appropriate. After recovery from toxicity grade 3 to
grade 1 or less, a dose reduction of oxaliplatin to 100 mg/m² in subsequent cycles should be made. In case of no resolution to grade 1 or less after a maximum of 3 weeks from the planned date of next cycle, the patient should be permanently discontinued from oxaliplatin treatment. In case of grade 4 toxicity, the patient will be removed from oxaliplatin treatment permanently and followed until resolution of toxicity according to the protocol. If the investigator considers it to be in the best interest of the patient to continue capecitabine after resolution of grade 4 toxicity, it must be discussed with and approved by the investigator physician.

Table VI.2. Oxaliplatin dose adjustments for non-hematologic adverse effects

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Allergic reactions</td>
<td>3 or 4</td>
<td></td>
</tr>
<tr>
<td>* Respiratory symptoms indicative of pulmonary fibrosis</td>
<td>Any</td>
<td>Interrupt treatment and investigate cause of symptoms</td>
</tr>
<tr>
<td>* Interstitial pulmonary fibrosis not present at baseline</td>
<td>Any</td>
<td>Stop treatment permanently</td>
</tr>
<tr>
<td>Nausea and/or vomiting despite premedication with an effective antiemetic therapy</td>
<td>3</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>Nausea and/or Vomiting</td>
<td>4</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 or 4</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3</td>
<td>No dose reduction</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>Skin toxicity (extend rest period until recovery to grade ≤1)</td>
<td>3 or 4</td>
<td>No dose reduction</td>
</tr>
</tbody>
</table>

* No dose adjustment for capecitabine (if in the best interest of the patient).

Table VI.3. Neurologic toxicity scale for oxaliplatin dose adjustments

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Duration of toxicity</th>
<th>Persist between cycles³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic; clinical or diagnostic observations only; interventions not indicated; loss of deep tendon reflexes or paresthesia</td>
<td>1</td>
<td>1-7 Days</td>
<td>&gt; 7 Days</td>
</tr>
<tr>
<td>Paresthesias/dysthesias⁵, moderate symptoms limiting instrumental activities of daily living</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### VI.3 XELOX dose modifications for hematologic toxicity

In the XELOX regimen dose of capecitabine and oxaliplatin will be modified according to guidance in Table IV.4. Capecitabine is not expected to worsen or unduly prolong episodes of neutropenia/granulocytopenia. If toxicity recurs after dose reduction for previous toxicity, the next cycle should be given with a 25% dose reduction of capecitabine. If these toxicities occur again, a 50% dose reduction of oxaliplatin should be given. Treatment should be discontinued if toxicities recur despite these dose reductions. No dose reductions or interruptions will be required for anemia (non-hemolytic) as it can be satisfactorily managed by transfusions. The next treatment cycle can only start if hematologic toxicity (except anemia) has been recovered to grade ≤1 (e.g. ANC ≥ 1.5 x10⁹/L, Platelets ≥75 x10⁹/L).

### Table VI.4. Hematological toxicity: dose modifications for XELOX regimen

<table>
<thead>
<tr>
<th>ANC (10⁹/L)</th>
<th>Platelets (10⁹/L)</th>
<th>Next dose oxaliplatin</th>
<th>Next dose capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.5 (grade 4) or febrile neutropenia</td>
<td>&lt; 25 (grade 4)</td>
<td>100 mg/m²</td>
<td>No adjustment</td>
</tr>
</tbody>
</table>

### VI. 4 5-FU/LV precautions

Fluorouracil should be given with care to weak or malnourished patients, to those with a history of heart disease, or to those with hepatic or renal insufficiency. The main adverse effects of fluorouracil are on the bone marrow and the gastro-intestinal tract, and may be dose-limiting.
Toxicity is schedule dependent: reducing the rate of injection to a slow infusion is associated with less haematological toxicity but does not decrease gastro-intestinal toxicity. With protracted continuous infusion in particular, the hand-foot syndrome may occur. Gastro-intestinal toxicity may be exacerbated if fluorouracil is given with folinic acid.

