The role of surgery of the primary tumour with few or - absent symptoms in patients with synchronous unresectable metastases of colorectal cancer, a randomized phase III study

CAIRO 4

A study of the Dutch Colorectal Cancer Group (DCCG)

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Index 2/2

12. LOCAL DATAMONITORING.................................................................23
13. STATISTICAL CONSIDERATIONS ..................................................23
   13.1 SAMPLE SIZE .............................................................................23
   13.2 RANDOMIZATION AND STRATIFICATION ...................................23
   13.3 PRIMARY ANALYSIS ....................................................................24
   13.4 SUBGROUP ANALYSES AND ADJUSTED COMPARISONS ................24
   13.5 OVERALL SURVIVAL .................................................................24
   13.6 RESPONSE RATE ........................................................................24
   13.7 QUALITY OF LIFE ANALYSIS ....................................................24
   13.8 SAFETY ANALYSIS ......................................................................24
   13.9 INTERIM ANALYSIS AND STOPPING RULES ..............................25
14. TRANSLATIONAL RESEARCH ............................................................25
15. ETHICS .............................................................................................25
   15.1 ETHICAL AND LEGAL ASPECTS ...............................................25
   15.2 INSURANCE ................................................................................25
   15.3 INDEPENDENT PHYSICIAN ......................................................25
16 REFERENCES ....................................................................................26
APPENDIX 1 RECIST CRITERIA (VERSION 1.1) .......................................30
APPENDIX 2 NCI CTCAE VERSION 4.0 ..................................................33
APPENDIX 3 WHO PERFORMANCE SCORE ........................................34
APPENDIX 4 EORTC QLQ-C30 AND CR38 .........................................34
APPENDIX 5 BEVACIZUMAB ADMINISTRATION ...................................39
APPENDIX 6 SERIOUS ADVERSE EVENT FORM .................................44
APPENDIX 7 PATIENT INFORMED CONSENT FORM ...........................46
## 1. PROTOCOL SYNOPSIS

**Title**  
The role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer

**Study phase**  
Randomized phase III

**Background**  
The clinical benefit of resection of the primary tumour in patients with synchronous unresectable metastases is not known. In the literature, studies usually describe retrospective selected patients with synchronous metastases treated with or without resection of the primary tumour. All these studies are biased in patient selection and there are no prospective randomized studies on this topic. In patients with few or absent symptoms of the primary tumour, arguments both in favour and against initial resection have been presented, and therefore a randomized trial is warranted.

**Rationale**  
Although recent publications suggest that resection of the primary tumour in synchronous metastasized colorectal cancer patients might not be necessary, this appears to be based on feasibility and not on clinical outcome. Several studies comparing large groups of patients with or without resection of the primary tumour suggest an improved survival when the primary tumour is resected. A potential benefit of resection of the primary tumour is to prevent complications of the primary tumour during chemotherapy treatment or during later stages of the disease. A recent analysis of the CAIRO and CAIRO2 data showed that metastatic colorectal cancer patients who had a resection of the primary tumour prior to study entry, had an improved survival compared to patients without a resection of the primary tumour. However, these patients were selected after the primary tumour was resected and therefore these results are not corrected for surgical morbidity and mortality. We here propose a randomized trial in order to demonstrate that resection of the primary tumour does improve overall survival.

**Objectives**  
To determine the clinical benefit in terms of overall survival of resection of the primary tumour in synchronous unresectable metastatic colorectal cancer.

**Study design**  
Patients with synchronous metastatic colorectal cancer with few or absent symptoms of their primary tumour are randomized 1:1 between systemic treatment without resection of the primary tumour and resection of the primary tumour followed by systemic treatment

**Stratification parameters**  
1. Number of metastatic sites (1 versus more)  
2. Institution  
3. WHO PS (0-1 versus 2)  
4. Serum LDH (normal versus > ULN)  
5. Location of the primary tumor (leftsided versus rightsided primary tumor)
<table>
<thead>
<tr>
<th>Study endpoints</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall survival intent-to-treat population</td>
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</table>

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Progression-free survival</td>
</tr>
<tr>
<td>2. Systemic therapy related toxicity</td>
</tr>
<tr>
<td>3. Surgery related morbidity and mortality (30- and 90-day)</td>
</tr>
<tr>
<td>4. Quality of life (QoL)</td>
</tr>
<tr>
<td>5. Number of patients undergoing secondary surgery of initially unresectable metastases</td>
</tr>
<tr>
<td>6. Number of patients who never receive systemic therapy after resection of the primary tumour</td>
</tr>
<tr>
<td>7. Interval between randomization and initiation of systemic treatment</td>
</tr>
<tr>
<td>8. Cost-benefit analysis</td>
</tr>
<tr>
<td>9. Patients requiring resection of the primary tumour in the non-resection arm</td>
</tr>
<tr>
<td>10. Patients requiring stenting or radiotherapy for symptom palliation.</td>
</tr>
<tr>
<td>11. Overall survival in patients in whom treatment according to protocol was initiated (i.e. having received at least one cycle of systemic treatment in arm A and surgery in arm B)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Main criteria for inclusion and exclusion</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Histological proof of colorectal cancer</td>
</tr>
<tr>
<td></td>
<td>- Resectable primary tumour in situ</td>
</tr>
<tr>
<td></td>
<td>- Unresectable distant metastases</td>
</tr>
<tr>
<td></td>
<td>- No indication for neo-adjuvant (chemo)radiation.</td>
</tr>
<tr>
<td></td>
<td>- No severe signs or symptoms related to the primary tumour (i.e. severe bleeding, obstruction, severe abdominal pain)</td>
</tr>
<tr>
<td></td>
<td>- No prior systemic treatment for advanced disease</td>
</tr>
<tr>
<td></td>
<td>- Age ≥ 18 years</td>
</tr>
<tr>
<td></td>
<td>- WHO performance status 0-2</td>
</tr>
<tr>
<td></td>
<td>- Laboratory values obtained ≤ 4 weeks prior to randomization: Adequate bone marrow function (Hb ≥ 6.0 mmol/L, absolute neutrophil count ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L), renal function (serum creatinine ≤ 1.5x ULN and creatinine clearance, Cockroft formula, ≥ 30 ml/min), liver function (serum bilirubin ≤ 2 x ULN, serum transaminases ≤ 3 x ULN without presence of liver metastases or ≤ 5x ULN with presence of liver metastases)</td>
</tr>
<tr>
<td></td>
<td>- Expected adequacy of follow-up</td>
</tr>
<tr>
<td></td>
<td>- Written informed consent</td>
</tr>
<tr>
<td></td>
<td>- CT scan thorax and abdomen performed ≤ 4 weeks prior to randomization (if pre-study chest X-ray shows lung metastases ≥2cm and surrounded by air, lung lesions can be followed by chest X-ray instead of CT thorax)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pregnancy, lactation</td>
</tr>
<tr>
<td>- Unresectable primary tumour (e.g. neurovascular encasement, substantial ingrowth in pancreatic head)</td>
</tr>
<tr>
<td>- Any condition preventing the safety or feasibility of resection of the primary tumour, e.g. massive ascites</td>
</tr>
</tbody>
</table>
- Second primary malignancy ≤ 5 years prior to randomisation with the exception of basal cell carcinoma of the skin or adequately treated in situ carcinoma of any organ
- Any medical condition that prevents the safe administration of systemic treatment
- Previous intolerance of fluoropyrimidines
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency
- Possibility of radical resection of all metastatic disease
- Uncontrolled hypertension, i.e. values consistently > 150/100 mmHg
- Use of > 3 antihypertensive drugs
- Significant cardiovascular disease < 1 yr before randomization (symptomatic congestive heart failure, myocardial infarction, unstable angina pectoris, serious uncontrolled cardiac arrhythmia, cerebrovascular event)
- Chronic active infection
- Concurrent treatment with any other anti-cancer therapy as described per protocol
- Requirement of neoadjuvant (chemo)radiation therapy

### Treatment

| Arm A | First-line fluoropyrimidine-based chemotherapy with bevacizumab initiated within 4 weeks of randomization, followed by salvage therapy upon progression at the discretion of the local investigator. Surgery of primary tumour will be performed only when indicated by local signs or symptoms. |
| Arm B | Surgery within 4 weeks of randomization followed by fluoropyrimidine-based chemotherapy with bevacizumab until progression or unacceptable toxicity, followed by salvage therapy upon progression at the discretion of the local investigator. |

### Duration of treatment and follow-up

| Arm A and B | Treatment is continued until disease progression, or unacceptable toxicity. Patients will be evaluated every 9-10 weeks for response while on treatment, or at any other time point when progression is suspected. In case of drug related toxicity, this drug should be discontinued, and if possible, the other drugs of the treatment should be continued. If a treatment-free interval is considered to be in the best interest of the patients, this is allowed. After permanent discontinuation of therapy, patients will be followed every 3 months until progression or death. Death and/or progression should be reported whenever it occurs. |

### Criteria for evaluation

| Efficacy | All eligible randomized patients will be included in the analysis (intent-to-treat). Overall survival is estimated from the date of randomization to death from any cause, progression free survival is estimated from the time of randomization to the date of first documented progression or death from any cause. Patients having completed the baseline Quality Of Life (QoL) questionnaire and at least one QoL questionnaire during treatment are evaluable for QoL. |
| Safety profile | Safety will be analysed in each treatment group. Patients having received ≥ 1 dose of systemic treatment are evaluable for toxicity of... |
systemic treatment. All patients having undergone surgery of the primary tumour are evaluable for toxicity of surgery. Evaluation will be performed on the safety population (having received treatment, assignment to treatment groups as treated). Clinical and laboratory toxicity/symptomatology will be graded according to NCI common toxicity criteria, version 4.0. The adverse events which are not reported in NCI common toxicity criteria will be graded as: mild, moderate, severe, life threatening.

| Statistics       | In the control arm (non-resection group) the expected median OS is 13 months. In order to demonstrate a clinically relevant increase of 6 months of the median OS in the experimental arm (resection group) which would justify resection of the primary tumour in general practice, a total of 218 deaths are required (80% power, significance level 0.05). With a recruitment rate of 12 patients per month, an accrual period of 30 months and a follow-up period of 8 months, a total of 360 patients are required in order to detect a difference in median OS of 13 vs 19 months with a power of 80%. |
| Subset analysis  | An interim analysis at a significance level of 0.001 will be performed when one third of the events have occurred. The primary analysis will be a stratified log rank test on the OS at a significance level of 0.049. The sample size of 360 (180 per group) is such that still 79.6% power is retained when testing a level of 0.049. Secondary parameters will be compared between groups using stratified log rank tests (time-to-event endpoints such as PFS, interval between randomization and initiation of systemic treatment), chi-square tests (disease and outcome characteristics such as morbidity, mortality, number of patients requiring secondary surgery), and t-tests (e.g. quality of life). Regression analysis (e.g. proportional hazards models for time to event endpoints) will be used for translational research questions. |
| Translational research | Patients will be asked separately for informed consent for collection of tissue and blood samples. |
# 2. STUDY FLOW CHART

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>PRE-STUDY SCREENING</th>
<th>If arm B: After surgery, before start systemic therapy</th>
<th>During first-line systemic therapy</th>
<th>Until death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Written informed consent</td>
<td>prior to randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Tumour measurement¹</td>
<td>≤ 4 weeks prior to randomization</td>
<td>X</td>
<td>every 8 weeks (cycles of 2 weeks) or every 9 weeks (cycles of 3 weeks)</td>
<td></td>
</tr>
<tr>
<td>3. History, weight, PS</td>
<td>≤ 4 weeks prior to randomization</td>
<td></td>
<td>≤ 3 days of day 1 of each cycle</td>
<td>At least every 3 months</td>
</tr>
<tr>
<td>4. Blood pressure</td>
<td>≤ 4 weeks prior to randomization</td>
<td></td>
<td>prior to and after each dose of bevacizumab</td>
<td></td>
</tr>
<tr>
<td>5. Concomitant medication</td>
<td>≤ 4 weeks prior to randomization</td>
<td>X</td>
<td>every 2 (cycles of 2 weeks) or 3 weeks (cycles of 3 weeks)</td>
<td></td>
</tr>
<tr>
<td>6. Haematology²</td>
<td>≤ 4 weeks prior to randomization</td>
<td>X</td>
<td>≤ 3 days of day 1 of each cycle</td>
<td></td>
</tr>
<tr>
<td>7. Biochemistry³</td>
<td>≤ 4 weeks prior to randomization</td>
<td>X</td>
<td>≤ 3 days of day 1 of each cycle</td>
<td></td>
</tr>
<tr>
<td>8. Urine analysis (protein, dipstick)</td>
<td>≤ 4 weeks prior to randomization</td>
<td></td>
<td>≤ 3 days of day 1 of each cycle</td>
<td></td>
</tr>
<tr>
<td>9. CEA</td>
<td>≤ 4 weeks prior to randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Adverse events⁴ signs and symptoms</td>
<td>≤ 4 weeks prior to randomization</td>
<td>X</td>
<td>after each cycle</td>
<td></td>
</tr>
<tr>
<td>10. Quality of Life⁵</td>
<td>≤ 4 weeks prior to randomization</td>
<td>X</td>
<td>Every 6 months</td>
<td></td>
</tr>
<tr>
<td>11. Pathology tumour tissue⁶</td>
<td>After randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Translational research angiogenic factors⁷</td>
<td>Before start of treatment (systemic treatment or resection)</td>
<td>2-4 weeks after surgery AND before the start of first cycle systemic treatment</td>
<td>In arm A before start of second cycle</td>
<td></td>
</tr>
<tr>
<td>13. Translational research CD95L⁷</td>
<td>Before start of treatment (systemic treatment or resection)</td>
<td>2-4 weeks after surgery AND before the start of first cycle systemic treatment</td>
<td>In arm A before start of second cycle</td>
<td></td>
</tr>
</tbody>
</table>

¹ Tumour measurement: a CT-scan abdomen should be performed. CT thorax should be performed when chest X-ray shows metastasis ≤2 cm. When pre-study chest X-ray shows lung metastasis ≥2 cm and surrounded by air, lung lesions may be followed by chest X-ray without CT thorax. Liver ultrasound or CEA is NOT acceptable for evaluation of tumour status.

