CLINICAL STUDY PROTOCOL

AIO CRC 0306/FIRE-3
Randomized study
to investigate the efficacy of FOLFIRI
in combination with Cetuximab vs. Bevacizumab in the
first-line treatment of metastatic colorectal
cancer

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Confidentiality notice

The content of the clinical study protocol and the case report forms shall be treated confidentially and may not be disclosed to unauthorized third parties either verbally or in writing without consent from the director of the study.
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LIST OF ABBREVIATIONS

5-FU  5-Fluorouracil  
ALAT  alanine aminotransferase  
AMG  Arzneimittelgesetz [Medicines Act]  
ASAT  aspartate aminotransferase  
AP  alkaline phosphatase  
ASA  acetyl salicylic acid  
CEA  carcinoembryonic antigen  
CR  complete remission  
CRF  case report form  
CT  computed tomography  
ECOG  Eastern Cooperative Oncology Group  
EGF(R)  epidermal growth factor (receptor)  
ECG  electrocardiography  
GCP-V  GCP Ordinance dated August 9, 2004, last amended with Article 4 of the Ordinance dated November 3, 2006  
HFS  hand-foot syndrome  
BW  body weight  
NCI CTCAE  National Cancer Institute Common Terminology Criteria for Adverse Events  
ULN  upper limit of normal  
OR  overall response  
OS  overall survival  
PD  progressive disease  
PFS  progression-free survival  
PR  partial remission  
PTT  prothrombin time  
RECIST  response to treatment in solid tumors (response criteria)  
TFS  time to failure of strategy  
TTP  time to progression
**STUDY SYNOPSIS**

<table>
<thead>
<tr>
<th><strong>Randomized study to investigate the efficacy of FOLFIRI in combination with Cetuximab vs. Bevacizumab in the first-line treatment of metastatic colorectal cancer</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Type of study</strong></td>
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<td><strong>Director of the study</strong></td>
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<td><strong>Study objectives</strong></td>
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<td><strong>Number of patients</strong></td>
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<td><strong>Inclusion criteria</strong></td>
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### Eligibility Criteria

- age: 18-75 years
- inpatient or outpatient treatment
- estimated life expectancy >3 months
- presence of at least one measurable reference lesion according to the RECIST criteria.
- Evaluation of the tumor manifestation 2 weeks or less before study enrolment
- effective contraception for men and women if contraception is possible
- white blood cell count ≥3.0 x 10^9/L with neutrophils ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, hemoglobin ≥5.6 mmol/L (corresponding to 9 g/dL)
- serum bilirubin ≤1.5 x upper limit of normal
- ALAT and ASAT ≤2.5 x upper limit of normal. ALAT and ASAT ≤5 x upper limit of normal in the presence of liver metastases
- serum creatinine ≤1.5 x upper limit of normal
- surgery must have been performed more than 4 weeks, fine needle biopsy more than 1 week before study enrolment. Surgical wounds must have healed completely. No need for major surgery during the course of the study is expected, except a possible resection of liver metastases. If there is an option for secondary curative surgery, Bevacizumab should be discontinued 6 to 8 weeks and Cetuximab approximately 2 weeks before the surgery
- relevant toxicities of prior therapies must have subsided

### Exclusion Criteria

- demonstrated KRAS mutation
- prior anti EGFR-targeted therapy
- prior Bevacizumab treatment
- prior chemotherapy of the colorectal cancer, except for adjuvant therapy completed at least 6 months before study enrolment
- experimental drug treatment within 30 days of enrolment
- known hypersensitivity to any component of the investigational drug
- pregnancy (exclusion confirmed with beta-hCG test) or lactation
- pre-existing or clinically suspected brain metastases
- clinically relevant coronary heart disease, myocardial infarction within the past 12 months or risk of uncontrolled arrhythmia
- acute or subacute intestinal obstruction or history of chronic inflammatory disease or chronic diarrhea
- symptomatic peritoneal carcinomatosis
- serious, non-healing wounds, ulcers or bone fractures
- uncontrolled hypertension
- pronounced proteinuria (nephrotic syndrome)
- arterial thromboembolisms or severe hemorrhages within 6 months before study enrolment (except bleeding tumor before tumor resection surgery)
- hemorrhagic diathesis or thrombotic tendency
- therapeutic anticoagulation (Marcumar therapy, heparinization affecting the PTT)
- pre-existing DPD deficiency (no special screening required)
- pre-existing glucuronidation defect (Gilbert-Meulengracht syndrome) (no special screening required)
- history of secondary malignancy within the past 5 years, except for basalioma or carcinoma in situ of the cervix uteri, if treated with curative intent
- pre-existing alcohol or drug abuse
- medical or mental impairments which make it impossible to obtain the patient’s consent or to conduct the study
- a significant concomitant medical condition which the clinical investigator believes precludes the patient from enrolling in the study
- absent or limited legal competence

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Arm A:</th>
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<tbody>
<tr>
<td></td>
<td>1 cycle consisting of:</td>
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<tr>
<td></td>
<td><strong>FOLFIRI regimen</strong>, every 2 weeks</td>
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<tr>
<td></td>
<td>Irinotecan 180 mg/m² i.v., 30 - 90 min</td>
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<tr>
<td></td>
<td>Folinic acid (racemic) 400 mg/m² i.v., 120 min</td>
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<td></td>
<td>5-FU 400 mg/m² bolus</td>
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<tr>
<td></td>
<td>5-FU 2400 mg/m² i.v. over a period of 46 h</td>
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<tr>
<td></td>
<td>Cetuximab initially 400mg/m² as 120-min infusion, followed by 250 mg/m² i.v. as 60-min infusion each</td>
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</tbody>
</table>

Arm B:
1 cycle consisting of:

- **FOLFIRI regimen**, every 2 weeks
  - Irinotecan 180 mg/m² i.v., 30 - 90 min  
  - Folinic acid (racemic) 400 mg/m² i.v., 120 min  
  - 5-FU 400 mg/m² bolus  
  - 5-FU 2400 mg/m² i.v. over a period of 46 h  
  - Bevacizumab 5 mg/kg of BW i.v. for 30 to 90* minutes

* The 1st administration is given over a period of 90 min, if tolerated well, the second administration over a period of 60 min and the further administrations over a period of 30 min each

Continuation of the treatment until:

- the tumor progresses
- unacceptable toxicity is observed
- confirmed CR is achieved
- a status for surgical treatment is achieved
- the patient asks to end the treatment
- the treating physician decides that the therapy should be withdrawn

<table>
<thead>
<tr>
<th>Examinations:</th>
<th>Accompanying translational research project</th>
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<tbody>
<tr>
<td>One-time collection of a 10 mL PAXgene blood DNA sample (corresponding tubes are provided by the LMU). Blood is collected from all patients enrolled in the study after amendment 3 entered into effect during the pre-treatment phase. For all patients who were already enrolled in the study before amendment 3 entered into effect, the blood sample is collected during the next scheduled visit. <strong>The written consent (signature of the patient information and declaration of consent, version 2.0 dated 01-25-2011) is required for the one-time blood collection.</strong></td>
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<tr>
<td>Within 14 days before the therapy start:</td>
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<tr>
<td>- measurement of the reference lesions according to the RECIST criteria (CT scan of the abdomen/pelvis, chest X-ray in 2 planes if necessary, additional chest CT in case of suspected lung metastases), bone scintigraphy/X-ray in case of suspected</td>
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</table>
bone metastases, brain CT in case of suspected CNS metastases

**Within 7 days before the therapy start:**

- written declaration of consent
- medical history
- comorbidities and medications
- physical examination including measurement of height, body weight and vital signs (blood pressure and heart rate)
- evaluation of the performance status (ECOG scale)
- ECG
- pre-existing symptoms (NCI-CTCAE V3.0)
- complete blood count (white blood cells, neutrophil granulocytes, platelets, red blood cells, hemoglobin)
- clinical chemistry (bilirubin, creatinine, ALAT, ASAT, alkaline phosphatase, potassium, calcium, magnesium)
- INR
- pregnancy test (serum or urine) for women of child-bearing potential
- urine dipstick analysis, 24-hour urine test for proteinuria of >1+ or ≥30 mg/dL

**Examinations during chemotherapy and antibody therapy (before every cycle):**

- physical examination, vital signs (blood pressure, heart rate) body weight
- complete blood count (white blood cells, neutrophil granulocytes, platelets, red blood cells, hemoglobin)
- clinical chemistry (bilirubin, creatinine, ALAT, ASAT, alkaline phosphatase, potassium, calcium, magnesium)
- documentation of clinical symptoms and toxicities (NCI-CTCAE V3.0), concurrent medication
- ECOG performance status
- urine dipstick analysis, 24-hour urine test for proteinuria of >1+ of > 30mg/dL
**Tumor assessment**

- The tumor is assessed according to the RECIST criteria after the completion of cycle 3 (after 6 weeks of treatment) and cycle 6 (after 12 weeks of treatment) and then after every 10 weeks of treatment (CT scan of the abdomen/pelvis, chest X-ray in 2 planes, if necessary, additional chest CT in case of suspected lung metastases). It is intended to have the imaging results evaluated additionally by independent experts. Moreover, the other tumor manifestations as well as the tumor markers CEA and/or CA 19-9 are determined and documented.

**Final examinations**

The following examinations are conducted at the end of the treatment (i.e. when the tumor progresses or if the treatment is withdrawn prematurely):

- physical examination including ECOG performance status, body weight
- complete blood count (white blood cells, neutrophil granulocytes, platelets, red blood cells, hemoglobin)
- clinical chemistry (bilirubin, creatinine, ALAT, ASAT, alkaline phosphatase, potassium, calcium, magnesium)
- ECG
- documentation of clinical symptoms and toxicities (NCI-CTCAE V3.0)
- measurement of the reference lesion (RECIST) (CT scan of the abdomen/pelvis, chest X-ray in 2 planes, if necessary, additional chest CT in case of suspected lung metastases), bone scintigraphy/X-ray if necessary, in case of bone metastases and brain CT in case of CNS metastases
- determination and documentation of the remaining tumor manifestations

**Follow-up**

Cancer follow-up care is provided every 3 months after completion of the treatment (until the subject dies or for a maximum of 5 years):
- survival/disease status, ECOG performance status
- measurement of the reference lesion (RECIST) (CT scan of the abdomen/pelvis, chest X-ray in 2 planes, if necessary, additional chest CT in case of suspected lung metastases), determination and documentation of the remaining tumor manifestations as long as no confirmed progression has been documented under/after 1st-line therapy
- documentation of relevant protracted toxicity
- documentation of the follow-up therapy

**Statistical aspects:**

This is a randomized phase II study aimed at investigating whether the combination of FOLFIRI plus Cetuximab is more effective than the combination of FOLFIRI plus Bevacizumab with respect to the surrogate endpoint tumor remission rate (CR+PR). A case number of 284 subjects eligible for evaluation is required in each arm to demonstrate an increase in the response rate from 50% to 62% in the Cetuximab arm with a one-sided alpha error of 2.5% and a power of 80%.