**Hematological:** Depending upon schedule used, the nadir of the white cell count may occur from 7 to 20 days after a dose. Thrombocytopenia is usually at a maximum 7 to 17 days after a dose. Anemia may also occur.

**Gastro-intestinal:** Stomatitis, gastro-intestinal ulceration and bleeding, diarrhea, or hemorrhages from any site are signs that treatment should be stopped if appropriate. Nausea and vomiting are common.

**Coagulopathy:** Caution should be taken with the concomitant use of coumarin-derived anticoagulants, as warfarin interaction has been documented in the literature.

**Cardiovascular:** Life-threatening cardiotoxicity (arrhythmias, ventricular tachycardia, and cardiac arrest, secondary to transmural ischaemia) has been reported to occur in 0.55% of patients given fluorouracil, although the incidence of angina and less severe cardiotoxicity associated with coronary artery spasm may be higher. Myocardial ischemia has occurred. Possible risk factors include pre-existing heart disease or mediastinal radiotherapy and administration by prolonged infusion, but symptoms can also occur in patients without these risk factors.

**Neurological:** Central neurotoxicity, including cerebellar ataxia, confusion, disorientation, and emotional lability is reported to occur rarely in patients receiving fluorouracil.

**Skin:** Hand-foot syndrome (palmar-plantar erythrodysesthesia) has been reported. Although particularly associated with administration by protracted infusion, the syndrome may also occur following bolus doses. Symptoms generally resolve upon discontinuation of the drug. In addition, local inflammatory and photosensitivity reactions have occurred following topical use. Dermatitis and rarely, erythema multiforme have been reported.

**Ocular:** Systemic fluorouracil therapy has been associated with various types of ocular toxicity including several cases of excessive lacrimation, watering of the eyes or corneal epithelial erosion.

### VI.5 FOLFOX dose modifications for toxicities

Table VI.5 and Table VI.6 provide guidance for dose reductions for the first appearance of the specified toxicities excluding neurotoxicity (Table VI.7). At the second appearance of the toxicities, despite a prior dose reduction, the 5-FU dose could be further adjusted, if the investigator considers this to be in the best interest of the patient (otherwise the treatment should be discontinued). The second step, dose adjustment of 5-FU bolus is to 200 mg/m²/day, and of total 5-FU infusion to 1200 mg/ m². This is not applicable to the second appearance of grade 4
stomatitis or grade 3/4 skin toxicity, in which case the treatment should be discontinued. Note: when reducing the dose of 5-FU, the dose of leucovorin should remain the same.

Table VI.5. Hematologic toxicities: oxaliplatin + 5-FU dose reductions for FOLFOX regimen

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>5-FU bolus</th>
<th>5-FU infusion</th>
<th>oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>All</td>
<td>no dose reduction</td>
<td>no dose reduction</td>
<td>no dose reduction</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>no dose reduction</td>
<td>no dose reduction</td>
<td>no dose reduction</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4</td>
<td>300 mg/m²</td>
<td>1800 mg/m²</td>
<td>65 mg/m²</td>
</tr>
<tr>
<td>Febrile neutropenia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 or 4</td>
<td>300 mg/m²</td>
<td>1800 mg/m²</td>
<td>65 mg/m²</td>
</tr>
<tr>
<td>Thrombocytopenia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 or 4</td>
<td>300 mg/m²</td>
<td>1800 mg/m²</td>
<td>65 mg/m²</td>
</tr>
</tbody>
</table>

<sup>a</sup>Febrile neutropenia Gr. 3=ANC<1.0 x10⁹/L with fever ≥38.5°C,<br>Febrile neutropenia Gr. 4=ANC<1.0 x10⁹/L with fever ≥38.5°C; and life threatening sepsis

<sup>b</sup>Dose reduction to be applied at the second occurrence of persisting grade 2 hematological toxicity leading to an extended rest period of ≥2 weeks. The dose of leucovorin should remain the same.