² Haematology: WBC and differential count, platelet counts, haemoglobin ≤ 3 days of day 1 of each cycle, except prior to cycle 1

³ Biochemistry: sodium, potassium, serum alkaline phosphatase, total bilirubin, ASAT (SGOT) and/or ALAT (SGPT), LDH, creatinine, albumin ≤ 3 days of day 1 of each cycle, except prior to cycle 1.

⁴ Adverse events: will be recorded and graded according to the NCI CTCAE version 4.0;

⁵ Quality of life: QLQ-C30 and C38. Baseline QoL form is mandatory for evaluation.

⁶ Pathology: informed consent is necessary.

⁷ Informed consent is necessary.
3. INTRODUCTION

3.1 Colorectal cancer
Colorectal cancer (CRC) is one of the most common types of cancer with an annual incidence of 150,000 new cases in Europe. The incidence in the Netherlands in 2008 was 12000 new cases. Its incidence is increasing due to the rise in living standard and aging of the population. In 70-80% of patients a macroscopically curative resection can be performed; however, about 50% of these patients will finally be confronted with distant metastases. Approximately 20% of patients with colorectal disease present with synchronous metastases (stage IV disease).(1) Some patients with stage IV disease are appropriate candidates for curative (predominantly liver) surgery and undergo treatment of both the primary tumour and the metastases. The majority of stage IV patients, however, have extensive unresectable disease and surgery is often performed as a prophylactic procedure to prevent local complications or symptoms. Tumour complications such as obstruction, perforation, and bleeding often require emergency operations especially during chemotherapy treatment, which can be avoided by surgery of the primary tumour at an early stage. Approximately 50% of all patients with stage IV disease undergo resection of the primary tumour, as was found in the SEER registry in the US(2) and the cancer registry of the comprehensive Rotterdam cancer region.(1) Several risk factors have been identified for limited postoperative survival such as extensive hepatic tumour load, pT4 tumours, lymphatic spread, and R1-2 resection.(3) Mortality after surgery of the primary tumour for patients with stage IV disease is reported to be higher than reported for elective surgery for stage I-III patients who are operated on, and ranges between 1.3-11.7%.(4) However, mortality rate reflects usually both symptomatic and asymptomatic patients and patients of all age and co-morbidity. It is estimated that the postoperative mortality rate is increased in patients with more complex problems such as symptomatic tumours, higher age or co-morbidity.

3.2 Treatment of stage IV colorectal cancer

For the majority of patients with metastatic colorectal cancer (mCRC) there are no curative options, but a significant benefit in median overall survival (OS) can be achieved with palliative systemic treatment.(5) This treatment currently consists of cytotoxic chemotherapy and targeted therapy. The 5-year OS for patients who are diagnosed with distant metastases ranges from 5-20%.(6-8) The median OS is improved when patients are being exposed to all available cytotoxic drugs during the course of their disease.(9) Standard of care in firstline treatment consists of fluoropyrimidine-based chemotherapy in combination with bevacizumab.

Metastatic colorectal cancer (mCRC) patients with synchronous metastases may present with a variable degree of symptoms of their primary tumour and/or metastases, and a palliative resection of the primary tumour prior to the initiation of systemic treatment is frequently performed.(2) This indication is obvious in patients with a symptomatic primary. However in patients with few or absent symptoms the indication for resection is under debate, and its effect on survival and quality of life is still uncertain.(10-12)

Currently, there are no data from prospective randomized trials to assess the value of resection of the primary tumour in stage IV patients with mild or absent symptoms of their primary tumour. All data on this topic are derived from retrospective analyses, which do not provide reliable information on the symptoms of the primary tumour at diagnosis and/or on the indication to perform or to refrain from resection of the primary tumour. Most randomized studies in mCRC do not even report whether a resection of the primary tumour has been performed.(13)

The two main objectives in the management of patients presenting with unresectable mCRC are to improve or maintain the quality of life and to prolong the survival. In patients with few or absent symptoms of the primary tumour, arguments both in favour and against initial resection have been presented.
The most important argument against an initial resection of the primary tumour is that the survival benefit of resection has not been demonstrated and that the morbidity and mortality associated with surgery should therefore be avoided.(14-16) More arguments against an initial resection include some preclinical and clinical data showing that a resection of the primary tumour may have a stimulating effect on the growth of distant metastases, (17) however, clinical data to support this concept are lacking. Further arguments include the fact that systemic treatment for distant metastases can safely be administered without resection (18), and that systemic treatment is postponed when surgery is started first with a possible inferior outcome. Recent studies have shown that systemic treatment with chemotherapy and targeted agents may be safely administered to stage IV patients with their primary tumour in situ.(18-20) Poultsides et al.(18) concluded that most patients with synchronous, advanced CRC who receive up-front systemic therapy never require palliative surgery for their primary tumour, and that systemic therapy can be safely administered to these patients. However, the median overall survival of these patients was only 13 months, while median overall survival times of 20-24 months have consistently been reported for the general population of mCRC patients in phase III trial. Karoui et al.(21) have demonstrated that 70% of stage IV colon cancer patients show major histological responses in the primary tumour when treated with preoperative chemotherapy, suggesting that treatment with chemotherapy can be effective in the majority of patients. When chemotherapy is started with the primary tumour in situ, only few patients undergo resection of the primary tumour during the course of their disease, which has prompted some authors to conclude that routine surgery is not necessary in this group of patients.(20;22) These recent publications have changed the policy in many centres in the U.S. and also in the Netherlands, and systemic therapy is now started in several hospitals in asymptomatic patients with metastatic disease. However, there are also surgeons who still prefer to remove the primary tumour first before starting systemic therapy. Again, this policy is based only on the feasibility of this strategy.

The most dominant argument in favour of initial resection is the prevention of complications of the primary tumour with subsequent prolongation of symptom-free and OS.(23-25) Stillwell et al. found that patients initially managed with chemotherapy were 7.3 times more likely to have a complication from the primary tumour(26) and, when operated for such complications, were more likely to have a poor postoperative outcome.(19;27) Another argument in favour of resection of the primary tumour is the more accurate staging of disease(28;29), since extrahepatic metastases may be better identified by visual exploration of the peritoneal cavity.(29)

A recent retrospective analysis of the CAIRO studies demonstrated that survival of patients with synchronous advanced colorectal cancer who had surgery of the primary tumour prior to study treatment was significantly higher compared to patients who had the primary tumour in situ in both the CAIRO (16.7 vs 11.4 months) and CAIRO2 study (20.7 versus 13.4 months), respectively.(30) In this analysis we also observed a higher incidence of toxicity in the non-resection group compared to the resection group, especially in the CAIRO2 study. Patients in the non-resection group experienced more nausea, vomiting and ileus, which might be related to the primary tumour. A major limitation of this study is that the decision to resect the primary tumour was made prior to study entry, and that we have no information about the reasons for non-resection, such as unresectability of the primary tumour, poor condition of the patient, symptomatic metastases requiring priority for systemic treatment, or absence of symptoms of the primary tumour.

Although a selection bias in this respect cannot be excluded, since patients experiencing serious morbidity following resection obviously did not qualify for the CAIRO entry criteria and were therefore not included, the benefit of resection was consistent in both trials and several reviews of the literature supported the survival benefit for patients with a resected primary tumour (4;31). On the other hand, in the CAIRO studies patients were randomized at the time of starting systemic treatment, survival rates were calculated from the randomization date, and therefore do not include the time from surgery until starting systemic treatment.
which is usually 1-3 months after surgery. This additional survival was not accounted for in this and other studies comparing surgery with chemotherapy.

In summary, data in the literature do not provide an outright support for either of the two strategies, although most support seems to exist for surgery of the primary first (see table 1). There is consensus in most multidisciplinary teams in the Netherlands and abroad that scientific evidence is lacking and that prospective trials are necessary to identify the best strategy in this common clinical situation. During several meetings and presentations by the principal investigators there was agreement between surgeons and medical oncologists that evidence-based decisions are needed in this group of patients, and there was a broad support for the design of this study.

Table 1 Data on resection versus non-resection of the primary tumour in metastatic colorectal cancer patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Years of study</th>
<th>Number of patients</th>
<th>Survival in months</th>
<th>pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Resection</td>
<td>Non-resection</td>
</tr>
<tr>
<td>Ruo (27)</td>
<td>1996-1999</td>
<td>127</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Kaufman (33)</td>
<td>1998-2003</td>
<td>115</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Scoggins (16)</td>
<td>1985-1997</td>
<td>66</td>
<td>14.5</td>
<td>16.6</td>
</tr>
<tr>
<td>Tebbutt (34)</td>
<td>1990-1999</td>
<td>280</td>
<td>14</td>
<td>8.2</td>
</tr>
<tr>
<td>Michel (29)</td>
<td>1996-1999</td>
<td>31</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Evans (35)</td>
<td>1999-2006</td>
<td>45</td>
<td>11</td>
<td>2</td>
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<tr>
<td>Poultsides (18)</td>
<td>2000-2006</td>
<td>-</td>
<td>178</td>
<td>-</td>
</tr>
<tr>
<td>Venderbosch (30)</td>
<td>2003-2004</td>
<td>258</td>
<td>16.7</td>
<td>11.4</td>
</tr>
<tr>
<td>Stage IV disease</td>
<td>2005-2006</td>
<td>289</td>
<td>20.7</td>
<td>13.4</td>
</tr>
</tbody>
</table>
3.3 Bevacizumab (Avastin®)
Tumour neoangiogenesis is a prerequisite for tumour growth. VEGF and VEGF-receptors have been implicated in this process, and have been associated with poor prognosis. Bevacizumab (Avastin®) inhibits tumour neoangiogenesis by blocking VEGF. It was tested versus placebo in combination with the bolus 5FU/LV/Campto® (IFL) regimen in 815 previously untreated patients. Median overall survival was significantly improved by the addition of bevacizumab with almost 5 months from 15.6 months to 20.3 months. Grade 3 hypertension was more common with bevacizumab compared to placebo (11% versus 2%), but was easily managed. No increase in the incidence of venous thromboembolism, or bleeding during concurrent use of anticoagulants was observed. Based on these and other results bevacizumab has been approved for the use in 1st-line treatment of advanced CRC, and has been accepted for this indication in the western world on a wide scale.

3.4 Rationale for the present study
We propose a multicentre randomized phase III study to analyze the role of resection of the primary tumour in unresectable metastatic colorectal cancer. The hypothesis of this trial is that surgery of the primary tumour improves survival in patients with asymptomatic unresectable stage IV colorectal cancer. Both treatment strategies (i.e. surgery of the primary first vs. chemotherapy first) are proposed to patients in daily practice in different centres in the Netherlands and therefore randomization is not believed to be a problem. In contrast to phase III trials in which patients are randomized in a placebo or no treatment arm, both randomization arms in this study contain an accepted treatment modality, which can be easily explained to patients. Because patients with locally advanced rectal cancer require different preoperative treatment regimen such as (chemo) radiation therapy and encounter more serious postoperative complications, these patients are excluded from the study. The primary study endpoint is overall survival and the study is designed to demonstrate a difference in overall survival of 6 months between both arms. This is less than demonstrated in both CAIRO studies, but is believed to be a minimal difference to justify any surgical procedure in advanced patients. Although this difference of 6 months seems a rather large difference between the two randomization arms, this difference is less than demonstrated in most of the studies presented with more than 100 patients (Table 1).
4. STUDY OBJECTIVES

4.1 Primary objective
The primary objective is overall survival (OS).

4.2 Secondary objectives
Secondary objectives are progression free survival (PFS), grade 3 and 4 systemic therapy related toxicity, surgery related morbidity and mortality (30-day and 90-day), quality of life (QoL), number of patients who undergo secondary surgery of initially unresectable metastases, number of patients who never receive systemic therapy after resection of the primary tumor, interval between randomization and initiation of systemic treatment, cost-benefit analysis, overall survival in patients in whom treatment according to protocol was initiated (i.e. having received at least one cycle of systemic treatment in arm A, and surgery in arm B) and in the non-resection arm the percentage of patients requiring resection of the primary tumour or stenting/radiotherapy for symptom palliation. Translational research will be performed on prognostic/predictive markers (resected tumour tissue, and in blood samples, i.e. angiogenic factors, and sCD95L levels).