The primary target criterion is analyzed based on the intention-to-treat collective using Fisher’s exact test.
## EXAMINATION SCHEDULE

<table>
<thead>
<tr>
<th></th>
<th>Before the therapy start (within 7 days)</th>
<th>Before each cycle</th>
<th>Restaging: after 6 and 12 weeks of treatment, and then always after 10 weeks of treatment</th>
<th>End of therapy</th>
<th>Follow-up every 3 months (until the subject dies or for a maximum of 5 years)</th>
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<tbody>
<tr>
<td>Declaration of consent</td>
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<tr>
<td>Inclusion and exclusion criteria</td>
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<tr>
<td>Accompanying translational research project</td>
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<td>one-time blood sampling</td>
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<td>Medical history</td>
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<td>Physical examination</td>
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<td>Body weight</td>
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<td>Height</td>
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<td>Vital signs (blood pressure, heart rate)</td>
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<td>ECOG performance status</td>
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<td>ECG</td>
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<tr>
<td>Measurement of the reference lesion (RECIST) (CT scan of the abdomen/pelvis, chest X-ray in 2 planes, if necessary)</td>
<td>X¹</td>
<td>X</td>
<td>X</td>
<td>X⁶</td>
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<tr>
<td>Bone scintigraphy/X-ray in case of suspected bone metastases</td>
<td>X¹</td>
<td>X</td>
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<td>Brain CT in case of suspected CNS metastases</td>
<td>X¹</td>
<td>X</td>
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<tr>
<td>Blood count²</td>
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<td>Clinical chemistry³</td>
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<td>INR</td>
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<td>CEA and/or CA 19-9 markers</td>
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<tr>
<td>Urine dipstick test⁴</td>
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<tr>
<td>Pregnancy test (serum or urine) for women of child-bearing potential</td>
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<td>Relevant concomitant therapy</td>
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<tr>
<td>Clinical symptoms/toxicity (NCI-CTCAE V3.0)</td>
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<tr>
<td>Follow-up therapy</td>
<td>X</td>
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</table>

1: within 14 days before the therapy start, additional chest CT in case of suspected lung metastases
2: white blood cells, red blood cells, platelets, hemoglobin, neutrophil granulocytes
3: bilirubin, creatinine, ALAT, ASAT, AP, INR, potassium, calcium, magnesium
4: in case of detected protein of >30mg or >1+ in the urine dipstick analysis: quantitative protein determination in the 24-hour urine sample
5: survival/disease status only
6: as long as no confirmed progression under/after 1st-line therapy has been documented
7: one-time blood sampling (for the timing of the examination see synopsis, number 7.1 and 7.2). **The written consent (signature of the patient information and declaration of consent, version 2.0 dated 01-25-2011 and version 3.0 dated 04-20-2012, respectively) is required for the one-time blood sampling.**
SIGNATURES

1.1 GENERAL SIGNATURES

EudraCT no.: 2006-004030-32

Sponsor’s protocol code number: AIO CRC 0306

This is to confirm that the study protocol, the case report forms and the annexes contain all the information and provisions required for the conduct of the study and that the study will be conducted and documented in full compliance with the content of this study protocol and that the legal provisions and described covenants will be complied with.

[handwritten:] Munich, 04-24-2012
Place, date

[signature]
Director of the clinical study
and representative of the sponsor
Prof. Dr. V. Heinemann

[handwritten:] Leverkusen, 04-25-2012
Place, date

[signature]
ClinAssess GmbH
Dr. B. Deuβ
1.2 Signatures from the study site

Site no.:__________

I have carefully read and reviewed the study protocol including amendment 5; I agree with the requirements and conditions set forth therein and consent to the conduct of the study in accordance with the principles of Good Clinical Practice (GCP) and the requirements from the regulatory authorities with respect to the source data verification and the auditing/inspection of the study.

I agree to use the study material, including the medication, exclusively as provided in the study protocol. I understand that any changes of the study protocol may only be implemented in the format of amendments requiring the written approval from the director of the clinical study.

I know that any protocol violation can result in the premature withdrawal of the study.

I agree to report any clinical adverse event considered serious to the director of the study within one business day, irrespective of whether or not it is deemed to be therapy-related.

________________________________________  ______________________________
Place, date                                Clinical investigator in charge

________________________________________
Name in printed letters

Seal of the hospital/practice
2 SCIENTIFIC BACKGROUND AND RATIONALE

2.1 INTRODUCTION

Colorectal cancer (CRC) ranks number two among cancer-related deaths in western industrialized nations. This tumor entity ranks third with respect to incidence. More than 60,000 patients are diagnosed with the disease each year in Germany. The individual life-time risk is approximately 4 to 6%. In 90% of cases, colorectal cancer is diagnosed after age 50. From this age onward, the incidence and mortality rates double for each following decade of life. At the time of diagnosis, 38% of patients are already diagnosed with a regional spread and distant regions are affected in 25% of cases. Complete surgical resection of the primary tumor during early stages of the disease represents the only curative treatment. The 5-year survival rate is close to 80-90% after curative resection and adjuvant follow-up therapy, if applicable. The life expectancy is determined by the occurrence of local tumor relapses (uncommon) as well as distant metastases (common). 85% are diagnosed within the first 2½ years of the surgery.

For many years, the standard of care involved the administration of 5-Fluorouracil (5-FU) combined with an effect-enhancing biomodulator, folinic acid (FA). A meta-analysis of 9 studies with 1381 patients revealed that the response rate doubled from 11% to 23% as a result of biochemical modulation of 5-FU with folinic acid (FA). However, no extension of the median survival was achieved. An update of this meta-analysis with now 19 studies and 3300 patients, however, confirmed a statistically significant moderate survival benefit (median 11.5 vs. 10.5 months). Compared with the bolus application of 5-FU, the continuous 5-FU administration proved to be more effective with respect to the response rate (22% vs. 14%, p=0.0002) and additionally achieved a minor yet significant survival benefit (HR = 0.88; 95% CI, 0.78-0.99; p=0.04).

Within the scope of an EORTC study, the bolus application of 5-FU (FU 425 mg/m² plus FA 20 mg/m², day 1-5, Q 4 weeks) was compared with the high-dose infusional 5-FU administration (2,600 mg/m² as 24 h infusion weekly) alone or in combination with FA 500 mg/m². Survival was the primary objective of this study conducted in 497 patients. No significant survival benefit was achieved with any of the mentioned regimens (bolus FUFA: 11.1 months vs. FU24h 13.0 months vs. FU24h + FA 13.7 months). However, it was demonstrated that the progression-free survival was considerably longer under the FU24h+FA regimen compared to the FU24h or the bolus regimens (5.6 vs. 4.1 vs. 4.0 months) and it was therefore also used as reference therapy in the follow-up studies. Furthermore, it was determined that the FU24h application was less...
toxic than the bolus regimen\textsuperscript{10}. Finally, these results are confirmed with a randomized study in which the de Gramont regimen was compared with the Mayo regimen. A significant extension of the PFS from 5.5 months to 6.9 months (p=0.001) was again observed with the use of the infusional de Gramont regimen, while the trend of survival was only minor (15.5 vs. 14.2 months)\textsuperscript{11}.

In recent years, a considerable improvement of the response rates as well as the median survival was achieved in patients with advanced CRC with the use of novel chemotherapeutic agents from the group of topoisomerase inhibitors (Irinotecan) and platinum derivatives (Oxaliplatin). While the median survival remained limited to approximately 12 months with the FUFA-based regimens alone, the recent sequential use of these newer substances achieved survival times in excess of 20 months\textsuperscript{12}. It is impossible to decide which therapy sequence should be preferred, FOLFIRI followed by FOLFOX or vice versa, since the sequences are equally effective in terms of the survival (21.5 months vs. 20.6 months). However, the lower rate of grade 3-4 toxicities (53\% vs. 74\%, p=0.001) compared with the FOLFOX regimen as well as the higher 2\textsuperscript{nd}-line activity of FOLFOX might help endorse the primary use of FOLFOX (SD+PR = 63\% vs. 35\%)\textsuperscript{13}. Furthermore, FOLFOX is increasingly already being used in the adjuvant therapy and primary palliative therapy with FOLFIRI may therefore be a sensible option.

The objective is now to considerably extend the patient’s survival and preserve his/her quality of life with the further continuous improvement of the therapeutic strategies such that the therapy and prognosis of metastatic colorectal cancer ultimately start resembling chronic diseases including diabetes, asthma or rheumatoid arthritis. Molecular biological diagnostic advances achieved in recent years and the resulting knowledge of cell biological characteristics involving tumor development and growth along with the associated signal cascades meanwhile made it possible to develop specific therapeutic substances which directly target these molecular processes. The introduction of these so-called “biologics” into the therapy of metastatic CRC might help get one significant step closer to the objective mentioned above. In so doing, the current focus is on strategies that

1) inhibit the new formation of tumor blood vessels by means of blocking antibodies against the vascular endothelial growth factor (VEGF) through which cancer cells induce angiogenesis;
2) block the receptor of the epidermal growth factor receptor (EGFR) which is overexpressed in the majority of CRC cases by means of antibodies or inhibit its receptor tyrosine kinase through so-called “small molecules”.

With respect to the two principles of action, the first approved medications which have already been evaluated in major phase III studies in combination with chemotherapy are meanwhile available, namely in the form of the monoclonal antibodies Cetuximab and Bevacizumab (cp. chapters 2.3 and 2.4).

2.2 IRINOTECAN

2.2.1 General information

Irinotecan is a semi-synthetic camptothecin derivative. It does not exhibit any cross-resistance with substances currently available for the treatment of colorectal cancer. Irinotecan is quickly hydrolyzed to the active metabolite SN-38 in the organism. This reaction is catalyzed by carboxylesterases and predominantly takes place in the liver and gastrointestinal tract. Both Irinotecan as well as its active metabolite SN-38 inhibit topoisomerase I. This S-phase-dependent action results in the stabilization of the DNA topoisomerase I complex. As a result, DNA single-strand breaks develop during the replication phase of the cell, ultimately leading to cell death.

Irinotecan is essentially eliminated by way of glucuronidation of SN-38 which is subsequently eliminated by excretion in the bile. If glucuronidation is impaired, such as is the case e.g. with Meulengracht syndrome, a considerable increase in the drug-related toxicity is expected. Patients with 1.5-fold elevated bilirubin levels from baseline (unconjugated bilirubin) are therefore not eligible for Irinotecan treatment. Delayed-onset diarrhea is one of the main adverse effects induced by Irinotecan. It is caused in particular by the bacterial cleavage of the SN-38 glucuronide bond and hence the release of toxic SN-38 in the gastrointestinal tract.

2.2.2 Irinotecan for colorectal cancer

Within the scope of phase II studies, Irinotecan achieved a response rate of 19% to 31% in the 1st-line therapy of metastatic CRC and a response rate of about 10% in the 2nd-line therapy. The comparison between Irinotecan and the best supportive care after prior therapy with 5-FU showed a 2.6 times higher 1-year survival rate (36.2% vs. 61.4%).
13.8%) in 279 patients\textsuperscript{15}. Another study with a total of 256 patients compared Irinotecan with different FUFA regimens (de Gramont, AIO). A 1.4 times higher 1-year survival rate was demonstrated here for Irinotecan compared with the FUFA group (44.8% versus 32.4%, p=0.0035)\textsuperscript{16}.