Based on the most severe toxicity experienced since the last treatment, the following dose modifications should be used for non-hematological toxicities (see Table VI.6). The rest period should be extended until all non-hematological toxicities have subsided to grade 1 or less, except increased bilirubin and ALAT which must recover to grade 1 or baseline grade, whichever is higher.

**Nausea and vomiting**

For grade 3 nausea and/or vomiting that occurs with suboptimal antiemetic therapy, treatment should be continued for the next course with an effective anti-emetic treatment and without dose modification.

**Diarrhea**

If grade 3 or 4 diarrhea occurs at any time, the doses should be reduced according to Table 7. After grade 3 or 4 diarrhea, the patient must have recovered to grade 1 or less before treatment can be re-initiated.

**Stomatitis**
After grade 3 or 4 stomatitis, the doses should be reduced according to Table 7. The patient must have recovered to grade 1 or less before treatment can be re-initiated.

**Cardiac toxicity**
For grade ≥2 cardiac toxicity which is attributable to 5-FU, patients will be permanently discontinued from 5-FU/LV therapy (Table VI.6).

**Gastro-intestinal ulceration and bleeding**
For grade ≥2 gastrointestinal toxicity which is attributable to 5-FU, treatment will be held until recovery to grade ≤1.

**Skin toxicity**
Treatment will be held for grade 3 or 4 toxicity until recovery to grade ≤1 (Table VI.6). Treatment may be withheld to allow for recovery. The extended rest period should not exceed 3 weeks from the scheduled administration. If the patient does not recover to grade ≤1 in this timeframe, he/she will be taken off treatment.

**Table VI.6. Non-hematologic toxicity: Oxaliplatin + 5-FU/LV. Dose reductions for FOLFOX regimen**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>5-FU Bolus</th>
<th>5-FU infusion</th>
<th>Oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reaction</td>
<td>3 or 4</td>
<td>no dose reduction</td>
<td>no dose reduction</td>
<td>Stop treatment permanently</td>
</tr>
<tr>
<td>Respiratory symptoms indicative of pulmonary fibrosis</td>
<td>any</td>
<td>no dose reduction</td>
<td>no dose reduction</td>
<td>Interrupt treatment and investigate cause of symptoms</td>
</tr>
<tr>
<td>Interstitial pulmonary fibrosis not present at baseline</td>
<td>Any</td>
<td>no dose reduction</td>
<td>no dose reduction</td>
<td>Stop treatment permanently</td>
</tr>
<tr>
<td>Nausea and/or vomiting despite premedication with an effective antiemetic therapy</td>
<td>3</td>
<td>no dose reduction</td>
<td>no dose reduction</td>
<td>no dose reduction</td>
</tr>
<tr>
<td>Nausea and/or vomiting</td>
<td>4</td>
<td>300 mg/m²</td>
<td>1800 mg/m²</td>
<td>65 mg/m²</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 or 4</td>
<td>300 mg/m²</td>
<td>1800 mg/m²</td>
<td>65 mg/m²</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3</td>
<td>300 mg/m²</td>
<td>1800 mg/m²</td>
<td>no dose reduction</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4</td>
<td>200 mg/m²</td>
<td>1200 mg/m²</td>
<td>65 mg/m²</td>
</tr>
</tbody>
</table>
Cardiac toxicity (attributed to 5-FU)

- ≥2: Stop treatment permanently
- ≥3: Stop treatment permanently

Skin toxicity (extended rest period until recovery to grade ≤ 1)

- ≥3: 200 mg/m²
- ≥4: 1200 mg/m²
- No dose reduction

Note: the dose of leucovorin should remain the same.

Neurologic toxicity

In case of neurological toxicity dose reductions should be done according to Table VI.7.