5. SELECTION OF STUDY POPULATION

5.1 Inclusion/exclusion criteria

Inclusion criteria
- Histological proof of colorectal cancer
- Resectable primary tumour in situ
- Unresectable distant metastases
- No indication for neo-adjuvant (chemo)radiation.
- No severe signs or symptoms related to the primary tumour (i.e. severe bleeding, obstruction, severe abdominal pain)
- No prior systemic treatment for advanced disease
- Age ≥ 18 years
- WHO performance status 0-2
- Laboratory values obtained ≤ 4 weeks prior to randomization: Adequate bone marrow function (Hb ≥ 6.0 mmol/L, absolute neutrophil count ≥ 1.5 x 10⁹/L, platelets ≥ 100 x 10⁹/L), renal function (serum creatinine ≤ 1.5x ULN and creatinine clearance, Cockcroft formula, ≥ 30 ml/min), liver function (serum bilirubin ≤ 2 x ULN, serum transaminases ≤ 3 x ULN without presence of liver metastases or ≤ 5x ULN with presence of liver metastases)
- Expected adequacy of follow-up
- Written informed consent
- CT scan thorax and abdomen performed ≤ 4 weeks prior to randomization (if pre-study chest X-ray shows lung metastases ≥2cm and surrounded by air, lung lesions can be followed by chest X-ray instead of CT thorax)
- Unidimensionally measurable disease (≥ 1 cm on CT scan or ≥ 2 cm on chest X-ray; liver ultrasound is not allowed, according to RECIST 1.1)

Resectability
The following definition of few or absent symptoms is used: patients without signs or symptoms related to the primary tumour that require immediate intervention (i.e. surgery, stenting, systemic therapy or radiotherapy). The necessity of immediate intervention is left to the discretion of the treating physician. Whether or not metastases are resectable will be decided by the local multidisciplinary tumour board.
**Exclusion criteria**
- Pregnancy, lactation
- Unresectable primary tumour (e.g. neurovascular encasement, substantial ingrowth in pancreatic head)
- Any condition preventing the safety or feasibility of resection of the primary tumour, e.g. massive ascites
- Second primary malignancy ≤ 5 years prior to randomisation with the exception of basal cell carcinoma of the skin or adequately treated in situ carcinoma of any organ
- Any medical condition that prevents the safe administration of systemic treatment
- Previous intolerance of fluoropyrimidines
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency*
- Possibility of radical resection of all metastatic disease
- Uncontrolled hypertension, i.e. values consistently > 150/100 mmHg
- Use of > 3 antihypertensive drugs
- Significant cardiovascular disease < 1 yr before randomization (symptomatic congestive heart failure, myocardial infarction, unstable angina pectoris, serious uncontrolled cardiac arrhythmia, cerebrovascular event)
- Chronic active infection
- Concurrent treatment with any other anti-cancer therapy as described per protocol
- Requirement of neoadjuvant (chemo)radiation therapy

* Patients with a partial DPD deficiency can be included, adequate dose modifications of the fluoropyrimidine according to the guidelines are required

**6. PLAN OF THE STUDY**

**6.1 Study design**
Randomized phase III study.

**6.2 Randomization procedure**
Eligible patients will be randomized between the two treatment arms, and written informed consent should be obtained prior to randomization.
A total of 360 patients will be randomized. At randomization, after having properly checked all eligibility criteria and stratification parameters, patients will be randomized by emailing the signed randomisation form to the IKNL clinical research department (trialbureau@iknl.nl, tel. 088-2346500). Randomization will be performed 1:1 for upfront systemic treatment versus upfront surgery of the primary tumour followed by systemic treatment. The allocated treatment will be confirmed by fax or e-mail within one working day.

**6.3 Method for assigning patients to treatment groups**
Patients will be randomized based on stratification by
- Number of organs involved with metastatic disease (1 versus more)
- Performance status (0,1 versus 2)
- Serum LDH (normal versus abnormal)
- Institution
- Location of the primary colon tumor (rightsided versus leftsided primary tumor, demarcation at splenic flexure*)

*Rightsided colon: caecum, ascending colon, transverse colon. Lefsided colorectal: splenic flexure, descending colon, sigmoid, rectum. (41)
6.4 Surgical resection of metastases, other surgical procedures
Patients who underwent an emergency procedure of the primary tumour without resection of the primary tumour (e.g. stent placement of the primary tumour or defunctioning ileostomy or colostomy) can be randomized when the obstruction is treated adequately and the patients’ condition is improved. These patients should be amenable for both randomisation arms when the study is proposed and the multidisciplinary team (e.g. surgeon and medical oncologist) should agree that both arm A or B of the randomisation are safe treatment options.

Patients in whom radical surgical resection of all macroscopic tumour deposits is planned during or directly after chemotherapy treatment are not eligible for this study. For any elective surgical procedure in the control arm, an interval of at least 6 weeks is advised between last administration of bevacizumab and surgery.

7. STUDY TREATMENT

7.1 Treatment after randomization
After randomization patients will be treated with systemic treatment (arm A) or surgery of the primary tumour followed by systemic treatment (arm B).

7.2 Arm A
First-line fluoropyrimidine-based chemotherapy with bevacizumab within 4 weeks of randomization and continued until progression or unacceptable toxicity, followed by salvage therapy at the discretion of the local investigator. Surgery of primary tumour will be performed only when indicated by local signs or symptoms (e.g. obstruction, pain, bleeding).

7.3 Arm B
Surgery within 4 weeks of randomization followed by fluoropyrimidine-based chemotherapy with bevacizumab until progression or unacceptable toxicity, followed by salvage therapy at the discretion of the local investigator.

7.4 Surgery
In patients who are randomized to primary surgery followed by systemic treatment, a surgical resection of the colorectal tumour aimed at R0 resection will be performed. The surgical procedure may be performed by laparoscopy or open surgery, depending on the preference of the surgeon. If a complete resection of the primary tumour cannot be performed according to the operating team, a diverting stoma or entero-enterostomy is advised in order to prevent obstructing symptoms during follow-up.

In patients randomized to primary systemic treatment, surgery of the primary tumour should only be performed in case of obstruction, pain, bleeding or other local signs or symptoms during systemic treatment. Alternatively, other palliative treatment options such as endoscopic stenting (obstruction) or radiotherapy (bleeding) may be used in patients unfit to undergo surgery. All participating centres are entering the data of the surgically treated patients in the Dutch Surgical Colorectal Audit (DSCA). This is not in conflict with the proposed study and data entry in the DSCA database is independently organised by local investigators.

7.5 Chemotherapy regimen
In both study arms bevacizumab will be used in combination with fluoropyrimidine-based schedules. The chemotherapy regimen is to the discretion of the local investigator, who may choose from the following schedules:

- 5FU/LV (36)
- capecitabine (37)
- capecitabine + oxaliplatin, CAPOX (37)
- 5FU + oxaliplatin (FOLFOX 4 (38) or FOLFOX 7 (39)
- 5FU + irinotecan (FOLFIRI (40))
- capecitabine + irinotecan, CAPIRI (37)
- S-1

**Recommended bevacizumab dose:** 7.5 mg/kg bodyweight i.v. on day 1 in 3-weekly schedules and 5 mg/kg in 2-weekly schedules.

**5FU/LV**
Every 2 weeks: 2-hour infusion of LV (200mg/m2/d) followed by a 5FU bolus (400 mg/m2/d) and 22-hour infusion (600 mg/m2/d) for 2 consecutive days every 2 weeks

**Capecitabine:**
Every 3 weeks: capecitabine 1250 mg/m2 orally b.i.d. on day 1-14 (28 doses).

**FOLFOX-4**
Every 2 weeks: 2-hour infusion of I-LV (100 mg/m2) or dl-LV (200 mg/m2) followed by an FU bolus (400 mg/m2) and 22-hour infusion (600 mg/m2) for 2 consecutive days every 2 weeks, with oxaliplatin (85 mg/m2) as a 2-hour infusion on day 1.

**FOLFOX-7**
Every 2 weeks: 2-hour infusion of I-LV 200 mg/m2 or dl-LV 400 mg/m2 followed by an FU 46-hour infusion of 2,400 mg/m2 every 2 weeks, with oxaliplatin 130 mg/m2 as a 2-hour infusion on day 1.

**CAPOX**
Every 3 weeks: 2-hour infusion of oxaliplatin 130 mg/m2 in 250 ml glucose 5% IV infusion on day 1, 1-2 hours after discontinuation of the infusion followed by capecitabine 1000 mg/m2 orally b.i.d. on day 1-14 (28 doses).

**FOLFIRI**
Every 2 weeks: 2-hour infusion of I-LV 200 mg/m2 or dl-LV 400 mg/m2 followed by a FU bolus 400 mg/m2 and 46-hour infusion 2,400 to 3,000 mg/m2 every 46 hours every 2 weeks, with irinotecan 180 mg/m2 as a 2-hour infusion on day 1

**CAPIRI**
Every 3 weeks: irinotecan 250 mg/m2 in 250 ml NaCl 0.9% IV infusion in 30 minutes on day 1, 2 hours after discontinuation of the infusion followed by capecitabine 1000 mg/m2 orally b.i.d. on day 1-14 (28 doses).

**7.6 Dosing of chemotherapy in relation to body surface area and weight.**
It is not recommended to dose any drug above a body surface area of 2.2 m2 or a bodyweight of 100 kg unless this is justified by the lean body mass. In case of a change in body weight of >10% the doses for each drug should be recalculated. Patients with a partial DPD deficiency should receive modified doses of the fluoropyrimidine according to guidelines or recommendation of the pharmacogenomics laboratory.

**7.7 Duration of treatment**
After surgical resection of the primary tumor in arm B, or when clinically indicated in arm A, patients should commence or resume palliative systemic treatment with chemotherapy and bevacizumab when they have sufficiently recovered from any morbidity of surgery, but not earlier than 4 weeks after surgery.
Treatment is continued until disease progression, or unacceptable toxicity. Patients will be evaluated every 9-10 weeks for response while on treatment, or at any other time point when progression is suspected. In case of drug related toxicity, this drug should be discontinued, and if possible, the other drugs of the treatment should be continued. If a treatment-free interval is considered to be in the best interest of the patients, this is allowed. After permanent discontinuation of therapy, patients will be followed every 3 months until progression or death. Death and/or progression should be reported whenever it occurs.

7.8 Dose reductions of study medication and criteria for redosing
Dose reduction of chemotherapy is planned in case of severe haematological and/or non-haematological toxicities. Toxicities will be graded using the NCI common criteria Version 4.0 (see Appendix 2).

8. ADVERSE EFFECTS OF TREATMENT
The chemotherapeutic schedules as mentioned in paragraph 7.5 are standard regimens used for metastatic colorectal cancer patients and medical oncologists have experience using these regimens. If grade 3 or 4 (non-hematologic) toxicities occur this should be reported. Dose adjustments should also be reported, but are the responsibility of the investigator.

8.1 Bevacizumab
The most frequently occurring non-hematologic toxicities are: hypertension and proteinuria. Asthenia, nausea, and headache have been observed less frequently. Although bleeding and thrombo-embolic events have been described for patients treated with bevacizumab, in randomized trials with chemotherapy with or without bevacizumab in patients with colorectal cancer these events did not occur with a significant higher frequency compared to chemotherapy alone. Wound healing may be impaired by bevacizumab. Bowel perforation has been observed during treatment with bevacizumab, however a clear relationship has not been established. Dose reductions for bevacizumab should preferably not be performed. For more detailed safety information on bevacizumab, see Appendix 5.

8.2. At the start of each treatment cycle.
WBC and platelet counts should have been recovered to ≥ 3.0 and ≥ 75 x 10⁹/L, respectively, before the start of the next treatment cycle. If these conditions are not met dosing should be delayed for a maximum of 2 weeks. If haematological toxicity has not recovered to the above mentioned values after 2 weeks delay, patients will discontinue treatment with chemotherapeutic agents. In case of drug related toxicity, this drug should be discontinued, and if possible, the other drugs of the treatment should be continued.

8.3 Permanent discontinuation of individual drugs due to toxicity
If patients experience severe toxicity despite dose reductions which necessitate the discontinuation of individual drugs, these patients should be followed for progression of disease according to the specified timelines (evaluation q 9 weeks or earlier in case of clinical symptoms of disease progression).

8.4 Concomitant medication
All concomitant medication must be documented in the patients’ file at time of randomization, and at the end of study treatment or death.

8.5 Surgery related toxicity
All surgical complications will be monitored. These include duration of surgery, length of stay in hospital, perioperative blood loss and number of transfusions. Postoperative complications such as infections (e.g. pulmonary, urinary and wound infections, abdominal abscesses),
anastomotic leakage and thromboembolic events, will be specifically monitored. All unexpected long term complications will also be analysed.
9 STUDY ASSESSMENTS

9.1 Efficacy

All eligible randomized patients will be included in the analysis (intent-to-treat). Overall survival is estimated from the date of randomization to death from any cause. Progression free survival is estimated from the time of randomization to the date of first documented progression or death from any cause. Patients having completed the baseline QoL questionnaire and at least one QoL questionnaire during treatment are evaluable for QoL analysis.

9.2 Efficacy evaluation

Measurable lesions have at least one dimension (longest diameter to be recorded) as \( \geq 1 \) cm (10 mm). In case of a lung metastasis fully surrounded by air, a chest X-ray may be used instead of CT scanning provided the lung lesion is unidimensionally measurable and has a diameter of \( \geq 2 \) cm (20 mm). Index lesions should not be in a previously irradiated area. Ultrasound is not allowed for measurements of liver metastases.

Lesions that are previously irradiated, or which have arisen in previously irradiated fields, may not be used as target lesions, but should be included in the overall response analysis. Baseline measurement should be performed within 4 weeks prior to the start of treatment. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging technique or clinically). The sum of the longest diameter (LD) of all target lesions and the short axis of lymph nodes will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumour response.

Response will be assessed according to the RECIST criteria for evaluation of response (see Appendix 1) every 9 weeks (from randomisation), at onset of clinical signs of progression and in case of premature discontinuation of study treatment. Partial (PR) or complete response (CR), has to be confirmed after a minimum of 4 weeks. In case of a stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimal interval of 6 weeks.

The period for CR lasts from the date the CR was achieved to the date on which progressive disease is first noted. In those patients who achieved PR, only the period of overall response should be recorded. The period of overall response lasts from the time that measurement criteria are met for PR or CR whichever comes first to the date of first objective documentation of progressive disease. Serum CEA may not be used as a parameter for disease evaluation.

9.3 Secondary surgical treatment of metastases

Radical surgical resection of liver or other metastases may offer long-term survival in patients with colorectal cancer. The number of patients in whom previously unresectable metastases become resectable after chemotherapy is increasing because of the availability of more effective chemotherapy and more aggressive surgical strategies. Although the true effect of secondary radical surgery has not been evaluated in a prospective randomized study, this option may off course be offered to patients on study when applicable. Patients in whom a secondary resection of metastases seems likely after downsizing by systemic treatment are excluded from this study, since in these patients a resection of the primary tumour will always be performed, which is not in agreement with the study concept. However, if radical resection of metastases appear to be feasible and may be of benefit to patients, this should be performed in any patient on study. All patients in both randomization arms will be analysed as intention to treat. Of note: for elective surgical procedures, an interval of at least 28 days is advised between last administration of bevacizumab and surgery, given the long half-life of
bevacizumab and the possible adverse effects of bevacizumab. Other study drugs may be continued when considered safe and feasible.