The randomized comparison of a weekly versus 3-weekly application of Irinotecan in 5-FU-refractory subjects revealed that the efficacy of the 3-weekly administration and the weekly administration of Irinotecan was similar, but that the first mentioned was associated with a significantly lower incidence of severe diarrhea (diarrhea grade 3-4: 19% vs. 36%)\textsuperscript{17}.

Combining Irinotecan and 5-FU appeared to make sense, because Irinotecan was effective both in not pre-treated colorectal cancer as well as in 5-FU ± FA-resistant colorectal cancer. In addition, different molecular mechanisms of the cytotoxic activity of 5-FUFA and Irinotecan as well as a synergistic cytotoxic activity exist for both chemotherapeutic agents, which are dependent on the dose and time of administration.

Several randomized studies compared the effectiveness of combined Irinotecan and FUFA with FUFA alone. Saltz et al. demonstrated that a significantly higher rate of remission (39% vs. 21%, p<0.001), a longer progression-free survival (7.0 months vs. 4.3 months, p=0.004) and a significantly longer overall survival (14.8 months vs. 12.6 months, p=0.04) were achieved with the combination of Irinotecan plus bolus FUFA (IFL regime) compared to the Mayo regimen\textsuperscript{18}.

In contrast, Douillard compared a combination of Irinotecan and infusional FUFA (FOLFIRI), administered either according to the de Gramont regimen or the AIO regimen\textsuperscript{19} (Tab. 1). Again, the combination therapy achieved a significantly higher rate of remission (41% vs. 23%, p<0.001), a longer PFS (6.7 months vs. 4.4 months, p<0.001) as well as a significantly longer overall survival (16.8 months vs. 14 months, p=0.03). The data presented by Douillard were reviewed once more by the EORTC, by comparing the FOLFIRI-AIO regimen with the AIO regimen. This study demonstrated a significant superiority of the FOLFIRI regimen with respect to the progression-free survival (8.5 months vs. 6.4 months, p=0.0001), which was evaluated as primary target criterion\textsuperscript{20}. While the median survival for FOLFIRI-treated patients was close to 20.1 months, a median survival of 16.9 months was reported for the AIO regimen. This difference did not reach the conventional level of significance either in the traditional log-rank test or in the weighted variant of this family of tests based on the Wilcoxon analysis.
Tab. 1  FOLFIRI versus folinic acid/5-FU (de Gramont/AIO)

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRI</th>
<th>FAFU</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (confirmed) (%)</td>
<td>41</td>
<td>23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR (%)</td>
<td>4</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of remission (months)</td>
<td>8.6</td>
<td>6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median TTP (months)</td>
<td>6.7</td>
<td>4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>16.8</td>
<td>14</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>1-year survival (%)</td>
<td>69</td>
<td>59</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>

2.3 Cetuximab

2.3.1 General information

New molecular therapy strategies for advanced colorectal cancer are predominantly based on the inhibition of the growth factor-mediated signal transduction and blockade of the neoplastic angiogenesis. The family of human epidermal growth factor receptors forms a group of four transmembranous cell surface receptors (HER-1[EGFR], HER-2/neu, HER-3 and -4), which express signals with respect to cellular proliferation, differentiation, mobility, invasive activity and apoptosis. EGFR receptors are expressed by the majority of solid tumors. EGFR expression is successfully detected by means of immunohistochemical techniques in more than 80% of colorectal cancer cases. EGFR over-expression in colorectal cancer is associated with a poorer prognosis within the meaning of a shorter progression-free overall survival.

Cetuximab is a chimeric monoclonal IgG1 antibody produced by a recombinant cell line in mouse myeloma cells. The antibody is directed against the epidermal growth factor receptor (EGFR). The significance of the EGFR and the signal transduction mediated by it on the development and progression of malignant tumors has been demonstrated in a number of studies. The EGFR signal transduction is involved in the control of the cancer cells’ ability to survive, the cell cycle progression, angiogenesis, cell migration as well as mechanisms which determine the metastatization through migration and invasion. EGFR expression is
generally associated with a poorer prognosis of the tumor.

The binding affinity of Cetuximab between EGFR is approximately 5-10 times greater than the one of endogenous ligands and the binding inhibits the receptor function. Cetuximab induces the internalization and hence the down regulation of the EGFR. In addition, there is evidence that Cetuximab makes EGFR-expressing tumor cells discernible for natural killer cells. Furthermore, an immunogenic effect of Cetuximab can also be expected because of the mediation of the antibody-related cellular cytotoxicity. Antichimeric antibodies against Cetuximab (HACA) were identified in 3.7% of examined patients, but they were not associated with any hypersensitivity reactions or loss of efficacy of Cetuximab.

2.3.2 Cetuximab for colorectal cancer

The efficacy of Cetuximab for colorectal cancer was initially examined in two phase II studies with Irinotecan-pre-treated patients. In the project IMCL CPO2-0141, 57 patients were treated with monotherapy of the antibody. 9% achieved an objective response (CR+PR). An analogous study of Cetuximab + Irinotecan as salvage regimen demonstrated a response rate of 15% in 36% of additional subjects whose disease was stabilized.

In a randomized phase II/III study (so-called BOND study), 329 patients with Irinotecan-refractory, EGFR-positive colorectal cancer were either given Cetuximab monotherapy or the same Irinotecan regimen combined with Cetuximab. In this study, Cetuximab was administered at an initial dose of 400 mg/m², followed by 250 mg/m² weekly in both therapy arms. The remission rate of 11% for the Cetuximab monotherapy and 23% for the combination of Cetuximab plus Irinotecan indicates a significant antitumor efficacy. As a specific adverse effect, the majority of patients developed cutaneous toxicity (acneiform exanthema), which was observed in 9.4% of subjects with NCI-CTCAE grade 3 and 4. The studies investigating the efficacy of Cetuximab for colorectal cancer, either as monotherapy or combined with Irinotecan published to date are illustrated in Tab. 2.

The CRYSTAL study compared Cetuximab plus FOLFIRI with FOLFIRI treatment alone in the first-line therapy of metastatic colorectal cancer. 1198 patients were included in the intention-to-treat (ITT) population. The remission rate rose from 38.7% to 46.9% with the additional administration of Cetuximab. The progression-free survival (PFS) was evaluated as primary study endpoint and increased from 8.0 to 8.9 months (p=0.0479).
Phase II studies demonstrate that Cetuximab equally improves the therapeutic efficacy in combination with Oxaliplatin\textsuperscript{30,31}. Cetuximab plus FOLFOX4 was compared with FOLFOX4 within the scope of a randomized phase II study. The combination with Cetuximab increased the remission rate from 36\% to 46\%\textsuperscript{32}.

**Tab. 2 Phase-II and III studies with Cetuximab in patients with colorectal cancer**

<table>
<thead>
<tr>
<th>Study type</th>
<th>Number of patients</th>
<th>Regimen</th>
<th>Toxicity</th>
<th>Activity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II (Irinotecan-refractory)</td>
<td>57</td>
<td>Cetuximab: 400 mg/m\textsuperscript{2} followed by 250 mg/m\textsuperscript{2} weekly</td>
<td>Acne-like skin rash, asthenia, allergic reactions</td>
<td>5/57 PR; 21/57 SD; TTP 1.4 months</td>
<td>[26]</td>
</tr>
<tr>
<td>Phase II (Irinotecan/5-FU-refractory)</td>
<td>120</td>
<td>Cetuximab: 400 mg/m\textsuperscript{2} followed by 250 mg/m\textsuperscript{2} weekly and Irinotecan</td>
<td>diarrhea, neutropenia, fatigue, acne-like skin rash, allergic reactions</td>
<td>22.5% PR; 7.5% SD</td>
<td>[27]</td>
</tr>
<tr>
<td>Phase II/III (randomized) (Irinotecan-refractory)</td>
<td>329</td>
<td>Cetuximab 400 mg/m\textsuperscript{2} followed by 250 mg/m\textsuperscript{2} weekly and Irinotecan vs. Cetuximab alone</td>
<td></td>
<td>RR 22.9% vs. 10.8%; TTP 4.1 vs. 1.5 months</td>
<td>[28]</td>
</tr>
<tr>
<td>Phase II (1\textsuperscript{st}-line)</td>
<td>29</td>
<td>Cetuximab and weekly Irinotecan 125 mg/m\textsuperscript{2} and 5-FU 500 mg/m\textsuperscript{2}/LV, 20 mg/m\textsuperscript{2}, Cetuximab + 5-FU, Leucovorin and Irinotecan</td>
<td>Diarrhea, neutropenia, acne-like skin rash</td>
<td>48% PR; 41% SD</td>
<td>[33]</td>
</tr>
<tr>
<td>Phase I/II (1\textsuperscript{st}-line)</td>
<td>52</td>
<td>Cetuximab + 5-FU, Leucovorin and Irinotecan</td>
<td>diarrhea, neutropenia, vomiting, acne-like skin rash</td>
<td>43% PR; 45% SD</td>
<td>[34]</td>
</tr>
<tr>
<td>Phase I/II (1\textsuperscript{st}-line)</td>
<td>21</td>
<td>Cetuximab + Irinotecan 80 mg/m\textsuperscript{2} and 5-FU 1500 mg/m\textsuperscript{2} (6 patients)/2000 mg/m\textsuperscript{2} and LV 500 mg/m\textsuperscript{2}</td>
<td>diarrhea, acne-like skin rash</td>
<td>11% CR; 63% PR; 21% SD</td>
<td>[36]</td>
</tr>
<tr>
<td>Phase III</td>
<td>1198</td>
<td>Cetuximab + Irinotecan 180 mg/m\textsuperscript{2} and 5-FU 400 mg/m\textsuperscript{2} bolus and 5-FU 2400 mg/m\textsuperscript{2} and LV Irinotecan 180 mg/m\textsuperscript{2} and 5-FU 400 mg/m\textsuperscript{2} bolus and 5-FU 2400 mg/m\textsuperscript{2} and LV</td>
<td>Neutropenia, acne-like skin reactions, diarrhea</td>
<td>0.5% CR; 46% PR; 37% SD</td>
<td>[29]</td>
</tr>
</tbody>
</table>

PR: partial remission; SD: stable disease; RR: response rate; TTP: time to progression.
2.3.3 Significance of the KRAS mutation status for the effectiveness of Cetuximab

Recent studies show that colorectal cancer patients with a KRAS mutation fail to respond to anti-EGFR therapy. According to previously conducted studies, this mutation is present in 30-40% of all patients with metastatic colorectal cancer. Therefore, Cetuximab should not be used in patients with a KRAS mutation. Patients who were enrolled in the study before the 2nd amendment entered into effect and in whom a KRAS mutation was detected afterward should stop treatment with Cetuximab.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Regimen</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>w-t KRAS</td>
<td>KRAS mut.</td>
</tr>
<tr>
<td>[41]</td>
<td>337</td>
<td>FOLFOX + Cetuximab</td>
<td>61(^a)</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FOLFOX</td>
<td>37(^a)</td>
<td>49</td>
</tr>
<tr>
<td>[42]</td>
<td>1198</td>
<td>FOLFIRI + Cetuximab</td>
<td>59(^d)</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FOLFIRI</td>
<td>43(^a)</td>
<td>40</td>
</tr>
</tbody>
</table>

Legend: \(^a\)\(p=0.011\); \(^b\)\(p=0.016\); \(^c\)\(p=0.019\); \(^d\)\(p=0.0025\); \(^e\)\(p=0.017\);

2.4 BEVACIZUMAB (AVASTIN\textsuperscript{®})

2.4.1 General information

In addition to the development of new highly effective and easy to apply cytostatic agents, novel groups of active ingredients based on discoveries of molecular biology have been introduced in recent years. They are not only aimed at the direct traditional attack of the tumor cell, but increasingly target the conditions of the stromal “micro environment” which is crucial for the development and growth of tumors and metastases. The blood supply of the neoplastic lesions plays a key role in this respect.