Table VI.7. Neurologic toxicity scale: oxaliplatin dose adjustments for FOLFOX regimen

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Duration of toxicity</th>
<th>Persist between cycles&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesias/dysthesias&lt;sup&gt;b&lt;/sup&gt; that do not interfere with function</td>
<td>1</td>
<td>No dose reduction</td>
<td>No dose reduction</td>
</tr>
<tr>
<td>Paresthesias/dysthesias&lt;sup&gt;b&lt;/sup&gt;, interfering with function, but not with activities of daily living (ADL)</td>
<td>2</td>
<td>No dose reduction</td>
<td>No dose reduction, 75 mg/m²</td>
</tr>
<tr>
<td>Paresthesias/dysthesias&lt;sup&gt;b&lt;/sup&gt; with pain or with functional impairment that also interfere with ADL</td>
<td>3</td>
<td>No dose reduction</td>
<td>65 mg/m², Stop treatment permanently</td>
</tr>
<tr>
<td>Persistent paresthesias/dysthesias that are disabling or life-threatening</td>
<td>4</td>
<td>Stop treatment permanently</td>
<td>Stop treatment permanently</td>
</tr>
<tr>
<td>ACUTE: (during or after the 2 hour infusion) laryngopharyngeal dysesthesias&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Increase duration of next infusion to 6 hours&lt;sup&gt;c&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<sup>a</sup> Not resolved by the beginning of the next cycle.

<sup>b</sup> May be cold-induced.

<sup>c</sup> May also be pro-treated with benzodiazepines

Other toxicities or miscellaneous events

Other toxicities or miscellaneous events not listed above (which could include i.e. auditory, ocular, metabolic, hepatic, central nervous system, renal, or pulmonary AEs) should be managed symptomatically if possible, if these are grade < 3 AEs. For grade ≥3 AEs the extended rest period
Chemotherapy and maximal tumor debulking of multi-organ CRC metastases

to allow for recovery from toxicity to grade 1 or less until readministration of chemotherapy should not exceed 3 additional weeks from the schedule. If medically appropriate, treatment can be reinstituted at a lower dose. After recovery from toxicity grade 3 to grade 1 or less, a dose reduction of all drugs in subsequent cycles should be performed as follows: oxaliplatin to 65 mg/m², 5-FU bolus to 300 mg/m² and 5-FU infusion to 1800 mg/m². In case of no resolution to grade 1 or less after a maximum of 3 weeks from the planned date of next cycle, the patient should be discontinued from treatment. In case of grade 4 toxicity and otherwise not specified above, the patient will be removed from treatment permanently and followed until resolution of toxicity according to the protocol.

VI.6 Bevacizumab

Bevacizumab: precautions

Hypertension: An increased incidence of hypertension was observed in patients treated with bevacizumab. Hypertension can be generally treated with oral anti-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. Monitoring of blood pressure is recommended during bevacizumab therapy.

Proteinuria: Proteinuria, reported as adverse event, was observed in 23.3% of all patients treated with bevacizumab ranging in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome, with the great majority as grade 1 proteinuria. The proteinuria seen in bevacizumab clinical trials was not associated with renal dysfunction and rarely required permanent discontinuation of bevacizumab therapy. Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during bevacizumab therapy.

Gastrointestinal Perforation: Bevacizumab has been associated with serious cases of gastrointestinal perforation in patients with metastatic carcinoma of the colon or rectum. Caution should be exercised when treating patients with intra-abdominal inflammatory process with bevacizumab.

Wound Healing: Caution should be exercised in patients undergoing major surgery during bevacizumab therapy since they may be at increased risk for postoperative bleeding and/or wound healing complications during bevacizumab therapy. Patients included in study arm B (maximal tumor debulking) should therefore not receive bevacizumab in addition to XELOX or FOLFOX in the first three or four cycles (or 6 or 8 cycles in case of stable disease after 3 or 4 cycles), respectively. Bevacizumab therapy should not be initiated within 28 days following major surgery.
Haemorrhage: Increased bleeding events were observed in patients treated with bevacizumab, but were predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage. Patients with metastatic cancer of the colon or rectum might have an increased risk of tumor-associated hemorrhage.