After radical resection, systemic treatment will only be continued when advised by a multidisciplinary board of the local treatment centre. Patients will remain on-study and will be included in the analysis.

9.4 Progression free survival and overall survival
Progression-free survival (PFS) is defined as the time measured from the day of randomization to first progression or death, whichever comes first. Overall survival (OS) is defined as the time from randomization to death.

9.5 Subsequent off-study treatments
Any treatment after completion or permanent discontinuation of protocol treatment is at the discretion of the investigator. These off-study treatments should be recorded on the CRF forms.

9.6 Quality of life
Quality of life will be measured using the EORTC-QLQC30 and 38 questionnaires (Appendix 4), which will be filled in by the patients within 2 weeks prior to randomization (but at least prior to surgery or the administration of the first dose chemotherapy), and every 6 months thereafter, until the end of the study treatment.

9.7 Safety evaluations
Safety will be analysed in each treatment group. Patients having received ≥ 1 dose of systemic treatment are evaluable for toxicity of systemic treatment. All patients having undergone surgery of the primary tumour are evaluable for toxicity of surgery. Evaluation will be performed on the safety population (having received treatment, assignment to treatment groups as treated). Clinical and laboratory toxicity/symptomatology will be graded according to NCI common toxicity criteria, version 4.0. The adverse events which are not reported in NCI common toxicity criteria will be graded as: mild, moderate, severe, life threatening.

Clinical safety
The following evaluations will be performed prior to and/or on specified days during and following therapy:
- Complete medical history of malignant and non-malignant diseases.
- Clinical examination: weight, assessment of residual toxicity due to prior therapy and disease symptoms according to NCI-CTC (Appendix 2), performance status according to WHO criteria (Appendix 3).
- Adverse events/signs and symptoms of disease: at all contacts.

Laboratory determinations
The following tests will be performed as indicated in the flowchart (paragraph 2):
Haematology: Total and differential white blood cell count, platelets, haemoglobin.
Biochemistry: Total bilirubin, alkaline phosphatase, ASAT, ALAT, creatinine, albumin, LDH at baseline, urine protein (dipstick). CEA may not be used as a parameter for disease evaluation.
10. REPORTING OF ADVERSE EVENTS

10.1 Definitions
An adverse event (AE) is any symptom, sign, illness or experience, which develops or worsens in severity from informed consent to up to 30 days following the last administration of any of the study drugs or after surgery. Intercurrent illnesses or injuries should be regarded as adverse events.

Adverse events are classified as either serious or non-serious.

A serious adverse event (SAE) is any event that is:
- fatal
- life-threatening
- requires or prolongs hospitalisation
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event.

Important medical events are those which may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardise the patient, and may require intervention to prevent one of the other serious outcomes.

10.2 Recording of adverse events (AE)
Information on all grade 3 and 4 AEs should be recorded at each contact on the AE-module of the CRF. Grading will be done according to the NCI-CTCAE version 4.0 or if not applicable, the event will be graded as 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening.

The clinical course of each event should be followed until resolution, stabilisation or until it has been determined that study treatment or participation is not the cause. SAEs, which are still ongoing at the end of the study period, must be followed up to determine the final outcome.

10.3 Reporting of serious adverse events (SAE)

Serious Adverse Events
A SAE is defined as: 1) a bleeding and or wound infection for which an operation is needed or, 2) a serious surgical related event. Information about SAEs that occur within 30 days after surgery is collected and recorded on the Serious Adverse Event Report Form. The SAE must be reported by to the clinical research department of IKNL within 24 hours, preferably by email, otherwise by fax (trialbureau@iknl.nl, fax nr 088-2346011). All SAEs will be reported in the annual safety report.

The DCCG ("verrichter" in the terminology of the Dutch law) is responsible for SAE assessment and expedited reporting through the web portal ToetsingOnline. The DCCG has delegated these responsibilities to the principal investigator of this study. All SAEs will be reported to the CMO Arnhem-Nijmegen in monthly line listings. 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.

11. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An IDMC consisting of three senior medical and surgical oncologists and a statistician who are not involved in the study will review the safety data on a regular basis and report their
findings to the principal investigator. The principal investigator will submit these reports to the ethics committee.

12. LOCAL DATAMONITORING

The study team will monitor the recruitment, the reported serious adverse events and the data quality at least every 2 months. Problems which are identified will be discussed with the principal investigators, who will take appropriate measures. Relevant information will be included in regular study reports, and will be made available to an Independent Data Monitoring Committee (IDMC).

On-site quality control
The sponsor will perform limited on-site monitoring, at least once in each centre. The aim of on-site visits will be:
- To assess the consistency of the data reported on the CRF with the source data (source data verification)
- To check that all SAE’s have been properly reported
To assess any possible relationship with the study medication in patients who die within 30 days after surgery of within 30 days after the last administration of study drugs and whose death according to the local investigator or principal investigators cannot be attributed to disease progression alone.

13. STATISTICAL CONSIDERATIONS

13.1 Sample size
In the control arm (non-resection group) the expected median OS is 13 months. In order to demonstrate a clinically relevant increase of 6 months of the median OS in the experimental arm (resection group), a total of 218 deaths are required (80% power, significance level 0.05). With a recruitment rate of 12 patients per month, an accrual period of 30 months and a follow-up period of 8 months, a total of 360 patients are required in order to detect a difference in median OS of 13 vs 19 months with a power of 80%.

An increase of 6 months in the median OS is justified for the following reasons:
1. Data from analyses of resected versus non-resected patients demonstrate a difference in median OS of this magnitude
2. Given the morbidity, mortality, and use of healthcare resources which are associated with surgical resection of the primary tumour, a smaller benefit in median OS is considered not sufficiently clinically relevant to justify this procedure, and will therefore not change clinical practice.

13.2 Randomization and stratification
After confirmation of eligibility, patients will be randomized centrally (by phoning or faxing the data centre) for chemotherapy treatment versus surgery of the primary tumour in a 1:1 allocation ratio. Randomization will be done using minimization techniques, stratifying for the following prognostic criteria: number of metastatic sites (1 versus more), serum LDH (normal versus abnormal), WHO performance status (0,1 versus 2), institution, and location of the primary tumour (right sided versus left sided primary tumor, demarcation at splenic flexure) .
13.3 Primary analysis
The primary endpoint of the study is overall survival in the intent-to-treat population. Secondary endpoints are progression-free survival, response to chemotherapy of the primary tumour compared to the response of metastases, systemic therapy related toxicity, surgery related morbidity and mortality (30 days and 90 days), quality of life (QoL), interval between randomization and initiation of systemic treatment, cost-benefit analysis, patients requiring resection of the primary tumour in the non-resection arm, and overall survival in patients in whom treatment according to protocol was initiated (i.e. having received at least one cycle of systemic treatment in arm A, and surgery in arm B). Patients without recurrence and alive at the time of the analysis will be included as censored data. PFS curves will be constructed by means of the Kaplan Meier method. Comparisons of PFS curves will performed by mean of the Logrank test. Similar methods will be used to analyse the duration of survival. Analyses will be done in eligible patients according to the intention-to-treat principle.

13.4 Subgroup analyses and adjusted comparisons
Baseline factors will be used to describe the patients enrolled in the study. These factors include age, sex, WHO performance status, serum LDH levels, localization of metastases. Exploratory analysis of treatment effect within these subgroups will be performed. Subset analysis will be performed for:
- Number of sites of metastatic disease (primary tumour not included): 1 versus > 1
- Location of site of metastatic disease: hepatic versus extrahepatic +/- hepatic
- PS: 0,1 versus 2
- Serum LDH: normal versus abnormal
- Sex: male versus female
- Age: < 70 versus ≥ 70 years
- Location of the primary tumor: rightsided versus leftsided primary tumor (demarcation at splenic flexure)

In addition, Cox proportional hazard regression models will be used to investigate whether the primary treatment comparisons are modified by adjustments for various covariates. These analyses will be considered secondary and descriptive.

13.5 Overall survival
Overall survival will be calculated from the date of randomization to death or to last known to be alive and survival curves will be calculated by means of the Kaplan-Meier techniques and compared using the logrank test.

13.6 Response rate
Response will be assessed every 9 weeks according to standard RECIST criteria version 1.1.

13.7 Quality of life analysis
Quality of life data will be measured using the EORTC QLQ-C30 and CR38 questionnaires. Comparison of treatments in terms of the serial measurements of QoL will be done using repeated measurements methods and including treatment as factor. In addition, treatment differences at each QoL assessment time point will be compared by means of the Wilcoxon Rank Sum test.

13.8 Safety analysis
Clinical and laboratory toxicity/symptomatology will be graded according to NCI common toxicity criteria. Adverse events not reported in NCI CTCAE version 4.0 will be graded as: mild, moderate, severe, life-threatening. Safety will be analysed in each treatment group and per treatment regimen. Safety evaluation will be performed by patient and by cycle on the intent-to-treat population and per treatment received.
Comparisons of distribution and rates of toxicity will be done using Wilcoxon Rank Sum test (for ordinal data) or by the Chi$^2$ test (for categorical data).

13.9 Interim analysis and stopping rules
An interim analysis at a significance level of 0.001 will be performed when one third of the events have occurred. The primary analysis will be a stratified log rank test on the OS at a significance level of 0.049. The sample size of 360 (180 per group) is such that still 79.6\% power is retained when testing a level of 0.049. This interim analysis will be discussed in confidence by the Independent Data Monitoring Committee (IDMC).

Secondary parameters will be compared between groups using stratified log rank tests (time-to-event endpoints such as PFS, interval between randomization and initiation of systemic treatment), chi-square tests (disease and outcome characteristics such as morbidity, mortality, number of patients requiring secondary surgery), and t-tests (e.g. quality of life). Regression analysis (e.g. proportional hazards models for time to event endpoints) will be used for translational research questions.

14. TRANSLATIONAL RESEARCH
The focus of the translational research in the CAIRO4 study will be the detection of biomarkers that predict which patients are responding best to one of the treatment arms. Several studies are proposed, which concern patient-related factors and tumour-related factors.

15. ETHICS

15.1 Ethical and legal aspects
This study will be conducted in accordance to the standards of Good Clinical Practice, in agreement with the Declaration of Helsinki (latest amendment) and with Dutch law in general and with the W.M.O. (Wet Medisch-wetenschappelijk Onderzoek met mensen) in particular.

Before they agree to participation in this trial, all patients will be provided with written information in the form of a Patient Information Sheet (Appendix 7). The formal written consent of a patient must be obtained before initiation of any study-specific procedure.

15.2 Insurance
In accordance with Dutch law and the W.M.O., an insurance policy, covering all participating patients, has been effected with “HDI Gerling N.V.”

15.3 Independent physician
In accordance with Dutch law and the W.M.O., an independent physician has been assigned to this study. Dr. J. Bonenkamp, Surgeon, Radboud university medical center, who is not otherwise involved in this study, has agreed to act as the independent physician.
16 References

Reference List


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APPENDIX 1 RECIST criteria (version 1.1)

1 Definitions

At baseline, tumour lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable).
- 20 mm by chest X-ray. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Malignant lymph nodes
To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable
- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’.
- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

Specifications by methods of measurements

Measurement of lesions
- All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment
The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).
- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.
- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is
suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

- **Tumour markers:** CEA alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

2. Tumour response evaluation

Assessment of overall tumour burden and measurable disease.

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements.

**Baseline documentation of ‘target’ and ‘non-target’ lesions**

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

**Response Criteria**

**Evaluation of target lesions**

* **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10 mm.

* **Partial Response (PR):** At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.

* **Progression (PD):** At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

* **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum LD since the treatment started.

**Evaluation of non target lesions**

* **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumour marker level.

* **Non-CR/ Non–PD** Persistence of one or more non-target lesion or/and maintenance of tumour marker level above the normal limits.

* **Progression (PD):** Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions.

To achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy.

**Evaluation of best overall response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general the patient’s best response assignment will depend on the achievement of both measurement and confirmation criteria (see section 2.3.1).
Target lesions | Non-Target lesions | New Lesions | Overall response
---|---|---|---
CR | CR | No | CR
CR | Non-CR/Non-PD | No | PR
PR | Non-PD | No | PR
SD | Non-PD | No | SD
PD | Any | Yes or No | PD
Any | PD | Yes or No | PD
Any | Any | Yes | PD

Note:
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

Target lesions that become ‘too small to measure’.
While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being ‘too small to measure’.
If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

Best overall response
The best overall response is the best response recorded from the start of the study treatment until the end of treatment.