An additional step which is relevant for the malignant growth takes place as soon as tumor lesions exceed a size of 1 to 2 mm: the newly emerging hypoxia and other factors trigger a signal cascade which leads to de novo angiogenesis. Excessive release of the VEGF (vascular epithelial growth factor), a vital protein...
for fetal development from the tumor cells plays a key role in this respect. It is overexpressed in a number of tumor types and often correlates with a poor prognosis. By binding to special receptors on vascular endothelial cells, the growth factor typically causes chaotic, instable vascularization of the tumor, characterized by “dead ends” and leaks as well as functional deficits.

An active ingredient specifically targeted against this growth factor is now available with the humanized monoclonal anti-VEGF antibody Bevacizumab (Avastin®). This interruption of the stimulation pathway leads to the death of vascular endothelial cells and the degeneration of new immature tumor vessels. In contrast, mature, differentiated blood vessels remain intact and continue to allow the supply of cytotoxic active ingredients.

2.4.2 Bevacizumab in combination with 5-FU for colorectal cancer

A dose finding study of 104 patients with advanced colorectal cancer demonstrated that the additive Bevacizumab administration to the 5-FU bolus regimen (Roswell-Park) achieves a pronounced improvement in the response rates (17% 5-FU/LV alone, 40% 5-FU/LV/Bevacizumab 5mg/kg of BW) as well as the progression-free survival and the overall survival. The best outcomes were achieved with a Bevacizumab dose of 5mg/kg of BW. These results were confirmed in two other studies. The combined analysis of all three studies revealed a statistically significant extension of the PFS from 5.6 to 8.8 months (p=0.0001) and the median overall survival from 14.6 to 17.9 months (p=0.0081) with a dose of 5 mg/kg of BW.

2.4.3 Bevacizumab in combination with Irinotecan or Oxaliplatin for CRC

In a large double-blind phase III study investigating the first-line treatment of metastatic colorectal cancer, 402 subjects were given a combination of Irinotecan, 5-FU as bolus and Bevacizumab at a dose of 5 mg per kilogram of body weight, repeated every 2 weeks. 411 patients were given placebo instead of Bevacizumab (Tab. 3). With respect to the primary study objective overall survival, a highly significant superiority was observed for the arm with the active study drug (p<0.001) with a median period of 20.3 versus 15.6 months. The median progression-free survival was almost doubled (p < 0.001) with 10.6 vs. 6.2 months. Likewise, the objective tumor remission rate (CR+PR) under Bevacizumab was significantly higher with 44.8% vs. 34.8%. The therapeutic advantage is uniform in all sub-groups differentiated by age, gender, tumor type, etc. In comparison to the control group, an elevation of the blood pressure with an incidence close to 22% was the only relevant and significantly more common adverse effect (severity grade 3: 11%). The rates of proteinurin
hemorrhages and thromboembolic events were only slightly elevated compared to the placebo group. In addition, isolated cases of gastrointestinal perforations with an incidence of 1-2% were reported. Bevacizumab was approved for the indication of colorectal cancer in the USA and Europe based on this study.

**Tab. 3  Results of the phase III study investigating IFL with vs. without Bevacizumab**

<table>
<thead>
<tr>
<th>Survival and response rate</th>
<th>IFL + placebo (n = 412)</th>
<th>IFL + Bevacizumab (n = 403)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (months)</td>
<td>15.6</td>
<td>20.3</td>
<td>0.00003</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>6.2</td>
<td>10.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Objective response</td>
<td>35%</td>
<td>45%</td>
<td>0.0029</td>
</tr>
<tr>
<td>Duration of response</td>
<td>7.1</td>
<td>10.4</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicity</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3/4 hemorrhage</td>
<td>2.5%</td>
<td>3.1%</td>
<td></td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>16.1%</td>
<td>19.3%</td>
<td></td>
</tr>
<tr>
<td>Grade 3 hypertension</td>
<td>2.3%</td>
<td>10.9%</td>
<td></td>
</tr>
</tbody>
</table>

The combination of Bevacizumab and Oxaliplatin in first-line therapy is the object of current phase III studies conducted in the USA and Europe. In a large randomized study, Bevacizumab combined with FOLFOX significantly improved the response rate, the progression-free survival as well as the overall survival compared to FOLFOX alone in the second-line therapy. Toxicity analyses from this study did not reveal any elevated overall toxicity rates for the Bevacizumab combination regimen even with higher Bevacizumab dosing (10 mg/kg of BW), although the treatment duration was 67% longer in the Avastin arm than in the comparator arm. Consistent with the study conducted by Hurwitz, hemorrhages and hypertension are typical adverse effects of the Bevacizumab therapy. Overall, the rate of adverse effects is low after 18.7 months of follow-up. At 1.1%, GI perforations are uncommon, but they were only observed in the Bevacizumab arm. A preliminary evaluation of 932 additional patients treated with Bevacizumab after it was approved – 47.7% of them with the Oxaliplatin-based FOLFOX regimen – confirms the data of the pre-approval study (6.3% SAEs, including 1.7% GI perforations, 0.3% post-operative hemorrhages and impaired wound healing).
2.5 RATIONALE FOR THE CONDUCT OF THE STUDY

Treatment of advanced colorectal cancer by means of a combined chemotherapy regimen comprising 5-FU and Irinotecan is an established procedure. The angiogenesis inhibitor Bevacizumab (anti-VEGF) is an antibody for which an additional survival benefit has been demonstrated in combination with standard chemotherapy regimens in the first-line therapy. The question therefore arises whether an even more active first-line therapy could potentially achieve a further improvement of the prognosis for patients with metastatic CRC. Based on the obvious synergistic correlations between Irinotecan and Cetuximab, this combination represents a promising candidate for the mentioned objective.

A randomized phase II study with the tumor response rate (OR = CR + PR) as surrogate objective is conducted to assess the effectiveness of the combination consisting of FOLFIRI and Cetuximab. In view of the considerably extended progression-free overall survival times (PFS, OS) achieved in the meantime thanks to systemic treatment advances, a much greater case number would be required for the direct conduct of a phase III study to evaluate these definitive clinical endpoints. This would in turn raise ethical concerns. However, the option exists – and the latter is only made possible by randomizing subjects as early as in phase II – to “advance” the proposed study within the meaning of a phase III trial, provided the results are promising.

An additional rationale for selecting the remission rate as primary target criterion is the following: due to the introduction of a host of highly effective medications in recent years, it is now possible to treat patients with metastatic disease limited to certain organs (e.g. liver metastases only) with a curative intent, by converting an initially inoperable status into an operable status by means of successful systemic treatment. The extent to which this option is achieved is obviously predominantly dependent on the quality of the tumor response induced within a timeframe that is as short as possible.
3 Study objectives

3.1 Primary study objective

The primary study objective is the comparative evaluation of the anti-tumor effectiveness based on the objective remission rate (OR = CR + PR) determined according to the RECIST criteria and evaluated by means of the intention-to-treat collective.

3.2 Secondary study objectives

Secondary study objectives are:

- documentation of the progression-free survival
- documentation of the overall survival
- documentation of the time to failure of strategy (= TFS)
- depth of remission (maximum change in tumor size in percent compared to baseline)
- rate of secondary resections of liver metastases with a potentially curative intent
- documentation of the safety and tolerability (NCI-CTCAE V3.0 criteria)

4 General planning

4.1 Proposed schedule

Proposed start of the study (enrolment of the 1st patient): 4th quarter of 2006

Proposed start after amendment 2 entered into effect (enrolment of the 1st patient): 4th quarter of 2008

Patient recruitment: 72 months (6 months after amendment 4 entered into effect)

Duration of treatment per patient: generally until the disease progresses

Follow-up care: until the patient dies or at most 5 years
4.2 STUDY DESIGN

Two-arm, open label, multi-center, randomized phase II therapy study.

4.3 NUMBER OF PATIENTS

284 patients eligible for evaluation with wild-type KRAS mutation per randomization arm, corresponding to a total number of 568 patients. This case number includes all patients with wild-type KRAS enrolled in the study before amendment II entered into effect (for more information: see chapter 8.2.2; adjustment by means of sequential design, if necessary).

5 PATIENT SELECTION

5.1 INCLUSION CRITERIA

- histologically confirmed adenocarcinoma of the colon or rectum, stage IV
- demonstrated wild-type KRAS mutation status in the tumor (primary tumor or metastasis)
- general status: 0-2 (ECOG/WHO)
- eligible for application of a chemotherapy regimen
- patient’s written declaration of consent (first- and second-line therapy)
- age: 18-75 years
- inpatient or outpatient treatment
- estimated life expectancy >3 months
• presence of at least one measurable reference lesion according to the RECIST criteria
• evaluation of the tumor manifestation 2 weeks or less before study enrolment
• effective contraception for men and women if contraception is possible
• white blood cell count \( \geq 3.0 \times 10^9/L \) with neutrophils \( \geq 1.5 \times 10^9/L \), platelets \( \geq 100 \times 10^9/L \), hemoglobin \( \geq 5.6 \text{ mmol/L (corresponding to 9 g/dL)} \)
• serum bilirubin \( \leq 1.5 \times \) upper limit of normal
• ALAT and ASAT \( \leq 2.5 \times \) upper limit of normal. ALAT and ASAT \( \leq 5 \times \) upper limit of normal in the presence of liver metastases
• serum creatinine \( \leq 1.5 \times \) upper limit of normal
• surgery must have been performed more than 4 weeks, fine needle biopsy more than 1 week before study enrolment. Surgical wounds must have healed completely. No need for major surgery during the course of the study is expected, except a possible resection of liver metastases. If there is an option for secondary curative surgery, Bevacizumab should be discontinued 6 to 8 weeks and Cetuximab approximately 2 weeks before the surgery
• relevant toxicities of prior therapies must have subsided

No patient may undergo any procedure that is in any way associated with the clinical study before his/her written consent is obtained.