Arterial Thromboembolism: Arterial thromboembolic events (including CVAs, MIS, TIAs, and other arterial thromboembolic events) have been reported in patients receiving bevacizumab. A history of arterial thromboembolic events or age greater than 65 years was associated with an increased risk of arterial thromboembolic events during bevacizumab therapy. Caution should be taken when treating these patients with bevacizumab.

Venous Thromboembolism: Venous thromboembolic events, including deep venous thrombosis, pulmonary embolism and thrombophlebitis, have been reported in patients receiving bevacizumab.

Congestive Heart Failure: Congestive heart failure (CHF) has been reported in patients treated with bevacizumab. Patients who received prior radiotherapy to the left chest wall may be of increased risk. The events varied in severity from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF requiring hospitalization and treatment. Caution should be exercised before initiating bevacizumab therapy in patients with risk factors. In patients with metastatic cancer of the colon or rectum, there was no increased incidence of CHF reported in patients treated with bevacizumab.

Hypersensitivity reaction: The incidence of hypersensitivity reactions observed in patients treated with bevacizumab in clinical trials was similar to that in controls. In case of any grade of hypersensitivity reaction attributable to bevacizumab occurs, permanently discontinue bevacizumab treatment.

Bevacizumab: dose modifications for toxicities
Life threatening toxicities seen with bevacizumab to date have been hemorrhage, thromboembolic events and gastro-intestinal perforation. Less severe toxicities include proteinuria, hypertension, wound healing complications, diarrhea, nausea, pain, asthenia and epistaxis. Because of the long terminal half-life of bevacizumab (20 days) the discontinuation of treatment in case of an adverse events is not expected to influence its short-term clinical evolution and therefore, the management of adverse events is based on institution of adequate treatment.

Treatment modifications in case of events attributable to bevacizumab
No dose reduction of bevacizumab is foreseen for an individual patient. In general toxicity attributable to bevacizumab will require bevacizumab treatment to be held or withdrawal of the patient from treatment with this drug.
Appropriate diagnostic and therapeutic medical treatment including accurate antihypertensive treatment is mandatory for patients developing signs and symptoms of RPLS. Bevacizumab treatment has to be discontinued in these patients. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known, decisions will be at investigator’s discretion. Missed doses of bevacizumab will not be made up.

Any patient who develops any one of the following toxicities attributable to bevacizumab should not receive further bevacizumab:
- Gastrointestinal perforation,
- Arterial thromboembolic events,
- Grade 3/4 haemorrhagic events,
- Symptomatic grade 4 venous thromboembolic events,
- Grade 4 hypertension (hypertensive crisis) and hypertensive encephalopathy
- Grade 4 proteinuria (nephrotic syndrome).
- Allergic/hypersensitivity reactions (any grade).
- Grade 3/4 Left Ventricular Systolic Dysfunction.

**Hemorrhage**

All toxicity will be graded according to CTCAE v 4.0 guidelines. If a grade 3/4 bleeding occurs, appropriate treatment should be instituted and bevacizumab treatment will be discontinued permanently.

**Thrombosis/Embolism**

All toxicity will be graded according to CTCAE v 4.0 guidelines. Patients who develop the following grades of thrombosis/embolism must discontinue bevacizumab and the following action is recommended:
- Bevacizumab should be permanently discontinued in patients who develop any grade of arterial thromboembolic event.
- Venous thromboembolic event - grade 3 or incidentally discovered pulmonary embolus (first occurrence): hold bevacizumab 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 on a stable dose of anticoagulant and, if on an oral coumarin derivative, have an INR within the target range (usually between 2 and 3) prior to restarting study drug treatment,

Symptomatic grade 4 venous thromboembolic event (first occurrence) – permanently discontinue bevacizumab.
**Hypertension**