<table>
<thead>
<tr>
<th>Overall response</th>
<th>Overall response</th>
<th>BEST overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Time point</td>
<td>Second Time point</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>PR</td>
<td>SD, PD or PR</td>
</tr>
<tr>
<td>CR</td>
<td>SD</td>
<td>for SD duration met, otherwise, PD</td>
</tr>
<tr>
<td>CR</td>
<td>PD</td>
<td>for SD duration met, otherwise, PD</td>
</tr>
<tr>
<td>CR</td>
<td>NE</td>
<td>provided minimum criteria for SD duration met, otherwise NE</td>
</tr>
<tr>
<td>PR</td>
<td>CR</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>PR</td>
<td>PD</td>
<td>for SD duration met, otherwise, PD</td>
</tr>
<tr>
<td>PR</td>
<td>NE</td>
<td>provided minimum criteria for SD duration met, otherwise NE</td>
</tr>
<tr>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>PD</td>
<td>-</td>
<td>PD</td>
</tr>
</tbody>
</table>

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

* If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes ‘CR’ may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

More information about RECIST 1.1 can be found here: Eisenhauer et al. European Journal of Cancer 2009 45(228-247).
APPENDIX 2 NCI CTCAE version 4.0

The grading of adverse events and/or adverse drug reactions will be reported according to the NCI Common Terminology Criteria for Adverse Events, CTCAE version 4.0, published June 14, 2010. The complete document (194 pages) can be reviewed and downloaded from the following internet site:
- http://ctep.cancer.gov/

A useful application to search adverse events:
## APPENDIX 3 WHO Performance Score

<table>
<thead>
<tr>
<th>WHO PERFORMANCE STATUS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to carry out all normal activity without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to do light work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50% or waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% or waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled cannot carry on any self-care, totally confined to bed or chair.</td>
</tr>
</tbody>
</table>

NB: For information:
WHO Performance Status versus Karnofsky Performance Status scale:

<table>
<thead>
<tr>
<th>WHO/ECOG Performance Status</th>
<th>Karnofsky Performance Status scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal no complaints; no evidence of disease.</td>
</tr>
<tr>
<td>1</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease.</td>
</tr>
<tr>
<td>2</td>
<td>Normal activity with effort; some signs or symptoms of disease.</td>
</tr>
<tr>
<td>3</td>
<td>Requires occasional assistance, but is able to care for most of his personal needs.</td>
</tr>
<tr>
<td>4</td>
<td>Requires considerable assistance and frequent medical care.</td>
</tr>
<tr>
<td>5</td>
<td>Disabled; requires special care and assistance.</td>
</tr>
<tr>
<td>6</td>
<td>Severe disability; hospital admission is indicated although death not imminent.</td>
</tr>
<tr>
<td>7</td>
<td>Very sick; hospital admission necessary; active supportive treatment necessary.</td>
</tr>
<tr>
<td>8</td>
<td>Moribund; fatal processes progressing rapidly.</td>
</tr>
<tr>
<td>9</td>
<td>Dead</td>
</tr>
</tbody>
</table>

0                           | Dead                                                                                     |
EORTC QLQ-C30 (version 3.0.)

Wij zijn geïnteresseerd in bepaalde dingen over u en uw gezondheid. Wilt u alle vragen zelf beantwoorden door het getal te omcirkelen dat het meest op u van toepassing is. Er zijn geen "juiste" of "onjuiste" antwoorden. De informatie die u geeft zal strikt vertrouwelijk worden behandeld.

Wilt u uw voorletters invullen:  |__|__|__|__|
Uw geboortedatum (Dag, Maand, Jaar):  |__|__|__|__|__|__|__|__|
De datum van vandaag (Dag, Maand, Jaar):  |__|__|__|__|__|__|__|__|

Gedurende de afgelopen week:

<table>
<thead>
<tr>
<th></th>
<th>Gedurende de afgelopen week</th>
<th>Helemaal</th>
<th>Een beetje</th>
<th>Nogal erg</th>
<th>Heel erg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Heeft u moeite met het doen van inspannende activiteiten zoals het dragen van een zware boodschappentas of een koffer?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Heeft u moeite met het maken van een lange wandeling?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Heeft u moeite met het maken van een korte wandeling buitenshuis?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Moet u het grootste deel van de dag in bed of in een stoel blijven?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>Heeft u hulp nodig met eten, aankleden, u zelf wassen of naar het toilet gaan?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Gedurende de afgelopen week:

<table>
<thead>
<tr>
<th></th>
<th>Gedurende de afgelopen week</th>
<th>Helemaal</th>
<th>Een beetje</th>
<th>Nogal erg</th>
<th>Heel erg</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Was u beperkt bij het doen van uw werk of andere dagelijkse bezigheden?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>Was u beperkt in het uitoefenen van uw hobbies of bij andere bezigheden die u in uw vrije tijd doet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>Was u kortademig?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>Heeft u pijn gehad?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>Had u behoefte te rusten?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>Heeft u moeite met slapen gehad?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>Heeft u zich slap gevoeld?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>Heeft u gebrek aan eetlust gehad?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>Heeft u zich misselijk gevoeld?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Wilt u a.u.b. naar de volgende bladzijde gaan.
Gedurende de afgelopen week:

<table>
<thead>
<tr>
<th></th>
<th>Helemaal</th>
<th>Een beetje</th>
<th>Nogal</th>
<th>Heel erg</th>
</tr>
</thead>
<tbody>
<tr>
<td>15. Heeft u overgegeven?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. Had u last van obstipatie? (Was u verstopt?)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. Had u diarree?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Was u moe?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Heeft pijn u gehinderd in uw dagelijkse bezigheden?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Heeft u moeite gehad met het concentreren op dingen, zoals een krant lezen of televisie kijken?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21. Voelde u zich gespannen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Maakte u zich zorgen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Voelde u zich prikkelbaar?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Voelde u zich neerslachtig?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Heeft u moeite gehad met het herinneren van dingen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Heeft uw lichamelijke toestand of medische behandeling uw familieleven in de weg gestaan?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. Heeft uw lichamelijke toestand of medische behandeling u belemmerd in uw sociale bezigheden?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28. Heeft uw lichamelijke toestand of medische behandeling financiële moeilijkheden met zich meegebracht?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Wilt u voor de volgende vragen het getal tussen 1 en 7 omcirkelen dat het meest op u van toepassing is

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>29. Hoe zou u uw algehele gezondheid gedurende de afgelopen week beoordelen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Erg slecht</td>
<td>Uitstekend</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>30. Hoe zou u uw algehele “kwaliteit van het leven” gedurende de afgelopen week beoordelen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Erg slecht</td>
<td>Uitstekend</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DCCG CAIRO4 study, protocol version 1.6 09-03-2017
EORTC QLQ – CR38

Soms zeggen patiënten dat ze de volgende klachten of problemen hebben. Wilt u aangeven in welke mate u deze klachten of problemen gedurende de afgelopen week heeft ervaren

**Gedurende de afgelopen week:**

<table>
<thead>
<tr>
<th></th>
<th>Helemaal niet</th>
<th>Een beetje</th>
<th>Nogal</th>
<th>Heel erg</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. Heeft u overdag vaak geplast?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32. Heeft u ’s nachts vaak geplast?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33. Had u pijn bij het plassen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34. Had u een vol gevoel in uw buik?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35. Heeft u buikpijn gehad?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36. Heeft u pijn in uw zitvlak gehad?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37. Had u last van gasvorming (winderigheid)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38. Heeft u oprispingen gehad?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39. Bent u afgevallen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40. Had u een droge mond?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41. Had u dun of futloos haar ten gevolge van uw ziekte of behandeling?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>42. Smaakten voedsel en drank anders dan u gewend was?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43. Voelde u zich lichamelijk minder aantrekkelijk ten gevolge van uw ziekte of behandeling?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>44. Voelde u zich minder vrouwelijk / mannelijk ten gevolge van uw ziekte of behandeling?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45. Was u ontevreden met uw lichaam?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>46. Maakte u zich zorgen over uw gezondheid in de toekomst?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**Gedurende de afgelopen vier weken:**

<table>
<thead>
<tr>
<th></th>
<th>Helemaal niet</th>
<th>Een beetje</th>
<th>Nogal</th>
<th>Heel erg</th>
</tr>
</thead>
<tbody>
<tr>
<td>47. In hoeverre had u zin in sex?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>48. In hoeverre was u sexueel actief (met of zonder geslachtsgemeenschap)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49. Alleen invullen indien u sexueel actief was: In hoeverre was sex plezierig voor u?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**Alleen voor mannen:**

<table>
<thead>
<tr>
<th></th>
<th>Helemaal niet</th>
<th>Een beetje</th>
<th>Nogal</th>
<th>Heel erg</th>
</tr>
</thead>
<tbody>
<tr>
<td>50. Had u moeite met het stijf worden of blijven van uw penis?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>51. Had u problemen met het krijgen van een zaadlozing (bijv. zogenaamde droge zaadlozing)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Wilt u a.u.b. naar de volgende bladzijde gaan
Gedurende de afgelopen vier weken:

Alleen voor vrouwen die gemeenschap hebben gehad:

<table>
<thead>
<tr>
<th></th>
<th>Helemaal niet</th>
<th>Een beetje</th>
<th>Nogal</th>
<th>Heel erg</th>
</tr>
</thead>
<tbody>
<tr>
<td>52. Had u een droge vagina tijdens de gemeenschap?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>53. Had u pijn tijdens de gemeenschap?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

54. Heeft u een stoma?
- **Nee**  Wilt u de vragen 55 t/m 61 beantwoorden? (Wilt u Nee of Ja omcirkelen)
- **Ja**  Wilt u de vragen 55 t/m 61 overslaan, en de vragen 62 t/m 68 beantwoorden?

Gedurende de afgelopen week:

Alleen voor patiënten zonder stoma:

<table>
<thead>
<tr>
<th></th>
<th>Helemaal niet</th>
<th>Een beetje</th>
<th>Nogal</th>
<th>Heel erg</th>
</tr>
</thead>
<tbody>
<tr>
<td>55. Heeft u overdag vaak ontlasting gehad?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>56. Heeft u ’s nachts vaak ontlasting gehad?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>57. Heeft u loze aandrang (aandrang zonder ontlasting) gehad?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>58. Heeft u ongewild ontlasting verloren?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>59. Heeft u bloed bij uw ontlasting gehad?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>60. Had u een moeilijke stoelgang?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>61. Had u een pijnlijke stoelgang?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Alleen voor patiënten met een stoma:

<table>
<thead>
<tr>
<th></th>
<th>Helemaal niet</th>
<th>Een beetje</th>
<th>Nogal</th>
<th>Heel erg</th>
</tr>
</thead>
<tbody>
<tr>
<td>62. Was u bang dat anderen uw stoma zouden kunnen horen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>63. Was u bang dat anderen uw onlasting zouden kunnen ruiken?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>64. Heeft u loze aandrang (aandrang zonder ontlasting) gehad?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>65. Maakte u zich zorgen over mogelijke lekkage van de stoma-zakjes?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>66. Was uw huid rondom het stoma geïrriteerd?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>67. Had u problemen met de verzorging van uw stoma?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>68. Voelde u zich minder compleet vanwege uw stoma?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

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APPENDIX 5 Bevacizumab administration

The overall safety profile of bevacizumab is based on 1132 patients with metastatic carcinoma of the colon or rectum (691), locally advanced or metastatic non-small cell lung (85), metastatic breast cancer (304), hormone-resistant prostate cancer (15) and patients with various advanced malignancies in phase I trials (37), who received bevacizumab either as a single agent or in combination with chemotherapy in 9 Genentech-sponsored clinical trials.

In the pivotal phase III, randomized, double-blind, active-controlled study in metastatic carcinoma of the colon or rectum (Study AVF2107g), 396 patients were treated with IFL (Irinotecan/5-FU/Leucovorin) plus placebo (Arm 1), 392 patients were treated with IFL plus bevacizumab (Arm 2), and 109 patients were treated with 5-FU/LV (5-fluorouracil/leucovorin) plus bevacizumab (Arm 3). Enrolment in the 5-FU/LV plus bevacizumab arm of the study was discontinued, as pre-specified in the protocol, once the safety of combination of bevacizumab with IFL regimen was established and considered safe by an independent monitoring committee viewing an unblinded interim analysis.

In another phase II, randomized, double-blind, active-controlled study (Study AVF2192g), the safety of bevacizumab was investigated in 204 patients with metastatic carcinoma of the colon or rectum who were not optimal candidates for first-line irinotecan. Patients had to be either more susceptible to irinotecan toxicity (≥ 65 years, with prior radiotherapy to pelvis or abdomen) or less likely to benefit from irinotecan treatment (PS ≥ 1, baseline albumin < 3.5 g/dl) in order to be eligible for enrolment. Of these patients, 104 were treated with 5-fluorouracil/leucovorin (5-FU/placebo (Arm 1) and 100 patients were treated with 5-FU/LV + bevacizumab (Arm 2).

Hypertension

An increased incidence of hypertension was observed in patients treated with bevacizumab. Hypertension was generally treated with oral anti-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. It rarely resulted in discontinuation of therapy (0.7% of all patients treated with bevacizumab) or hospitalisation. A hypertensive encephalopathy was reported in one case (0.1%) only. The risk of bevacizumab associated hypertension did not correlate with the patients’ baseline characteristics, underlying disease or concomitant therapy.

In the phase III, randomized, double-blind, active-controlled study in metastatic carcinoma of the colon or rectum (AVF2107g), hypertension of any grade (NCI-CTC, version 2.0) occurred in 22.4% of patients receiving IFL (Irinotecan/5-FU/LV) plus bevacizumab compared with 8.3% of patients receiving IFL alone. Grade 3 hypertension (requiring oral anti-hypertensive medication) was reported in 11.0% of patients receiving IFL plus bevacizumab compared with 2.3% of patients receiving IFL alone. At week 24 of treatment, the mean change of blood pressure (BP) from baseline was diastolic BP +4.1 mmHg and systolic BP +5.5 mmHg in patients treated with bevacizumab.

In Study AVF2192g, hypertension of any grade occurred in 32.0% of patients treated with 5-FU/LV plus bevacizumab (Arm 2) compared to 4.8% of patients treated with 5-FU/LV plus placebo (Arm 1). Grade 3 hypertension was observed in 16.0% of patients in Arm 2 compared to 2.9% of patients in Arm 1. At week 24 of treatment, the mean change of BP from baseline was diastolic BP +5.4 mmHg and systolic +8.4 mmHg in Bevacizumab-treated patients. Hypertension did not lead to death or study drug discontinuation in this study. No hypertensive crisis (grade 4) was reported.