5.2 Exclusion criteria

• demonstrated KRAS mutation
• prior anti-EGFR-targeted therapy
• prior Bevacizumab treatment
• prior chemotherapy of the colorectal cancer, except for adjuvant therapy completed at least 6 months before study enrolment
- experimental drug treatment within 30 days of enrolment
- known hypersensitivity to any component of the investigational drug
- pregnancy (exclusion confirmed with beta-hCG test) or lactation
- pre-existing or clinically suspected brain metastases
- clinically relevant coronary heart disease, myocardial infarction within the past 12 months or risk of uncontrolled arrhythmia
- acute or subacute intestinal obstruction or history of chronic inflammatory disease or chronic diarrhea
- symptomatic peritoneal carcinomatosis
- serious, non-healing wounds, ulcers or bone fractures
- uncontrolled hypertension
- pronounced proteinuria (nephrotic syndrome)
- arterial thromboembolisms or severe hemorrhages within 6 months before study enrolment (except bleeding tumor before tumor resection surgery)
- hemorrhagic diathesis or thrombotic tendency
- therapeutic anticoagulation (Marcumar therapy, heparinization affecting the PTT)
- pre-existing DPD deficiency (no special screening required)
- pre-existing glucuronidation defect (Gilbert-Meulengracht syndrome) (no special screening required)
- history of secondary malignancy within the past 5 years, except for basalioma or carcinoma in situ of the cervix uteri, if treated with curative intent
- pre-existing alcohol or drug abuse
- medical or mental impairments which make it impossible to obtain the patient’s consent or to conduct the study
- a significant concomitant medical condition which the clinical investigator believes precludes the patient from enrolling in the study

- absent or limited legal competence
5.3 ANALYSIS OF THE EGFR-RELATED SIGNAL TRANSDUCTION

Due to the fact that Cetuximab specifically acts on the EGF receptor, analyses of existing tumor samples are being conducted which can be used to define impairments of the EGFR-related signal transduction. According to the 2nd amendment, patients with a KRAS mutation in the primary tumor or metastases of the colorectal cancer are not eligible for enrolment in the study.

Patients who were enrolled in the study before amendment 2 entered into effect and who were subsequently diagnosed with a KRAS mutation should not continue to receive Cetuximab. These patients will remain in the study (with FOLFIRI alone) until the next restaging is conducted. Patients with progressive disease at that time will be withdrawn from the study. In the presence of SD or therapy response, it is at the clinical investigator’s discretion to continue treating the patients with FOLFIRI alone outside of the study. In any case, these patients would be followed within the scope of the follow-up care.

6 TREATMENT SCHEDULE, MEDICATION AND THERAPY ASSIGNMENT

6.1 OVERVIEW

Arm A:
1 cycle consisting of:

- **FOLFIRI regimen**, every 2 weeks

<table>
<thead>
<tr>
<th>Drug NAME</th>
<th>dose</th>
<th>administration</th>
<th>time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan</td>
<td>180 mg/m² i.v., 30 - 90 min</td>
<td>day 1</td>
<td></td>
</tr>
<tr>
<td>Folinic acid (racemic)</td>
<td>400 mg/m² i.v., 120 min</td>
<td>day 1</td>
<td></td>
</tr>
<tr>
<td>5-FU 400 mg/m² bolus</td>
<td></td>
<td>day 1</td>
<td></td>
</tr>
<tr>
<td>5-FU 2400 mg/m² i.v. over a period of 46 h</td>
<td></td>
<td>day 1-2</td>
<td></td>
</tr>
<tr>
<td>Cetuximab initially 400 mg/m² as 120-min infusion, followed by 250 mg/m² i.v. as 60-min infusion each</td>
<td></td>
<td>day 1 + 8</td>
<td></td>
</tr>
</tbody>
</table>
Arm B (control arm):

1 cycle consisting of:

- **FOLFIRI regimen**, every 2 weeks

  - **Irinotecan** 180 mg/m² i.v., 30 - 90 min  
    day 1
  - **Folinic acid (racemic)** 400 mg/m² i.v., 120 min  
    day 1
  - **5-FU** 400 mg/m² bolus  
    day 1
  - **5-FU** 2400 mg/m² i.v. over a period of 46 h  
    day 1-2
  - **Bevacizumab** 5 mg/kg of BW i.v. for 30 to 90* minutes  
    day 1

1st administration given over a period of 90 min, if tolerated well, the second administration over a period of 60 min and the further administrations over a period of 30 min each

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6.2 **INVESTIGATIONAL DRUG AND STANDARD MEDICATION**

6.2.1 **Administration of the investigational drug**

In addition to the standard medication consisting of cytostatic agents and Bevacizumab (Avastin®) as approved combination partner in reference arm B, Cetuximab (Erbitux®) is used for patients enrolled before amendment 2 entered into effect. This drug is provided to the involved clinical centers by the sponsor or principal investigator in the form of a free delivery by the manufacturer. In order to be able to track the investigational drug and its application, the clinical investigator is asked to complete the patient file diligently such that the dispensing and intravenous application of the chemotherapy/immunotherapy can be verified any time. Likewise, the dates and quantities must also be documented in the CRF.

**After amendment 2 has entered into effect, Cetuximab is no longer provided as a free study drug, because the medication has meanwhile been approved for the first-line therapy.**

6.2.2 **Handling of the investigational drug**

The clinical investigator is responsible for making sure that the investigational drug (Cetuximab) provided before amendment 2 entered into effect is handled safely and correctly. Cetuximab must be stored in the refrigerator at +2 - +8°C, protected from moisture and light. Do not freeze! All provided medications must be
stored in a locked room or cabinet which is only accessible to the competent pharmacist, clinical investigator or an authorized person.

6.3 IRINOTECAN

6.3.1 Instructions for use

Registered trade name: Campto. 40 mg in 2 mL (injection bottle)
Campto. 100 mg in 5 mL (injection bottle)

Active ingredient: Irinotecan

Packaging format: injection bottle; concentrate for the manufacture of a solution for infusion

Content: 20 mg Irinotecan/mL

Pharmaceutical company: Pfizer GmbH, Karlsruhe

Excipients: D-glucitol, lactic acid, water for injection. The pH value of the solution is set to 3.5 by means of sodium hydroxide.

Preparation of the solution for infusion: the required quantity of Irinotecan solution is drawn up from the injection bottle with a calibrated syringe under aseptic conditions and injected into a 250 mL infusion bag/infusion bottle which contains either sodium chloride solution 0.9% or dextrose solution 5%. Next, the solution is thoroughly mixed by means of manual rotation.

Shelf life and storage: the shelf life of the unopened injection bottle is 36 months. If the solution was prepared under aseptic conditions, it should be used up (end of infusion) within 12 hours at room temperature or within 24 hours (stored at 2-8°C). Store injection bottles containing Irinotecan concentrate protected from light.
The concomitant use of Irinotecan and yellow fever vaccines is contraindicated because of the risk of a generalized reaction to the vaccines. In addition, the concomitant use of Irinotecan with attenuated live vaccines as well as inactivated vaccines is not recommended.

6.3.2 Mechanism of action

Irinotecan as well as its active metabolite SN-38 are topoisomerase I inhibitors. By stabilizing the DNA topoisomerase I complex during the replication phase of the cell, they induce DNA single-strand breaks and hence cell death.

6.3.3 Adverse effects

Adverse effects induced by Irinotecan include neutropenia, diarrhea and so-called delayed-onset diarrhea. In addition, nausea and vomiting as well as acute cholinergic syndrome may develop.

Prophylactic 5-HT3 antagonists or other anti-emetic agents can be used to treat nausea and vomiting.

Acute cholinergic syndrome

Acute cholinergic syndrome can develop within the first 24 hours after the Irinotecan infusion. Symptoms include early-onset diarrhea, abdominal cramps, sweating, salivating and lacrimation as well as typical narrowing of the pupils. If these symptoms develop, Atropine at a dose of 0.25 mg should be injected subcutaneously before any further Irinotecan infusions. Possible contraindications with respect to the use of Atropine must be observed.

Delayed-onset diarrhea (late diarrhea)

It is imperative that any diarrhea starting more than 24 h after the administration of Irinotecan (expected in about 35% of patients) be treated immediately with Loperamide at high doses deviating from the common dosing schedule. A prophylactic Loperamide administration is not indicated. However, prophylactic Loperamide should be prescribed to facilitate the initiation of outpatient treatment.

Loperamide dosing:
Start immediately after the first watery stool (initial dose 4 mg); followed by 1 capsule (2 mg) every 2 hours, up to a maximum daily dose of 8 capsules (16 mg).
Continue for up to 12 hours after the last watery stool

Maximum duration of the administration: 48 hours (uninterrupted).

As soon as the first watery stool is passed, the patient should start drinking large quantities of fluids containing electrolytes.

If late-onset diarrhea is accompanied by fever or grade 3/4 neutropenia, a prophylactic broad-spectrum antibiotic must be prescribed.

Hospitalization is required:

• if severe diarrhea (>6 bowel movements per day) persists for more than 48 hours
• if diarrhea and vomiting develop
• if diarrhea is accompanied by fever ≥38°C
• in the presence of febrile neutropenia.

See also summary of product characteristics for Campto® in the respective applicable version

6.4 CETUXIMAB

6.4.1 Instructions for use

Manufacturer: Merck KGaA, 64271 Darmstadt

Registered trade name: Erbitux®, 100 mg or 500 mg injection bottles (20 mL or 100 mL containing 5 mg of Cetuximab per mL)

Shelf life: 2 years in the original package. According to the expiry date printed on the original package. Store in the refrigerator (+2 - +8°C). Do not freeze. Keep away from direct sunlight and heat.

Solution: 1 mL of solution for infusion contains 5 mg of Cetuximab, colorless solution which is free of particles. Cetuximab is administered intravenously using a separate infusion set and the infusion tubing should be rinsed with sterile saline solution, 0.9% (9 mg/mL) at the end of the infusion. The use of filters is not required.

The chemical and physical stability of solution in a bottle that has been opened has been demonstrated for 48 hours at a temperature of 25°C. Store in the refrigerator (+2 - +8°C). Do not freeze.
Under microbiological aspects, the product should be used directly after it has been opened. If the product is not used promptly, the user is responsible for observing the storage times and conditions of the solution in the opened bottle. It is generally recommended that a period of 24 hours at a temperature of 2-8° C is not exceeded.

**Cetuximab is compatible with the following materials:**

The compatibility of infusion systems or syringes made of polyethylene, polyurethane, thermoplastic polyolefin, polyamide-glass microfiber, polypropylene and polyvinyl chloride with Cetuximab was analyzed; their use is recommended. Cetuximab is stable and when administered at room temperature (up to 25° C), it is compatible with infusion systems made of any combination of the recommended materials.