Patients should be monitored for the development or worsening of hypertension via frequent blood pressure measurement. Blood pressure measurements should be taken after the patient has been in a resting position for > 5 minutes. Repeated measurement of blood pressure for verification should be undertaken if the initial reading is > 140 mmHg systolic and/or > 90 mmHg diastolic blood pressure. All toxicity will be graded according to CTCAE v 4.0 guidelines:

- Grade 1 hypertension: Asymptomatic, transient (< 24 hrs) increase by > 20 mmHg (diastolic) or to > 150/100 mmHg if previously within normal limits. Intervention not indicated.
- Grade 2 hypertension: Recurrent or persistent (> 24 hr) or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100 mmHg if previously within normal limits. Monotherapy of anti-hypertensive may be indicated. Once controlled to <150/100 mmHg, patients may continue bevacizumab therapy.
- Grade 3 hypertension: Requiring more than one anti-hypertensive or more intensive therapy than previously. Bevacizumab should be withheld for persistent or symptomatic hypertension and should be permanently discontinued if hypertension is not controlled.
- Grade 4 hypertension: Life threatening consequence (e.g. hypertensive crisis). Occurrence of grade 4 hypertension should lead to permanent discontinuation of bevacizumab. All doses of anti-hypertensive medicines should be recorded at all visits.

**Proteinuria**

Patients in all study arms will have a dipstick urinalysis according to the Schedule of Assessment (SoA) unless proteinuria has been determined by 24-hour urine collection. All toxicity will be graded according to CTCAE v 4.0 guidelines. Proteinuria assessment and adjustment of bevacizumab administration for proteinuria will be handled according to standard local procedures.

**Gastro-intestinal perforations**

All toxicity will be graded according to CTCAE v 4.0 guidelines. If a gastro-intestinal perforation occurs, appropriate treatment should be instituted and bevacizumab treatment will be discontinued permanently.

**Wound healing complications**

Bevacizumab therapy should not be initiated earlier than 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 therapy should be withheld for elective surgery.
Fistula or intra-abdominal abscess
Patients who develop a fistula or intra-abdominal abscess should discontinue bevacizumab. However, it is at investigator's discretion to continue after resolution of the findings in selected patients.

In fusion-related or allergic reactions
In clinical studies, infusion reactions with the first dose of bevacizumab were uncommon (< 3%) and severe reactions occurred in 0.2% of patients.

If mild (grade 1 or 2) infusion-related reactions (e.g. fever, chills, headache. nausea) occur, premedications should be given with the next dose, but the infusion time may not be reduced for the subsequent infusion. If the next dose is well tolerated with premedication, the subsequent infusion time may be reduced by 30 ± 10 min as long as premedication continue to be used. If infusion-related AEs occur with the 60-min infusion, all subsequent doses should be given over 90 ± 15 min (with premedication). Similarly, if mild infusion-related AEs occur with the 30-min infusion, all subsequent doses should be given over 60 ± 10 min (with premedication).

For patients with grade 3 infusion-related reactions, the bevacizumab infusion should be stopped and not restarted on that day. Adequate information on rechallenge of bevacizumab is not available. At the physician's discretion, bevacizumab may be permanently discontinued or re-instituted with pre-medications and at a rate of 90 ± 15 minutes. If the reaction occurred at the 90-minute rate, initially challenge at a slower infusion rate and gradually increase to 90 minutes. In case of any doubt bevacizumab should be permanently discontinued. When bevacizumab is re-instituted, the patient should be monitored, per physician's usual practice, for duration comparable to duration of reaction. For patients with grade 4 infusion-related reactions, bevacizumab should be permanently discontinued.

Anaphylaxis: Anaphylaxis is defined as vascular collapse and shock (blood pressure <90 mm Hg that is unresponsive to IV fluids) believed to be allergic in origin, with or without antecedent respiratory distress and occurring within 30 minutes of initiation of bevacizumab infusion. Cutaneous manifestations include pruritus, urticaria, or angioedema. Anaphylaxis has not been observed in 1032 patients treated with bevacizumab in Genentech-sponsored trials. Patients experiencing any grade of allergic reactions should permanently discontinue bevacizumab. To patients experiencing severe infusion-related or allergic reactions appropriate medical therapy should be administered.