There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, these patients should be excluded from this study. Monitoring of blood pressure is mandatory during bevacizumab therapy, especially since recently case reports have been published on the occurrence of reversible posterior leukoencephalopathy syndrome (RPLS) in hypertensive patients treated with Bevacizumab (Glusker P, et al. N Engl J Med 2006;354:980-1; Ozcan C, et al. N Engl J Med 2006;354:981-2; Koopman M, et al. Dis Colon Rectum 2008;51:1425-6).
The following approach is recommended in case at any time point while on bevacizumab:

⇒ Blood pressure >150/100 mmHg and/or diastolic increase >20 mmHg (compared to baseline):
  • Delay next administration of bevacizumab (NB: chemotherapy should be administered as planned).
  • Start treatment with amlodipin 5 mg o.d.*).
  • Next blood pressure recordings within 3 days:
    
    In case
    ⇒ Blood pressure ≤150/100 and diastolic increase ≤20 mmHg (compared to baseline):
      • Administer bevacizumab (no more than 3 days after the originally planned administration date).
      • Continue antihypertensive therapy.
    
    In case
    ⇒ Blood pressure still >150/100 and/or diastolic increase >20 mmHg (compared to baseline):
      • Skip bevacizumab administration for this cycle.
      • Increase amlodipin to 10 mg o.d. Add ACE-inhibitor or beta-blocker in case of insufficient effect of amlodipin monotherapy.

*) As this procedure is a recommendation, the final choice of antihypertensive drug(s) is at the discretion of the treating physician.

Proteinuria
In study AVF2107g, proteinuria was reported as an adverse event in 21.7% of patients receiving IFL alone and 26.5% of patients receiving IFL plus bevacizumab. There was no Grade 4 (NCI-CTC, version 2.0) proteinuria, and incidences of grade 2 and 3 proteinuria were similar in both arms.

Proteinuria, reported as adverse event, was observed in 23.3% of all patients treated with bevacizumab. It ranged 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.

In Study AVF2192g, proteinuria was reported as adverse event in 38.0% of patients receiving 5-FU/LV plus bevacizumab (Arm 2) and 19.2% of patients receiving 5-FU/LV plus placebo (Arm 1). The majority of these events was grade 1 (30.0% vs. 15.4%). There was no Grade 4 proteinuria (nephrotic syndrome) and only one case of grade 3 proteinuria was reported in Arm 2. No proteinuria resulted in death or study drug discontinuation.

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that grade 1 proteinuria may be related to bevacizumab dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during bevacizumab therapy. Bevacizumab should be discontinued in patients who develop NCI-CTC (version 3.0) Grade 4 proteinuria (nephrotic syndrome).

Gastrointestinal Perforation
Bevacizumab has been associated with serious cases of gastrointestinal perforation in patients with metastatic carcinoma of the colon or rectum. In study AVF2107g in patients with metastatic colorectal cancer, there were six reports of gastrointestinal perforation in the IFL
plus bevacizumab arm and one report in the 5-FU/LV plus bevacizumab arm compared with none events in the IFL plus placebo arm. In two patients this event had a fatal outcome; the remaining five recovered but three patients resumed bevacizumab therapy. The presentation of these events varied in type and severity, ranging from free air seen only on the plain abdominal X-ray, which resolved without treatment, to a colonic perforation with abdominal abscess and fatal outcome. The common feature among these cases was intra-abdominal inflammation, either from gastric ulcer disease, tumour necrosis, diverticulitis or chemotherapy-associated colitis. Nevertheless, a causal association of an intra-abdominal inflammatory process and gastrointestinal perforation to treatment with bevacizumab has not been established. However, caution should be exercised when treating patients with intra-abdominal inflammatory process with bevacizumab.

In study AVF2192g, two cases of gastrointestinal perforation were observed in patients metastatic colorectal cancer treated with 5-FU/LV plus bevacizumab arm compared to none in 5-FU/LV plus placebo arm. One case had fatal outcome whereas the other resolved but study treatment was discontinued due to the event. In both cases, perforation occurred at the site of sigmoid colon diverticulum.

Patients with metastatic carcinoma of the colon or rectum may be at increased risk for the development of gastrointestinal perforation when treated with bevacizumab and chemotherapy.

No gastrointestinal perforation has been observed in any other Genentech-sponsored bevacizumab clinical trials.

Wound Healing
As bevacizumab may adversely impact wound healing, patients who had major surgery within the last 28 days prior to initiation of bevacizumab therapy were excluded from participation in study AVF2107g. In this study, 173 patients in IFL plus bevacizumab arm and 180 patients in IFL plus placebo arm underwent cancer-related surgery between 28 and 60 days prior to starting bevacizumab therapy. There was no increased risk of post-operative bleeding or wound healing complications observed in these patients.

Forty patients in the IFL plus bevacizumab arm underwent major surgery while receiving bevacizumab, of which 4 patients experienced an adverse event consistent with post-operative bleeding or wound healing complications. There were no similar complications observed in the 25 patients from the IFL plus placebo arm who also underwent major surgery.

In Study AVF2192g, 39 patients in 5-FU/LV plus placebo arm (Arm 1) and 43 patients in 5-FU/LV plus bevacizumab arm (Arm 2) underwent cancer-related surgery between 28 and 60 days prior to starting study drug. No patients experienced grade 3/4 wound healing and bleeding complications within 60 days after prior major surgery.

Fifteen patients in Arm 2 underwent major surgery while receiving bevacizumab, of which 3 experienced grade 3/4 wound healing or bleeding complications within 60 days of surgery. Three patients in Arm 1 underwent major surgery during study treatment and none experienced grade 3/4 wound healing or bleeding complications.

In the current Summary of Product Characteristics (SmPC) described by the European Medicines Agency (EMA) it is recommended to initiate bevacizumab not before 28 days after major surgery and after the surgical wound has fully healed. Therapy should also be withheld ≥ 28 days before elective surgery.

Haemorrhage
Overall, 4.0% of NCI-CTC (version 2.0) Grade 3 and 4 bleeding events were observed in all patients treated with Bevacizumab. In Study AVF2107g, there was no significant difference in the incidence of grade 3 and 4 bleeding events observed in IFL plus bevacizumab arm (3.1%) and IFL plus placebo arm (2.5%). A similar observation was noted in study AVF2192g; the overall incidence of grade 3 and 4 bleeding events was 5.0% in 5-FU/LV plus bevacizumab arm (5.0%) and 2.9% in 5-FU/LV plus placebo arm.
The haemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumour-associated haemorrhage (see below) and minor mucocutaneous haemorrhage.

**Tumour-associated haemorrhage** was observed in phase I and phase II bevacizumab studies. Six serious events, of which 4 had fatal outcome, were observed in patients with non-small cell lung cancer receiving bevacizumab. These events occurred suddenly and presented as major or massive haemoptysis in patients with either squamous cell histology and/or tumours located in the centre of the chest in close proximity to major blood vessels. In five of these cases, these haemorrhages were preceded by cavitation and/or necrosis of the tumour.

Tumour-associated haemorrhage was also seen rarely in other tumour types and locations, including central nervous system (CNS) bleeding in a patient with hepatoma with occult CNS metastases and continuous oozing of blood from a thigh sarcoma with necrosis. In Study AVF2107g, five haemorrhagic events in IFL plus bevacizumab arm (three rectal haemorrhages, one gastrointestinal haemorrhage and one melena) were assessed as tumour-associated haemorrhages. The addition of bevacizumab did not result in significant increase in the incidence or severity of Grade 3 or 4 haemorrhagic events in this study. In study AVF2192g, three patients in 5-FU/LV + bevacizumab arm (Arm 2) experienced Grade 3 and 4 gastrointestinal haemorrhages that were assessed as tumour-associated.

Across all bevacizumab clinical trials, **mucocutaneous haemorrhage** has been seen in 20% - 40% of patients treated with bevacizumab. These were most commonly grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. In Study AVF2107g, epistaxis was reported in 35.3% of patients receiving IFL plus bevacizumab compared with 10.2% of patients receiving IFL alone. In study AVF2192g, epistaxis (all Grade 1) was observed in 22.0% of patients receiving 5-FU/LV + bevacizumab arm (Arm 2) compared to 16.3% of patients receiving 5-FU/LV + placebo (Arm 1). There have also been less common events of minor mucocutaneous haemorrhage in other locations, such as gingival bleeding and vaginal bleeding. The risk of CNS haemorrhage in patients with CNS metastases receiving bevacizumab could not be evaluated, as patients with history or evidence upon physical examination of central nervous system (CNS) metastases were excluded from all clinical trials. The use of bevacizumab is contraindicated in patients with untreated CNS metastases. Patients with metastatic cancer of the colon or rectum might have an increased risk of tumour-associated haemorrhage.

There is no information on the safety profile of bevacizumab in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting bevacizumab treatment, as such patients were excluded from clinical trials. However, patients who developed venous thrombosis while receiving bevacizumab therapy did not appear to have increased rate of serious bleeding when treated with full dose of warfarin and bevacizumab concomitantly.

**Thrombosis/Embolism**

In study AVF2107g, 16.2% of patients receiving IFL plus placebo (Arm 1) and 19.4% of patients receiving IFL plus bevacizumab (Arm 2) experienced thromboembolic events. In study AVF2192g, the overall incidence of thromboembolic events was 18.0% in 5-FU/LV plus bevacizumab arm (Arm 2) and 18.3% in 5-FU/LV + placebo arm (Arm 1).

**Arterial Thromboembolism**

In study AVF2107g, the incidence of arterial thromboembolic events (including CVAs, MIs, TIs, and other arterial thromboembolic events) was higher in patients receiving IFL plus Bevacizumab (3.3%) compared to patients receiving IFL plus placebo (1.3%). In study AVF2192g the incidence of arterial thromboembolic events was also reported to be higher in the 5-FU/LV plus Bevacizumab arm (10.0%) compared to the 5FU/LV arm (4.8%). In five randomized trials including AVF2107g and AVF 2192g (N=1745), arterial thromboembolic events including CVAs, MIs, TIs, and other thromboembolic events...
occurred in 4.9% (49/1004) of patients treated with Bevacizumab in combination with chemotherapy compared to 2.3% (17/741) of patients treated with chemotherapy alone. In patients treated with Bevacizumab plus chemotherapy, arterial thromboembolic events led to a fatal outcome in 1.1% (11/1004). In patients treated with chemotherapy alone, a fatal outcome from arterial thromboembolic events was reported in 0.8% (6/741). CVAs (including TIs) occurred in 2.2% of patients treated with bevacizumab in combination with chemotherapy and 0.5% of patients treated with chemotherapy alone. MI occurred in 2.2% of patients treated with bevacizumab in combination with chemotherapy compared to 1.3% of patients treated with chemotherapy alone.

Bevacizumab should be permanently discontinued in patients who develop arterial thromboembolic events. 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. Patients receiving bevacizumab plus chemotherapy with a history of arterial thromboembolism and age greater than 65 years have a higher risk. Caution should be taken when treating these patients with bevacizumab.

Venous Thromboembolism
In Study AVF2107g, venous thromboembolic events, including deep venous thrombosis, pulmonary embolism and thrombophlebitis, occurred in 15.2% and 16.4% of patients in Arms 1 and 2, respectively. It could not be determined if these events were due to the patients’ underlying cancer, their cytotoxic chemotherapy, bevacizumab or other risk factors. In study AVF2192g, the incidence of venous thromboembolic events was lower in the 5-FU/LV plus bevacizumab arm compared to that in control (9.0% vs. 13.5%).

Congestive Heart Failure
In the phase III controlled clinical trial of metastatic breast cancer, there were 7 reports (3%) of congestive heart failure (CHF) in patients treated with bevacizumab compared with two (1%) seen in the control group. These events varied in severity from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF requiring hospitalisation and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose range 240 – 360mg/m²). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy. There was no information on patients with pre-existing CHF of NYHA II – IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials. Prior anthracyclines exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating Bevacizumab therapy in patients with these risk factors.

No increased incidence of CHF in patients treated with bevacizumab was observed in other Genentech-sponsored clinical trials apart from metastatic breast cancer.

Elderly Patients
In five randomized clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events including cerebrovascular accidents, transient ischaemic attacks and myocardial infarction as compared to those aged <65 years when treated with Bevacizumab (see sections 3.4 and 3.8 under Thromboembolism). No increased incidence of other Bevacizumab -related events including gastrointestinal perforation, wound healing complications, hypertension, proteinuria, haemorrhage and congestive heart failure was observed in elderly patients (>65 years) with metastatic cancer of the colon or rectum receiving Bevacizumab compared to those aged ≤ 65 years treated with bevacizumab . In study AVF2107g, 114 out of the 392 patients who received IFL plus bevacizumab were older than 65 years. A difference of greater or equal to 5% occurred only for grade 3/4 leukopenia in the elderly patients (age > 65 years) compared to those patients aged ≤ 65 years.
Physeal Development
In studies of up to 26 weeks duration in cynomolgus monkeys, bevacizumab was associated with physeal dysplasia. Physeal dysplasia was characterised primarily by thickened growth plate cartilage, subchondral bony plate formation and inhibition of vascular invasion of the growth plate. This effect occurred at doses ≥ 0.8 times the human therapeutic dose and exposure levels slightly below the expected human clinical exposure, based on average serum concentrations. It should be noted, however, that physeal dysplasia occurred only in actively growing animals with open growth plates. Because bevacizumab will most likely be administered to adult patients with closed growth plates, physeal dysplasia is not expected to occur in the clinical population.

It is not known whether bevacizumab is excreted in human milk. As maternal IgG is excreted in milk and bevacizumab could harm infant growth and development, women should be advised to discontinue nursing during bevacizumab therapy and not to breast feed for at least 6 months following the last dose of bevacizumab.
**APPENDIX 6 Serious Adverse Event form**

June 2015

**SERIOUS ADVERSE EVENT FORM**

Complete this form **WITHIN 24 HOURS** and send to IKNL clinical research department: e-mail: trialbureau@iknl.nl ; fax: +31 (0)88 – 234 6011. A follow up should be send within 2 weeks after initial report.

<table>
<thead>
<tr>
<th>Initial:</th>
<th>Patient Seqnr</th>
<th>Date of Birth (dd/mm/yyyy)</th>
<th>Gender (1=male; 2=female)</th>
<th>SAE onset date (dd/mm/yyyy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow up:</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Hospital………………………..………… Treatment arm: A / B Responsible physician: ……………………

1. EVENT:

Describe the symptoms and give severity grading acc. to CTCAE 4.0* for the main event. (*)

1=mild, 2=moderate, 3=severe, 4=life-threatening, 5=fatal

Category:  
1 = Death  
2 = Life threatening  
3 = Hospitalisation  
4 = other, specify: ………………..