**The Cetuximab solution for infusion is prepared as follows:**

**Syringe pump:**

- Calculate the Cetuximab quantity required for the respective infusion administered to the respective patient (e.g. 250 mg/m² for a patient with a body surface area of 2 m² = 500 mg of Cetuximab). Next, calculate the volume of Cetuximab solution 5 mg/mL which contains the required quantity (e.g. 500 mg of Cetuximab = 100 mL of Cetuximab solution 5 mg/mL).
- Draw up the calculated volume from one or several injection bottles containing Cetuximab solution 5 mg/mL into one or several sterile syringes using a matching needle.
- Remove the needle. Attach the infusion tubing to the first filled syringe and fill it with the Cetuximab solution. Insert the first filled syringe into the syringe pump and adjust the speed. Repeat this procedure with the other syringes.
- Monitor the infusion rate. The calculated infusion rate may **NOT EXCEED** the maximum infusion rate of 10 mg/min, i.e. 120 mL of ready-to-use solution per hour.
- Rinse the infusion tubing with sterile NaCl solution 0.9% at the end of the infusion.

**Infusion pump or drip infusion:**

- Calculate the Cetuximab quantity required for the respective infusion administered to the respective patient (e.g. 250 mg/m² for a patient with a body surface area of 2 m² = 500 mg of Cetuximab). Next, calculate the volume of Cetuximab solution 5 mg/mL which contains the required quantity (e.g. 500 mg of Cetuximab = 100 mL of Cetuximab solution 5 mg/mL).
- Select an infusion bag with the appropriate size (e.g. 250 mL) containing NaCl solution for infusion 0.9% (isotonic saline solution for infusion).
• Use a suitable sterile syringe and matching needle to draw up the previously calculated volume from the bag containing the NaCl solution. Discard the drawn up NaCl solution.
• Use a suitable sterile syringe with matching needle to draw up the calculated volume from one or several injection bottles containing Cetuximab solution 5 mg/mL.
• Introduce the calculated volume of Cetuximab solution into the infusion bag containing NaCl solution.
• Connect the infusion tubing and fill it with Cetuximab solution before the start of the infusion.
• Monitor the infusion rate. The calculated infusion rate may NOT EXCEED the maximum infusion rate of 10 mg/min.
• Rinse the infusion tubing with sterile NaCl solution 0.9% at the end of the infusion.
• It is recommended to monitor the patient for one hour after the Cetuximab infusion. For the initial dose, the recommended duration of the infusion is 120 minutes, and 60 minutes for the additional weekly doses. The maximum infusion rate may NOT EXCEED 10 mg/min (i.e. 2 mL of Cetuximab solution 5 mg/mL per minute, or 10 mL/min = 600 mL solution for infusion per hour after diluting 1 part of Cetuximab solution 5 mg/mL in 4 parts of sterile NaCl solution 0.9% (dilution ratio 1:5)).

Recommended premedication to prevent hypersensitivity reactions

See also chapter 6.4.4

Cetuximab must always be administered under the supervision of a clinician experienced with the use of cytostatic agents. The patient must be monitored closely during the infusion and for at least one hour thereafter. The necessary equipment for performing emergency procedures must be ready for use. Patients must be pre-treated with an antihistamine prior to the first infusion. This pre-medication is equally recommended for any further infusions. The recommended duration of the infusion is 120 minutes for the initial dose, while a 60-minute duration of the infusion is recommended for the subsequent once weekly administrations. Do not exceed the maximum infusion rate of 2 mL/min.

Please refer to the applicable version of the summary of product characteristics for Erbitux® for additional information about Cetuximab and its use.

6.4.2 Package and labeling

Each package contains 1 injection bottle with Cetuximab 500 mg/100 mL or 100 mg/20 mL. The package contains the following information:
Cetuximab

Intravenous administration.

Store in the refrigerator. Do not freeze. Available by prescription only.

1 mL contains 5 mg of Cetuximab. Sodium chloride, Glycine, Polysorbate 80 VS, citric acid monohydrate, sodium hydroxide, water for injection.

Keep out of the reach of children.

Merck KGaA, 64271 Darmstadt, Germany

Erbitux® is a registered trademark of ImClone Systems Inc.

Available by prescription only

Cetuximab genetically engineered by means of the Sp 2/0 mammalian cell line

EU/1/04/281/003 (20 mL) and EU/1/04/281/005 (100 mL)

Batch no.

Best before:

6.4.3 Mechanism of action

The HER1 receptor is located at the cell surface of tissue of all three cotyledons. Its extracellular domain is the binding site for specific ligands (e.g. epidermal growth factor (EGF), Heparin-binding EGF, transforming growth factor alpha (TGF-α)). The hydrophobic, transmembranous component forms the bridge with the intracellular receptor part, on which the domain with the intrinsic tyrosine kinase activity is located. The binding of extracellular ligands results in the dimerization of receptors of the EGFR family into homodimers or heterodimers, in the stabilization of the ligand-receptor complex and the receptor autophosphorylation with consecutive activation of the intrinsic tyrosine kinase, which in turn triggers a cascade of intracellular signal transduction mechanisms affecting the cellular replication and proliferation rate. Cetuximab is a chimeric monoclonal IgG1 antibody obtained by means of recombinant DNA technology. It competitively inhibits the binding of endogenous ligands and hence blocks the activation of intracellular tyrosine kinase. In addition, the internalization and the decomposition of receptors expressed in the tumor cells are promoted in the long term. As well, a mechanism of action through antibody-mediated cellular cytotoxicity (ADCC) is also being discussed.
6.4.4 Adverse effects

**Allergic reactions/hypersensitivity reactions:**

Grade 3 or 4 hypersensitivity reactions (including allergic and anaphylactic reactions) characterized by rapid onset obstruction of the airways (bronchospasm, stridor, hoarseness), urticaria and/or hypotension, were observed in 3% of Cetuximab-treated patients. Approximately 80% of all allergic reactions/hypersensitivity reactions occurred in connection with the first Cetuximab infusion and were observed during the administration of the infusion or within one hour after it had ended. Based on experience, the majority of cases develop relatively early in connection with the first infusion (after the infusion of approximately 10-20 mL). Therefore, the patient should be monitored very closely during the first 15 minutes of the first infusion.

Before the first Cetuximab administration, patients must be pre-treated with an **antihistamine** (H1 antagonist: e.g. Clemastine (Tavegil) or Dimetindene (Fenistil)). This **premedication** is equally recommended before all further Cetuximab infusions, because some patients only developed the first serious allergic reaction/hypersensitivity reaction in connection with later infusions. In previously conducted studies with Cetuximab, patients who developed serious reactions were given a standard treatment. The reactions subsided without any after-effects in all except for 3 patients. The affected patients were excluded from further participation in the respective studies. Three cases of death were reported.

The following differentiated approach is recommended as an intensified preventive procedure within the scope of this study protocol in connection with the first and if necessary also in connection with subsequent applications:

In addition to the administration of an H1 antagonist (see above):

a) Administration of an H2 antagonist (30 min. to 1 hour before the Cetuximab administration):

- 1 vial of Ranitidine (Zantic) i.v.; 5 mL
- 1 vial of Cimetidine (Cimetidine-CT) i.v.; 2 mL

b) Administration of glucocorticoids (30 min. before the Cetuximab administration):

- 1 vial of Fortecortin (8 mg) i.v.
Allergic reactions/hypersensitivity reactions appear to develop irrespective of the administration as monotherapy or combination therapy, the underlying disease or pre-treatment with murine monoclonal antibodies. Minor to moderate allergic reactions/hypersensitivity reactions are generally manageable by lowering the Cetuximab infusion speed.

**Eye diseases:**

It is expected that nearly 5% of patients develop conjunctivitis.

Keratitis to the point of ulcerative keratitis develops in rare cases. If the ulcerative keratitis diagnosis is confirmed, the Cetuximab treatment should be temporarily suspended or withdrawn. Cetuximab should be used with caution in patients with a history of keratitis, ulcerative keratitis or a severe form of dry eye.

**Diseases of the skin and the subcutaneous epithelium:**

Skin reactions are the most common adverse effects developing under Cetuximab therapy. They normally manifest themselves as acne-like skin rashes or, less commonly, as nail diseases. The acne-like skin rashes usually develop within the first 3 weeks of the treatment and affect the face as well as the upper chest and back region. Occasionally, they extend to the extremities. They manifest themselves as multiple follicular or pustular lesions, which histologically appear as lymphocytic perifolliculitis or suppurative superficial folliculitis. The rash usually heals over time without any after-effects after the end of the therapy. If Cetuximab was administered at a dose lower than 100 mg/m², the acne-like skin rash developed less often and only reached grade 1 to 2. It is assumed that the rash should etiologically be considered the result of an influence of the role of the EGFR on the homeostasis of the epidermis, hair follicles and sebaceous glands induced by Cetuximab as well as the regulation of cutaneous inflammatory processes. Clinical studies of patients with CRC demonstrated a correlation between the onset of acne-like skin reactions and a better efficacy (response, time to progression and survival).

**Nail diseases:**

Other typical, albeit less commonly reported adverse effects are nail diseases in the form of tenderness, sensitivity and fissures of the distal phalanges of the fingers with different degrees of severity. Patients developed inflammation of the nail fold with swelling of the nail fold on the sides of the nails of toes and fingers. The disorder most often involved the great toes and thumbs. Based on reports from clinical
investigators, these types of nail diseases can persist for up to 3 months after the withdrawal of the Cetuximab therapy. A dermatologist should be consulted for advice.

Hypomagnesemia:

Hypomagnesemia is commonly observed under Cetuximab, including severe forms of it. Regular controls of the serum magnesium levels and monitoring for concomitant hypocalcemia and hypokalemia are therefore recommended for patients under Cetuximab therapy. If hypomagnesemia is detected, substitution therapy should be conducted in accordance with the clinical requirements. Re-tests for electrolytes should be conducted over a period of 8 weeks after the end of the Cetuximab therapy for patients with hypomagnesemia.

6.4.5 Special precautions

Allergic reactions/hypersensitivity reactions:

As a routine precaution, all patients enrolled in the study should be monitored carefully for the development of possible adverse events. A clinician trained in emergency medicine must be present from the start of the Cetuximab infusion until at least one hour after the end of the infusion. The patient should be monitored in an area where resuscitation equipment as well as other potentially necessary substances (Adrenaline, Prednisolone equivalents, etc.) are available. Should the patient develop an allergic reaction/hypersensitivity reaction or reaction to the Cetuximab infusion, he/she should be treated according to the best available medical procedures. See chapter 6.6.2.2 & 6.6.6. for information about the adjustment of the Cetuximab treatment. If grade 3 or 4 allergic reactions/hypersensitivity reactions occur, the Cetuximab infusion must be suspended immediately, the necessary medical procedures initiated and the therapy withdrawn permanently. Patients must be monitored carefully until all symptoms and findings have resolved completely.

Reactions of the skin:

Reactions of the skin, particularly acne-like skin rash, are the most common adverse events associated with the use of Cetuximab. If a patient develops a grade 3 skin reaction, the treatment with Cetuximab must be temporarily suspended for up to two weeks in a row. Treatment may only resume once the skin reaction has receded to grade 2. See chapter 6.6.2.2 & 6.6.6. for recommended dose adjustments. If grade 3 skin reactions
develop for the fourth time or fail to reverse to grade ≤2 during the treatment suspension, the permanent withdrawal of the Cetuximab treatment is required.