Summary of bevacizumab schedule and dosage modification
The schedule of study drug administration will be modified in the event of certain grades of thrombotic, hemorrhagic, proteinuric, gastro-intestinal perforation, liver toxicity, wound healing
complications, fistula or intra-abdominal abscess, hypertensive adverse events and infusion-related or allergic reactions, as summarized in Table VI.8.

Table VI.8. Bevacizumab schedule modification due to adverse events
### Event to Be Taken

#### Venous thromboembolic

**Venous thromboembolic event**  
Grade 3 or incidental discovery of pulmonary embolus (first occurrence)  
- Hold bevacizumab 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 on a stable dose of anticoagulant and, if on an oral coumarin derivative, have an INR within the target range (usually between 2 and 3) prior to restarting study drug treatment.
  - The patient must not have had a Grade 3 or 4 hemorrhagic event since entering the study.

**Arterial thromboembolic event**  
- **Grade 3 or symptomatic Grade 4 venous thromboembolic event** (first occurrence)  
  - Permanently discontinue bevacizumab.

#### Hemorrhage

**Grade 1 and 2**  
- No schedule modification.

**Grade 3 or 4** (first occurrence)  
- Permanently discontinue bevacizumab.

#### Proteinuria (see Appendix 11)

- ≤ 2 g protein/24 hr  
  - No schedule modification.
  - Repeat 24 hr urine collection until proteinuria improves to ≤ 1 g of protein/24 hr.
  - Hold bevacizumab until proteinuria improves to ≤ 2 g of protein/24 hr.

- >2 g protein/24 hr  
  - Permanently discontinue bevacizumab.

#### Gastro-intestinal perforation

Gastro-intestinal perforation or abscess  
- Permanently discontinue bevacizumab.

#### Wound healing complications

**Prevention of 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. Bevacizumab therapy should be withheld for at least 28 days before elective surgery.

In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed.

#### Fistulas or intra-abdominal abscesses

Fistulas or intra-abdominal abscess  
Patients who develop a fistula or intra-abdominal abscess should discontinue bevacizumab.

#### Hypertension

**Grade 3**  
- Bevacizumab should be withheld for persistent or symptomatic hypertension.

**Grade 4**  
- Discontinue bevacizumab if hypertension is not controlled with medication.

#### Hypertensive Encephalopathy

- Permanently discontinue bevacizumab.

#### Infusion-related or allergic reactions

**Allergic reactions**  
- In the event of a suspected allergic reaction of any grade during infusion of bevacizumab stop bevacizumab infusion permanently and proceed as described in Appendix 12.

**Grade 3**  
- Stop bevacizumab infusion and do not restart on that day. At the physician's discretion, bevacizumab may be permanently discontinued or re-introduced with pre-medication.

**Grade 4**  
- Permanently discontinue bevacizumab.

#### Liver toxicity

- Applies only in cases when Grade 3 or 4 liver function test (ALAT, ASAT, ALP) increase is due to bevacizumab. If this is not the case, the guidelines provided in Sections 7.5.5.1, 7.5.5.3 and Table 1 should be followed.

**Grade 3 or 4 first occurrence**  
- Withhold bevacizumab until toxicity has improved to Grade ≤ 1 and then resume treatment.

**Grade 3 or 4 second occurrence**  
- Permanently discontinue bevacizumab.

#### Cardiac Dysfunction

**Grade 2 or 4 Left Ventricular Systolic Dysfunction**  
- Permanently discontinue bevacizumab.

### Notes

- A therapeutic dose of anticoagulant therapy is defined as a dose titrated to maintain an INR of at least 1.5 (usually within range of 2-3) for oral coumarin-derived anticoagulants or its equivalent for other anticoagulant medications administered to treat thromboembolic events. The oral coumarin-derived anticoagulant dose will be collected and INR will be assessed in baseline for all patients and throughout.

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