Date of Admission: |__|__||__|__||__|__|__|__|

Date of Discharge: |__|__||__|__||__|__|__|__|

Date of Death: |__|__||__|__||__|__|__|__|

2. CAUSALITY / STUDY DRUG INFO:

<table>
<thead>
<tr>
<th>Study Drugs:</th>
<th>Date 1st cycle: after randomization</th>
<th>Nr. + Date last cycle:</th>
<th>Daily dose (mg):</th>
<th>Relation to treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Date surgery: |__|__||__|__||__|__|__|__|

NA

3. MEDICAL HISTORY / LABDATA:

Relevant Medical History:  Resolution:  
1 = Resolved  
2 = Recovering  
3 = Recovered with symptoms  
4 = Unchanged  
5 = Fatal  

Date resolved: |__|__||__|__||__|__|__|__|

4. CONCOMITANT MEDICATION:

Concomitant Drugs at time of event:  Relevant Labtests:

5. REPORTER:

Name + Function:  E-mail (or faxnumber):  Telephone or pager:

Date: ………………….. Signature investigator: ……………………..
Gerandomiseerde fase III studie: De rol van chirurgie van de dikke darm of de endeldarm bij patiënten met niet-resectabele synchrone metastasen zonder of met beperkte klachten van de primaire tumor: CAIRO4- studie


Uw medische situatie en de bestaande behandelingsmogelijkheden

Uw arts heeft u verteld dat u kanker van de dikke darm of endeldarm (colorectaal carcinoom) heeft. De behandeling van deze kanker is een operatie waarbij een deel van de darm met de tumor wordt verwijderd. U heeft echter darmkanker in een gevorderd stadium met uitzettingen die niet te verwijderen zijn. De behandeling van deze uitzettingen is chemotherapie (medicijnen die de kankercellen doden) in combinatie met het geneesmiddel bevacizumab (Avastin®), een medicijn dat de vorming van bloedvaten van kankercellen remt. Hierdoor worden kankercellen gehinderd in hun groei. De chemotherapie die wordt toegediend bestaat uit de middelen 5-FU of capecitabine (Xeloda®) en/of oxaliplatin (Eloxatin®) en/of irinotecan (Campto®). Het doel van deze behandeling is verlenging van het leven en verminderen van eventuele klachten ten gevolge van de ziekte. Genezing mag van deze behandeling niet verwacht worden.

Bij patiënten die zich presenteren met uitgezaaide dikke darm of endeldarm kanker is het niet duidelijk of een darmoperatie moet worden verricht of dat er gelijk moet worden begonnen met chemotherapie. Er zijn artsen die adviseren om eerst de tumor in de darm te verwijderen en hiermee later klachten te voorkomen zoals verstopping of bloeding. Maar er zijn ook artsen die adviseren om direct te starten met chemotherapie omdat de operatie alleen maar vertraging geeft voordat chemotherapie kan worden gestart. Wat de beste behandeling voor u is kan niet met zekerheid worden gesteld omdat daar nog nooit goed onderzoek naar is verricht.

Nadelen en voordelen van een operatie

Een voordeel van het verrichten van een operatie is dat de tumor dan geen klachten meer kan geven. Darmtumoren kunnen een afsluiting van de darm geven, maar ook bloedingen of perforatie veroorzaken. Dit zal niet meer gebeuren als de tumor is verwijderd. Patiënten bij wie de darmtumor is verwijderd lijken uiteindelijk een betere overleving te hebben als ze met chemotherapie worden behandeld, maar dat is niet bewezen.

Een nadeel van eerst een operatie en daarna chemotherapie is het feit dat de behandeling van de uitzettingen door de chemotherapie vertraagd wordt. U moet immers eerst herstellen van de operatie voordat u kan starten met chemotherapie. Het zou zelfs kunnen dat u ernstige complicaties krijgt als gevolg van de operatie en u daardoor niet meer toekomt aan het krijgen van chemotherapie. Hoe vaak dit gebeurt is niet bekend.
Nadelen en voordelen van eerst chemotherapie
Een voordeel van starten met chemotherapie is dat de uitzaaïngen worden behandeld zodra u start met de chemotherapie. U hoeft dus niet te wachten op een operatie en het herstel hiervan. U heeft ook geen complicaties van de operatie.
Een nadeel is echter wel dat u tijdens de chemotherapiekuren of later alsnog last kan gaan krijgen van de tumor in de darm en dat u (met spoed) geopereerd moet worden. Dit lijkt in de beperkte studies die hierover bekend zijn niet vaak het geval, maar het is onduidelijk of patiënten die niet geopereerd worden wel even lang leven als patiënten waarbij de tumor wel wordt verwijderd.

Doel van het onderzoek
In Nederland werken in de Dutch Colorectal Cancer Group (DCCG) een groot aantal ziekenhuizen samen op het terrein van klinisch onderzoek bij patiënten met dikke darmkanker. De DCCG wil met deze CAIRO4 studie onderzoeken of het beter is om bij patiënten met uitgezaaide darmkanker te starten met chemotherapie of eerst de tumor in de darm te verwijderen.

In de CAIRO4 studie willen wij onderzoek doen wat de beste behandeling is:
- Starten van chemotherapie en alleen de tumor in de darm verwijderen indien er klachten ontstaan (arm A)
- Eerst de tumor in de darm verwijderen en daarna chemotherapie starten (arm B)

In beide gevallen wordt chemotherapie (5FU of capecitabine en/of oxaliplatin en/of irinotecan) en bevacizumab toegediend. In arm A worden patiënten alleen geopereerd als er klachten ontstaan van de tumor in de darm en in arm B worden al de patiënten eerst geopereerd voordat de chemotherapie wordt gestart. Tijdens poliklinische controles middels CT scan of röntgenfoto’s wordt gecontroleerd hoe de uitzaaïningen reageren op de behandeling met chemotherapie en eventueel wordt de chemotherapie behandeling daarop aangepast.

Opzet van het onderzoek
De opzet van deze studie is daarom als volgt:
Alle patiënten worden aangemeld bij de studiecoördinator en die bepaalt door loting of gestart wordt met chemotherapie of dat eerst de operatie zal plaatsvinden van de tumor in de darm.
Na elke 3 kuren met chemotherapie en bevacizumab van elk 3 weken (totale behandelduur dus ongeveer 3 maanden) wordt het effect van de behandeling met CT scans of röntgenfoto’s gecontroleerd. Als de ziekte na of al tijdens deze 3 kuren is verslechterd, zal uw arts in overleg met u, en afhankelijk van uw conditie, een andere behandeling voorstellen. Als de ziekte na 3 kuren niet is verslechterd, zal de behandeling met chemotherapie en bevacizumab doorgaan. Mocht het zo zijn dat u direct wordt behandeld met chemotherapie (arm A) en later toch last krijgt van de tumor in de darm, door bijvoorbeeld krampen, pijn of bloeding, dan zal uw arts alsnog over gaan tot het verwijderen van de tumor. Een alternatief zou ook kunnen zijn dat er wordt besloten om te bestralen of een stent te plaatsen in de vernauwing van de darm. De beslissing voor een van deze behandelingen wordt altijd in een speciale werkgroep gemaakt waar artsen van verschillende specialismen bij elkaar komen. Uiteraard gaat dit in nauw overleg met u.

Het effect van beide behandelingsstrategieën wordt beoordeeld op de volgende belangrijke resultaten:
- de totale levensduur,
- de tijd dat de uitzaaïningen groter worden,
- de complicaties van een eventuele operatie,
De vragen kunnen alleen beantwoord worden door middel van een zogenoemd gerandomiseerde fase III onderzoek, waarbij de effecten van de beide behandelingen (dus opereren of niet) met elkaar worden vergeleken. Om een betrouwbare vergelijking te kunnen maken worden de patiënten in twee groepen verdeeld. Deze twee groepen moeten zoveel mogelijk gelijk zijn. De verdeling gebeurt zo dat niemand, ook uw behandelend arts niet, daarop invloed kan uitoefenen. Dit gebeurt door loting ("randomisatie"). Als u deelneemt aan dit onderzoek heeft u 50% kans dat u direct start met chemotherapie en 50% kans dat u een operatie zult ondergaan waarbij de tumor wordt verwijderd en daarna chemotherapie wordt gegeven. Alle chemotherapie behandelingen kunnen poliklinisch worden gegeven, maar voor de operatie moet u uiteraard in het ziekenhuis worden opgenomen.

In het totaal zullen 360 patiënten uit verschillende Nederlandse ziekenhuizen aan deze studie deelnemen.

**Weefsel onderzoek**

Bij de meeste patiënten is de diagnose van darmkanker gesteld op weefsel dat bij een darmonderzoek (scopie) is verkregen. Het is bekend dat nader onderzoek van dit weefsel gegevens kan opleveren over de kansen op succes van chemotherapie en op bijwerkingen daarvan. Wanneer er van u nog tumorweefsel in het laboratorium aanwezig is, willen wij dit graag hierop testen. Voor dit weefselonderzoek hoeft u dus geen extra ingreep te ondergaan. Dit weefselonderzoek maakt deel uit van de CAIRO4 studie, maar heeft voor u geen direct voordeel. De uitslag wordt u dan ook niet meegedeeld. De gegevens van het weefselonderzoek zullen anoniem worden verwerkt.

Voor dit weefselonderzoek wordt u apart om toestemming gevraagd. Hiervoor vindt u een aparte toestemmingsverklaring aan het einde van deze informatiebrief. Wanneer u toestemming weigert, kunt u gewoon aan de CAIRO4 studie deelnemen.

**Extra bloedonderzoeken**

Er worden nieuwe methoden uitgetest waarbij met bloedonderzoek geprobeerd wordt om het verdere verloop van darmkanker te voorspellen. Om deze methoden nader te onderzoeken wordt uw toestemming gevraagd om een paar keer tijdens het onderzoek extra buisjes bloed te mogen afnemen. De uitslagen van deze bloedonderzoeken zijn niet van belang voor uw behandeling; u hebt hier dus geen direct voordeel van. De resultaten ervan worden u niet meegedeeld. Mogelijk dragen de resultaten wel bij aan een betere behandeling van toekomstige patiënten.

Het gaat om twee verschillende bloedonderzoeken. Beide onderzoeken onderzoeken de rol van circulerende factoren in het bloed die mogelijk een voorspellende waarde hebben voor het aanslaan van de behandeling. De bloedmonsters voor deze extra onderzoeken worden tegelijk afgenomen met bloedmonsters die in het kader van de behandeling worden afgenomen. Voor deze extra bloedonderzoeken wordt u apart om toestemming gevraagd. Hiervoor vindt u een aparte toestemmingsverklaring aan het einde van deze informatiebrief. Wanneer u toestemming weigert, kunt u gewoon aan de CAIRO4 studie deelnemen.

**Onderzoek en behandelingenplan**

Voorafgaande aan de studie zal door lichamelijk onderzoek, bloedonderzoek en een CT scan of röntgenfoto’s uw medische situatie worden gecontroleerd. Omdat chemotherapie een schadelijk effect op een ongeboren kind kan hebben, wordt bij vrouwen in de vruchtbare leeftijd een zwangerschapstest gedaan. Wanneer bij deze vóóronderzoeken afwijkingen aan
het licht komen die deelname aan het onderzoek tot een te groot risico maken, kunt u helaas niet deelnemen. In dat geval zal uw arts met u bespreken wat de beste behandeling voor u is. Als u wel aan alle voorwaarden tot deelname aan de CAIRO4 studie voldoet, zal u gevraagd worden om uw toestemming tot deelname schriftelijk te bevestigen door het zetten van uw handtekening op het toestemmingsformulier.

De duur van elke kuur bedraagt steeds 3 weken. Voor aanvang van elke kuur zal uw arts vragen naar eventuele klachten. Ook wordt een lichamelijk onderzoek en een bloedonderzoek gedaan. Als u last heeft van ernstige bijwerkingen kan uw arts de dosis van de medicijnen verlagen of de behandeling tijdelijk of definitief stop zetten. Het effect van de behandeling zal elke 9 weken (elke 3 kuren) met CT scans of röntgenfoto’s worden onderzocht. Ook als u niet meer met medicijnen wordt behandeld, zal u tenminste eenmaal per 3 maanden op de polikliniek worden gecontroleerd.

Om gegevens te krijgen over hoe u zich voelt en hoe u de behandeling ervaart, vragen wij u om regelmatig een vragenlijst in te vullen waarmee de kwaliteit van leven gemeten wordt. Ook deze gegevens worden anoniem verwerkt. Het is wel belangrijk dat u boven elk formulier steeds uw initialen, geboortedatum, en de datum van invullen vermeldt.

Darmoperatie
Indien u wordt geloot in arm B, zal binnen 4 weken een operatie plaatsvinden. Uw chirurg zal met u bespreken wat de mogelijkheden zijn. Dit is afhankelijk van de grootte en plaats van de tumor in de darm. Meestal kan het stuk darm waar de tumor zich in bevindt worden verwijderd en kunnen de restanten van de darm aan elkaar worden gezet (anastomose). Soms lukt dit niet of is dit zeer risicovol en moet een blijvend stoma of uitlaat worden aangelegd. Een enkele keer blijkt tijdens de operatie dat het niet mogelijk is om de tumor te verwijderen. Ook dan wordt soms een stoma aangelegd of kan een omloopje worden gemaakt.

Het effect van de behandeling zal elke 9 weken (elke 3 kuren) met CT scans of röntgenfoto’s worden onderzocht. Ook als u niet meer met medicijnen wordt behandeld, zal u tenminste eenmaal per 3 maanden op de polikliniek worden gecontroleerd.