**Interstitial pneumonitis:**

Severe interstitial pneumonitis was observed in subjects treated with Gefitinib, a substance that impacts the EGFR signal transduction pathways. So far, no elevated risk for interstitial pneumonitis was identified in connection with Cetuximab. Nevertheless, all subjects are required to undergo an imaging procedure to depict the chest prior to the start of the Cetuximab administration in the study. This is a precaution to document the baseline status of the lungs at the start of the study. If the patient is diagnosed with any respiratory symptoms at the time of enrolment in the study, additional pulmonary function tests and further diagnostic procedures must be conducted to diagnose pre-existing pulmonary fibrosis or interstitial pneumonitis. Moreover, subjects are regularly asked about the emergence of respiratory symptoms throughout the course of the study. If any respiratory symptoms develop or worsen during or after treatment with Cetuximab, a detailed description is required and the clinical investigators should prescribe diagnostic procedures to the best of their knowledge based on which it is possible to establish a secure diagnosis.

**6.4.6 Interactions with other therapies**

No further formal drug interaction studies in humans have yet been conducted with Cetuximab.

**6.4.7 Advice on surgeries and Cetuximab**

In the therapy arm with Cetuximab, the antibody therapy can be administered up to approximately 2 weeks before the scheduled surgery.

If the patient responds well to the therapy and there is an option for secondary curative surgery, the antibody should be withdrawn approximately 2 weeks before surgery. The patient can continue with the chemotherapy during this time. If medically indicated, the Cetuximab therapy can be resumed after the successful surgery and once the wounds have healed (this is not part of the therapy according to this study protocol).
6.5 BEVACIZUMAB

6.5.1 Instructions for use

Manufacturer: Roche Registration Limited
40 Broadwater Road
Welwyn Garden City
Hertfordshire, AL7 3AY
United Kingdom

Registered trade name: Avastin®, 4 mL or 16 mL injection bottles containing 100 or 400 mg of Bevacizumab

Solution: 1 mL solution for infusion contains 25 mg of Bevacizumab

Shelf life: original package: 2 years. According to the expiry date printed on the original package. Store in the refrigerator (+2 - +8° C). Do not freeze. Store the injection bottle in the covering box to protect the content from light.

The chemical and physical stability after opening was demonstrated for 48 hours at 2° C to 30° C in 0.9% saline solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, the user is responsible for the storage times and conditions after opening. Generally, they should not exceed 24 hours at 2-8° C unless the dilution was prepared under controlled and validated aseptic conditions.

The Bevacizumab solution for infusion is prepared as follows:

Bevacizumab must be prepared by properly trained personnel under aseptic conditions. Take out the quantity of Bevacizumab required for a 5 mg/kg dose and dilute it with saline solution 0.9% (9 mg/mL) to a total volume of 100 mL for the infusion. Discard any residual amount in the injection bottle because the product does not contain any preservatives. Visually check any medicinal products for parenteral use for suspended particles prior to the application. No incompatibilities between Bevacizumab and polyvinyl chloride or polyolefin bags or infusion sets have been observed. The chemical and physical stability after opening was demonstrated for 48 hours at 2° C to 30° C in 0.9% (9 mg/mL) saline solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, the user is responsible for the storage times and conditions after opening. Generally, they should not exceed 24
hours at 2-8°C unless the dilution was prepared under controlled and validated aseptic conditions.

Do not mix or apply Bevacizumab solution for infusion with glucose solutions. If Bevacizumab is administered after chemotherapy, rinse the infusion tubing with saline solution first.

The initial dose should be applied as i.v. infusion over a period of 90 minutes. If the first infusion is tolerated well, the second infusion can be administered over a period of 60 minutes. If the 60-minute infusion is tolerated well too, all subsequent infusions can be administered over a period of 30 minutes.

The first dose should be administered after the chemotherapy. All subsequent doses can be administered before or after the chemotherapy.

Please refer to the summary of product characteristics for Avastin® in the respective applicable version for more information about Bevacizumab and its use.

6.5.2 Mechanism of action

Bevacizumab is a VEGF growth factor antibody. The monoclonal antibody Bevacizumab is aimed against the VEGF (Vascular Endothelial Growth Factor) circulating in the blood and prevents the angiogenesis of tumor cells. Bevacizumab binds the VEGF and prevents the interaction between the VEGF and its receptors (Flt-1 and KDR) on the surface of endothelial cells. This interruption of the stimulation pathway results in the death of vascular endothelial cells and the degeneration of new immature tumor vessels. In contrast, mature, differentiated blood vessels remain intact and continue to allow the supply of cytotoxic active ingredients.

6.5.3 Adverse effects

The overall safety profile of Bevacizumab is based on data of 1132 patients with metastatic colon or rectal cancer, locally progressive or metastatic non-small cell lung cancer, metastatic breast cancer and hormone-refractory prostate cancer who were treated with Bevacizumab either as monotherapy or in combination with a chemotherapy regimen within the scope of clinical studies. The most serious adverse events were:

- gastrointestinal perforation
- hemorrhages
• arterial thromboembolism

The most commonly observed adverse events across all clinical studies in patients treated with Bevacizumab with or without chemotherapy were: asthenia, diarrhea, nausea and pain not specified in more detail. The evaluation of the clinical safety data indicates that the occurrence of hypertension and proteinuria under Bevacizumab therapy is likely dose-dependent. In a randomized, double-blind, active control phase III study of metastatic colon or rectal cancer (study AVF2107g)\(^36\), 396 patients were treated with IFL + placebo (arm 1), 392 patients with IFL + Bevacizumab (arm 2) and 109 patients with 5-Fluorouracil/folinic acid (5-FU/FA) + Bevacizumab (arm 3). A randomized, double-blind, active control phase II study (study AVF2192g) examined the safety of Bevacizumab in 204 patients with metastatic colon or rectal cancer for whom Irinotecan treatment was not a viable first choice therapy. 104 of these patients were treated with 5-FU/FA + placebo (arm 1) and 100 patients with 5-FU/FA + Bevacizumab (arm 2).

**Hypertension:**

An elevated incidence of hypertension was observed under Bevacizumab therapy. The hypertension was normally treated with oral blood pressure lowering medications, such as e.g. ACE inhibitors, diuretic agents and calcium antagonists. Withdrawal of the treatment (in 0.7% of all Bevacizumab-treated patients) or hospitalization was only required in rare cases; hypertensive encephalopathy developed in one case (0.1%). No correlation between the risk of Bevacizumab-related hypertension and the demographic data of the patients, the underlying disease or the concomitant therapy was identified in any of the cases.

In clinical studies examining metastatic colon or rectal cancer, 22.4%–32.0% of Bevacizumab-treated patients developed hypertension of any grade. Grade 3 hypertension requiring oral anti-hypertensive medication was reported in 11.0%–16.0% of Bevacizumab-treated patients. No case of hypertensive crisis (grade 4) was reported. The mean change in diastolic blood pressure compared to baseline at week 24 of the treatment was +4.1 to +5.4 mmHg and in systolic blood pressure +5.5 to +8.4 mmHg.

No data is available on the effect of Bevacizumab in patients with uncontrolled hypertension at the time the treatment was introduced. Caution is therefore indicated before starting the therapy in these patients. The blood pressure should generally be monitored throughout the duration of the therapy.
Proteinuria:

Proteinuria was reported as an adverse event in 23.3% of all Bevacizumab-treated patients. The degree of severity ranged from transient, clinically asymptomatic minor proteinuria to the point of nephrotic syndrome, with the majority of patients being diagnosed with grade 1 proteinuria. The proteinuria observed in the clinical studies did not induce renal failure and the withdrawal of the therapy was only required in rare cases. In clinical studies examining metastatic colon or rectal cancer, proteinuria was reported in 21.7%-38.0% of Bevacizumab-treated patients. No grade 4 proteinuria was reported.

Patients with a history of hypertension may have an elevated risk of developing proteinuria under Bevacizumab therapy. There is evidence that dose-dependent NCI-CTCAE grade 1 proteinuria can develop under Bevacizumab therapy.

Gastrointestinal perforation:

Bevacizumab is associated with severe cases of gastrointestinal perforation in patients with metastatic colon or rectal cancer. In clinical studies examining metastatic colon or rectal cancer, gastrointestinal perforations were observed in 1.4%-2.0% of Bevacizumab-treated patients. 0.4% to 1% of these had a lethal outcome. The nature and severity of the manifestations of these events varied, ranging from an accumulation of air observed on an unenhanced abdominal X-ray and resolving without any treatment to the point of colonic perforation with abdominal abscess and a lethal outcome. Intra-abdominal inflammation, either due to gastrointestinal ulcer, tumor necrosis, diverticulitis or chemotherapy-related colitis was the most common shared characteristic of these cases.

The risk of gastrointestinal perforation may be elevated under Bevacizumab treatment and chemotherapy in patients with metastatic colon or rectal cancer and an intra-abdominal inflammatory process.

Wound healing:

Since Bevacizumab may have a detrimental impact on the wound healing process, patients who underwent major surgical procedures within the past 28 days were excluded from enrolling in clinical studies examining metastatic colon or rectal cancer. In clinical studies examining metastatic colon or rectal cancer,
the risk of post-surgical hemorrhages or impaired wound healing was not elevated during the therapy in patients who had undergone cancer-related surgery 28 to 60 days before the initiation of the treatment compared to the control groups. Adverse events corresponding to post-surgical hemorrhages or impaired wound healing were observed in 10%-20% of Bevacizumab-treated patients who underwent a major surgical procedure during the therapy.

**Hemorrhages:**

Overall, NCI-CTCAE grade 3 and 4 hemorrhagic events were observed in 4.0% of Bevacizumab-treated patients. There was no significant difference in the incidence of grade 3 and 4 hemorrhages between Bevacizumab-treated patients (3.1% - 5.1%) and subjects in the control arm (2.5%-2.9%) in clinical studies examining metastatic colon or rectal cancer. The majority of hemorrhagic events observed in the clinical studies were tumor-related hemorrhages (see below) and minor mucosal hemorrhages.

*Tumor-related hemorrhages* were observed in the phase I and phase II studies. Severe hemorrhages were observed in 9% of patients with non-small cell lung cancer under Bevacizumab treatment. 6% of them had a lethal outcome. The events developed suddenly and in the form of severe or massive hemoptysis, namely in patients with either histology of squamous epithelium and/or tumors in the center of the thoracic cage, close to the main blood vessels. In some of these cases, the hemorrhages were preceded by tumor cavitation and/or necrosis. In rare cases, tumor-related hemorrhages were also observed in other tumor types and localizations, including hemorrhages of the CNS (central nervous system) in a patient with hepatoma and occult metastases of the CNS and a continuous seeping hemorrhage of a sarcoma of the thigh with necrosis. In clinical studies examining metastatic colon or rectal cancer, tumor-associated hemorrhagic events were observed in 1%-3% of Bevacizumab-treated patients. The additional administration of Bevacizumab did not result in a significant increase in the incidence or severity of grade 3 of 4 hemorrhagic events.