Bij de meeste patiënten zal de tumor worden verwijderd door een buikoperatie (laparotomie), maar in sommige situaties kan dit ook met een kijkoperatie (laparoscopie). Uw chirurg bespreekt met u wat de voorkeur heeft in elk individueel geval. Elke operatie heeft kans op algemene complicaties zoals infecties van de longen, urinewegen of de wond, maar ook kunnen trombose of longembolieën voorkomen. Als bij de darmoperatie de darmen weer op elkaar aangesloten zijn kan dit bij 5-10% van de patiënten gepaard gaan met een naadlekkage. Het kan gebeuren dat u daarvoor opnieuw moet worden geopereerd en dat alsnog een stoma moet worden aangelegd. Soms overlijden patiënten aan de gevolgen van complicaties. De kans dat complicaties optreden is afhankelijk van vele factoren zoals leeftijd en conditie van de patiënt.

Ook in arm A zal bij sommige of meerdere patiënten uiteindelijk de tumor in de darm worden verwijderd. Hoeveel patiënten uiteindelijk een operatie zullen (moeten) ondergaan in deze groep is onbekend en onderdeel van deze studie.

Bijwerkingen
De chemotherapie en bevacizumab die u krijgt in deze studie zijn standaard behandelingen, die ook worden gegeven aan patiënten met uitzonderingen die niet aan deze studie meedoen. Uw arts zal u voorlichten over de verschillende bijwerkingen van de medicijnen die u krijgt toegediend. Het is niet zo dat alle genoemde bijwerkingen bij u zullen optreden. Ook kunnen er altijd nieuwe, nog onbekende bijwerkingen optreden. Mochten er nieuwe gegevens naar voren komen die van belang zijn voor uw verdere deelname aan de CAIRO4 studie, dan zal uw arts u daarover informeren.

Zwangerschap
Zowel mannen als vrouwen kunnen mee doen aan dit onderzoek. Alle patiënten dienen indien van toepassing een doeltreffend anticonceptiemiddel te gebruiken. Indien u hierover verdere vragen heeft dient u deze met uw arts te bespreken.

DCCG CAIRO4 study, protocol version 1.6 09-03-2017
**Privacy**

Onderzoeksgevens kunnen slechts door daartoe geautoriseerde en gekwalificeerde medewerkers worden ingezien. Onderzoeksgevens zullen worden gehanteerd met inachtneming van de Wet Bescherming Persoonsgegevens. Alle medische gegevens die tijdens deze studie worden verzameld zullen niet worden voorzien van uw persoonsgegevens, maar van een codenummer. Alleen uw behandeldend arts kan het verband leggen tussen uw persoonsgegevens en de code. De persoonsgegevens zullen dus niet gebruikt worden op studiedocumentatie, in rapporten of publicaties van dit onderzoek. Uw medische gegevens zullen bewaard worden gedurende 15 jaar na afloop van het onderzoek. Uw huisarts zal worden ingelicht over de ingestelde behandeling.

**Weigering van deelname voor en tijdens het onderzoek**

U bent geheel vrij om wel of niet aan het onderzoek mee te doen. Als u weigert, hoeft u geen reden op te geven. Ook als u nu toestemming geeft, kunt u die toestemming op ieder moment zonder opgave van redenen weer intrekken. U zult dan op de best mogelijke wijze begeleid worden en uw arts zal met u bespreken welke behandeling wordt gekozen. Wat u ook besluit, het zal geen verandering brengen in de kwaliteit van de verzorging en begeleiding van uzelf en uw familie.

**Toetsing van het onderzoek en schadeverzekering**

Aan u is gevraagd om deel te nemen aan een medisch wetenschappelijk onderzoek. Dit onderzoek is getoetst door een erkende medisch-ethische toetsingscommissie. Deze commissie, bestaande uit onafhankelijke deskundigen en leken, heeft geoordeeld, dat het verantwoord is om de medewerking van patiënten te vragen voor dit onderzoek. Verder is het onderzoek goedgekeurd door de Raad van Bestuur van het ziekenhuis waar u onder behandeling bent. De voor dit onderzoek internationaal vastgestelde richtlijnen zullen nauwkeurig in acht worden genomen. Er is een schadeverzekering afgesloten voor de proefpersonen die meedoen aan dit wetenschappelijk onderzoek. Meer informatie over de verzekering vindt u in de bijlage "informatie schadeverzekering", verderop in deze brief.

**Nadere informatie**

Als u nog vragen over dit onderzoek heeft kunt u die voorleggen aan de verantwoordelijke onderzoeker in het [naam ziekenhuis], [naam arts], internist- oncoloog, telefoon [telefoon direct]. Buiten kantooruren kunt u contact opnemen met de dienstdoende specialist via het algemene nummer van het ziekenhuis [telefoon algemeen].

Voor vragen die niet door uw eigen arts beantwoord kunnen worden kunt u contact opnemen met de hoofdontonverters van de CAIRO4 studie, Prof. Dr. J.H.W. de Wilt, afdeling Chirurgie, UMC st. Radboud te Nijmegen, tel. 024-3617365 of Prof. Dr. M. Koopman, afdeling Medische Oncologie, UMCU te Utrecht, tel. 088-7556230.

Ook kunt u voor vragen over het onderzoek Dr. J Bonenkamp, tel. 024-3617365, benaderen. Hij is de onafhankelijk arts van dit onderzoek. Zijn rol bij dit onderzoek is om patiënten te adviseren wanneer zij na overleg met hun eigen arts of de hoofondonkeren met vragen blijven zitten die betrekking hebben op dit onderzoek.

Als u niet tevreden bent over het onderzoek of de behandeling kunt u terecht bij de onafhankelijke klachtencommissie van uw ziekenhuis. Het secretariaat van de afdeling klachtenbehandeling is te bereiken op telefoonnummer [xxxxxxxxx].

Tenslotte verwijzen wij u voor verdere informatie graag naar de brochure "Algemene informatie voor de proefpersoon" van het ministerie van VWS die wij voor u hebben toegevoegd.
TOESTEMMINGSVERKLARING voor het onderzoek:  (version 1.4 dd 19-12-2014)

Gerandomiseerde fase III studie: De rol van chirurgie van de dikke darm of de endeldarm bij patiënten met niet-resectabele synchrone metastasen zonder of met beperkte klachten van de primaire tumor: CAIRO4- studie

- Mijn behandeldend arts, ........................................... heeft mij uitgelegd wat de aard, duur, doel en risico's van bovenvermeld onderzoek zijn. Ik heb de schriftelijke informatie gelezen en de gelegenheid gehad om vragen te stellen. Ik heb redelijk de tijd gehad om een en ander te overdenken. Ik begrijp wat de aard en het doel van dit onderzoek is.

- Ik begrijp, dat deelname aan het onderzoek vrijwillig is en dat ik mij op elk moment zonder opgave van redenen uit dit onderzoek kan terugtrekken. Als ik dit doe, zal dit geen enkele invloed hebben op de voor mijn ziekte gebruikelijke behandeling en op de zorg van mijn behandendend arts.

- Ik weet, dat voor dit onderzoek relevante medische gegevens over mij gebruikt worden voor wetenschappelijk onderzoek en eventueel gepubliceerd worden. Hiermee stem ik in mits mijn privacy gewaarborgd wordt.

- Mijn behandendend arts mag ter controle van de verzamelde gegevens inzage in relevante delen van mijn medische dossier verstrekken aan daartoe geautoriseerde personen en autoriteiten, op voorwaarde dat hij/zij er voor instaat, dat de vertrouwelijkheid van deze gegevens niet zal en kan worden geschonden door deze personen.

- Ik geef toestemming om mijn medische gegevens te bewaren tot 15 jaar na afloop van het onderzoek.

- Ik geef toestemming om mijn huisarts in te lichten over mijn deelname aan dit onderzoek.

- Ik verklaar bekend te zijn en akkoord te gaan met de belangrijkste elementen van de verzekeringsvoorwaarden, zoals die voorafgaand aan deze verklaring staan weergegeven.

- Ik geef hierbij uit vrije wil mijn toestemming om deel te nemen aan dit onderzoek.

Naam patiënt: ________________________
Handtekening: ________________________________________

Datum: ____________ 201__.  

Ik bevestig hierbij, dat ik aan patiënt boven aangegeven onderzoek heb uitgelegd.

Naam behandendend arts: ________________________
Handtekening: ________________________________________

Datum: ____________ 201__.  

DCCG CAIRO4 study, protocol version 1.6  09-03-2017
Gerandomiseerde fase III studie: De rol van chirurgie van de dikke darm of de endeldarm bij patiënten met niet- resectabele synchrone metastasen zonder of met beperkte klachten van de primaire tumor: CAIRO4–studie

Kruist u alstublieft dat vakje aan dat van toepassing is op uw besluit over deelname aan de extra bloedonderzoeken en ondertekent u daarna de verklaring:

- Ik geef WEL toestemming voor het apart opslaan van het extra tumorweefsel voor onderzoek zoals in de schriftelijke informatie omschreven en doe dat uit vrije wil.

- Ik geef WEL toestemming voor het afnemen van extra buisjes bloed voor onderzoek zoals in de schriftelijke informatie omschreven en doe dat uit vrije wil.
  - Ik begrijp dat de resultaten van dit onderzoek in de toekomst gebruikt kunnen worden en dat deze onderzoeken voor mijzelf niet van direct belang zijn. Ik word niet geïnformeerd over de uitslagen.
  - Ik begrijp dat mijn weefsel en bloed hiervoor naar laboratoria buiten mijn eigen ziekenhuis wordt opgestuurd. Ik begrijp dat het wel of niet afstaan van weefsel en bloed geen invloed heeft op mijn deelname aan de studie met medicijnen tegen darmkanker.
  - Ik weet, dat voor deze onderzoeken relevante medische gegevens over mij gebruikt worden voor wetenschappelijk onderzoek en eventueel gepubliceerd worden. Hiermee stem ik in mits mijn privacy gewaarborgd wordt.
  - Mijn behandelend arts mag ter controle van de verzamelde gegevens inzage in relevante delen van mijn medische dossier verstrekken aan daartoe geautoriseerde personen en autoriteiten, op voorwaarde dat hij/zij er voor instaat, dat de vertrouwelijkheid van deze gegevens niet zal en kan worden geschonden door deze personen.

- Ik geef GEEN toestemming voor het doen van het weefselonderzoek en de extra bloedonderzoeken.
  - Ik weet dat ik toch aan de studie mee kan doen.

Naam patiënt: ___________________________ Handtekening: ___________________________

Datum: ____________ 201_.

Ik bevestig hierbij, dat ik aan patiënt boven aangegeven onderzoek heb uitgelegd.

Naam behandeld arts: ___________________________ Handtekening: ___________________________

Datum: ____________ 201_.
INFORMATIE SCHADEVERZEKERING

Gerandomiseerde fase III studie: De rol van chirurgie van het colon of rectum bij patiënten met niet-resectabele synchrone metastasen zonder of met beperkte klachten van de primaire tumor: CAIRO4– studie

Voor de deelnemers aan dit onderzoek is een verzekering afgesloten. Deze verzekering dekt schade door dood of letsel die het gevolg is van deelname aan het onderzoek, en die zich gedurende de deelname aan het onderzoek openbaart, of binnen vier jaar na beëindiging van de deelname aan het onderzoek. De schade wordt geacht zich te hebben geopenbaard wanneer deze bij de verzekerdaar is gemeld.

In geval van schade kunt u zich direct wenden tot de verzekerdaar. De verzekerdaar van het onderzoek is:

<table>
<thead>
<tr>
<th>Naam:</th>
<th>HDI-Gerling Verzekeringen NV</th>
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<tbody>
<tr>
<td>Adres:</td>
<td>Postbus 925, 3000 AX Rotterdam</td>
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<tr>
<td>Telefoonnummer:</td>
<td>020 – 5650 654</td>
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<td>Contactpersoon:</td>
<td>de heer M. Wijnsma</td>
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<td>Polisnummer :</td>
<td>300036393</td>
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<td>Verzekeringnemer :</td>
<td>Stichting D.C.C.G.</td>
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<td>Verzekerd onderzoek :</td>
<td>Cairo 4</td>
</tr>
</tbody>
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De verzekerdaar biedt een maximum dekking van 450.000 euro per proefpersoon en 3.500.000 voor het gehele onderzoek. De dekking van specifieke schades en kosten is verder tot bepaalde bedragen beperkt. Dit is opgenomen in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen. Informatie hierover kunt u vinden op de website van de Centrale Commissie Mensgebonden Onderzoek: www.ccmo.nl.

Voor deze verzekerdaar gelden een aantal uitsluitingen. De verzekerdaar dekt niet:
1. schade waarvan op grond van de aard van het onderzoek zeker of nagenoeg zeker was dat deze zich zou voordoen;
2. schade die het gevolg is van het uitblijven van een vermindering van de gezondheidsproblemen van de verzekerde, dan wel het gevolg is van een verdere verslechtering van de gezondheidsproblemen van de verzekerde, indien de deelname van de verzekerde aan het onderzoek geschiedt in het kader van de behandeling van deze gezondheidsproblemen;
3. schade waarvan aannemelijk is dat die zich ook zou hebben geopenbaard wanneer de verzekerde niet aan het onderzoek zou hebben deelgenomen;
4. in het geval verzekerde deelneemt aan een vergelijkend onderzoek zoals bedoeld in artikel 4, 2e lid van het Besluit en aannemelijk is dat de schade het gevolg is van de in dat lid bedoelde reeds toegepaste behandeling waaraan de proefpersoon wordt onderworpen;
5. schade die zich bij een nakomeling van de verzekerde openbaart als gevolg van een nadelige inwerking van het onderzoek op de verzekerde of de nakomeling;
6. schade veroorzaakt, bevorderd of verergerd doordat de verzekerde zich niet of niet volledig aan de voorschriften en instructies van de met de uitvoering van het onderzoek belaste personen heeft gehouden.