Looking at all the clinical studies combined, *mucosal hemorrhages* were observed in 20% to 40% of Bevacizumab-treated patients. In the majority of cases, they concerned NCI-CTC grade 1 nosebleeds with a maximum duration of 5 minutes which resolved without medical intervention and did not require any changes in the treatment regimen. In clinical studies examining metastatic colon or rectal cancer, nosebleeds were reported in 22.0%-34.3% of Bevacizumab-treated patients. Minor mucosal hemorrhages
at other sites, such as e.g. gingival and vaginal bleeding, were less common.

The risk of hemorrhages of the central nervous system (CNS) in patients with metastases of the CNS under Bevacizumab therapy has yet to be evaluated conclusively, because these patients have been excluded from clinical studies.

Patients with metastatic colon or rectal cancer may have an elevated risk of developing tumor-related hemorrhages.

No information is available about the safety profile of Bevacizumab in patients with congenital hemorrhagic diathesis, acquired coagulopathy or patients who received full doses of anticoagulants for the treatment of thromboembolism before the start of the Bevacizumab therapy, because these patients were excluded from clinical studies.

**Thromboembolisms:**

The overall incidence of thromboembolic events was similar between Bevacizumab-treated patients (18.0%-19.4%) and control patients (16.2%-18.3%) in clinical studies examining metastatic colon or rectal cancer.

**Arterial thromboembolism:** in clinical studies examining metastatic colon or rectal cancer, the incidence of arterial thromboembolic events including cerebral insults, myocardial infarctions and transient ischemic attacks and other arterial thromboembolic events was higher in Bevacizumab-treated patients (3.3%-10.0%) than patients in the control groups (1.3%-4.8%). In five randomized studies (N=1745), including studies examining metastatic colon or rectal cancer, arterial thromboembolic events including cerebral insults, myocardial infarctions and transient ischemic attacks and other arterial thromboembolic events developed in 4.5% (45/1004) of patients treated with the combination of Bevacizumab and chemotherapy, compared to 2.0% (15/741) of patients treated with chemotherapy alone. The arterial thromboembolic events had a lethal outcome in 0.8% (8/1004) of patients treated with Bevacizumab plus chemotherapy. Death due to arterial thromboembolic events was reported in 0.4% (3/741) under chemotherapy alone. Cerebral insults (including transient ischemic attacks) were observed in 2.2% of patients under combination of Bevacizumab and chemotherapy and in 0.5% of patients under chemotherapy alone. Myocardial infarctions developed in 1.9% of patients under the combination of Bevacizumab and chemotherapy, versus 1.1% under chemotherapy alone.
A history of arterial thromboembolic events or age older than 65 years was associated with an elevated risk of thromboembolic events during the therapy.

**Venous thromboembolisms:** in clinical studies examining metastatic colon or rectal cancer, venous thromboembolic events including deep vein thrombosis, pulmonary embolism and thrombophlebitis developed in 9.0%–16.6% of Bevacizumab-treated patients compared with 13.5%–15.2% in the control groups. It was impossible to determine whether these events were a consequence of the patient’s underlying cancer, the cytotoxic chemotherapy, Bevacizumab or other risk factors.

**Decompensated heart failure (DHF)/cardiomyopathy:**

In the controlled clinical phase III study examining metastatic breast cancer, DHF-cardiomyopathy was reported for 3% of Bevacizumab-treated patients compared to 1% in the control group. The severity of these events ranged from asymptomatic decreases in the left-ventricular ejection fraction to the point of symptomatic DHF requiring hospitalization and treatment. All Bevacizumab-treated patients had previously received Anthracyclines (Doxorubicin, cumulative dose range 240–360 mg/m²). Many of these patients had previously received radiation treatment of the left thoracic wall. Following adequate medical treatment, the symptoms and/or the left-ventricular function improved in the majority of patients. No information about patients with DHF (NYHA grade II – IV) at the start of the therapy is available, because these patients were excluded from the studies. The DHF incidence of Bevacizumab-treated subjects was not elevated in patients with metastatic colon or rectal cancer.

Prior Anthracycline treatment and/or prior radiation treatment of the thoracic wall may be risk factors for the development of decompensated heart failure.

**Elderly patients:**

Data from five randomized clinical studies indicate that the age of >65 years is associated with an elevated risk for the development of arterial thromboembolic events including cerebral insults, transient ischemic attacks and myocardial infarctions, if these patients are treated with Bevacizumab. The incidence of
Bevacizumab-related events, including gastrointestinal perforation, impaired wound healing, hypertension, proteinuria, hemorrhages and decompensated heart failure/cardiomyopathy was not elevated in elderly patients (>65 years) with metastatic colon or rectal cancer under Bevacizumab treatment compared to those under the age of 65 receiving Bevacizumab treatment. In the phase III study examining metastatic colon or rectal cancer (AVF2107g), 114 of the 392 patients treated with Bevacizumab were older than 65 years. Only the incidence of grade 3/4 leukopenia was higher with ≥5% in the elderly patients (>65 years) compared to the subjects aged ≤65. In the phase II study examining metastatic colon or rectal cancer (AVF2192g), the majority of Bevacizumab-treated patients was older than 65 years (83%). The overall safety profile of Bevacizumab in this study was comparable with the one observed in the study AVF2107g.

Pathological laboratory test results:

A reduced neutrophil count, reduced white blood cell count and the presence of protein in the urine can be a consequence of Bevacizumab. Decreased neutrophil counts and lower white blood cell counts were the most common grade 3 and 4 pathologies of laboratory test results in Bevacizumab-treated patients across all clinical studies. Grade 3 and 4 pathologies in laboratory test results determined in ≥5% of Bevacizumab-treated patients with or without chemotherapy in any study included reduced neutrophil and white blood cell counts, protein in the urine, reduced blood potassium levels, decreased blood phosphorus levels, elevated blood glucose and elevated blood alkaline phosphatase levels. The higher incidence rates for reduced neutrophil and white blood counts observed in the IFL + Bevacizumab arm potentially correlate with elevated levels of SN38, the active metabolite of Irinotecan.

6.5.4 Advice on potential interactions of Bevacizumab with other medications

In studies it has been observed that patients under Bevacizumab therapy developed severe gastrointestinal hemorrhages and perforation of the gastrointestinal tract (1.5%). Patients with inflammatory intestinal processes have an elevated risk for these events. If the patient experiences any unclear abdominal pain, he/she should seek immediate medical attention and a diagnostic evaluation should be performed.
Special precaution within the scope of the Bevacizumab therapy is indicated in connection with therapeutic anticoagulation during Marcumar or Heparin therapy, the regular intake of acetyl salicylic acid in daily doses of >325 mg or non-steroidal anti-inflammatory medications which are known to inhibit the platelet function, as well as hemorrhagic diathesis or thrombotic tendency.

For patients developing a venous thromboembolic event during the course of the study and who are treated with oral anticoagulants, the INR must be determined at least every two days during the first week and then at least twice every week until stable INR values are reached and at least once every three weeks once the weekly dose has been established.

Cases of necrosis of the jaw have been reported in patients treated with Bevacizumab. The majority of these patients had been treated with intravenous bisphosphonates before or simultaneously. Special precaution is therefore indicated in connection with the simultaneous or successive administration of Bevacizumab and intravenous bisphosphonates.

6.5.5 Advice on surgeries and Bevacizumab

Any surgeries performed during the course of the study must be documented in the CRF. Because Bevacizumab can cause impaired wound healing, elective surgeries should only be scheduled 6-8 weeks after the last administration of the antibody. In the event of emergency surgeries, the Bevacizumab therapy should be suspended immediately and only resumed 28 days after the surgery and completion of the wound healing process.

If the patient responds well to the therapy and secondary curative surgery is an option, the antibody should be temporarily suspended 6 to 8 weeks before the surgery. The patient can continue with the chemotherapy during this time. If medically indicated, the Bevacizumab can be resumed 28 days after the successful surgery (no longer part of the therapy according to the clinical study protocol).

6.5.6 Advice on radiation therapy and Bevacizumab

Almost no data about patients under Bevacizumab and radiation therapy is yet available. The evaluation is difficult. In vitro and in vivo studies have demonstrated that ionizing radiation induces the VEGF expression in tumor cells. This is an effect aimed to protect tumor cells from radiation-related damage in spite of sufficient oxygenation. If the patient receives radiation therapy during or 12 weeks after the end of the therapy, this should be documented.
6.6 DOSE AND THERAPY MODIFICATIONS

6.6.1 General guidelines

Toxicities are classified according to the NCI-CTCAE V3.0 criteria; dose modifications are based on the graduation outlined there.

At the clinical investigator’s discretion, the dose should be modified depending on the degree of deterioration associated with toxicities that were already present at the time of enrolment in the study. The treatment should not be modified if any adverse effects develop which the clinical investigator believes should not result in serious or life-threatening consequences (e.g. alopecia). If several different toxicities develop simultaneously, the respective greatest dose reduction step should be used.

If the clinical investigator believes that an adverse effect is exclusively induced by a cytostatic agent or the antibodies (e.g. elevated blood pressure induced by Bevacizumab, alterations of the skin induced by Cetuximab), the dose of the other substances should not be reduced. If it is necessary to reduce the dose, the reduced dose should be maintained for the complete remaining duration of the chemoimmunotherapy. The re-escalation of the dose is not permitted.

If toxicity develops which requires the suspension of the treatment with a delay of more than three weeks, the patient is withdrawn from the treatment according to the protocol. If only one of the three components of the combination is discontinued, treatment with the other two substances can continue. If two medications are discontinued, the patient is withdrawn from the treatment according to the protocol.

The response is evaluated with an analogous delay for patients with a therapy delay. The causes of the dose modification, delay in the therapy and supportive measures if necessary should be documented both in the patient records as well as the CRF.

6.6.2 General guidelines concerning the individual active ingredients

6.6.2.1 Dose modification of Irinotecan and 5-Fluorouracil

If toxicity or other events develop (e.g. metabolic, hepatic, renal, central venous, pulmonary adverse events) which are not specifically mentioned in chapter 6.6.6, symptomatic treatment should be provided for the first grade < 3 incidence and the dose should not be modified. No further therapy with the combination according to the protocol should be administered in the presence of grade 4 toxicity; if the clinical investigator believes
that the therapy with the combination or parts thereof is in the patient’s best interest, the therapy can be continued within the scope of the study after consulting with the study center.

The further procedure is specified in Tab. 4.

**Tab. 4  Chemotherapy dose modification for non-hematological toxicity**

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st incidence</td>
<td>No dose reduction, prophylaxis, if possible</td>
<td>75% of the initial dose, prophylaxis, if possible</td>
<td>Permanent withdrawal unless the continuation of the treatment is in the patient’s best interest. In this case, if applicable, 50% of the initial dose after consulting with the study center.</td>
</tr>
<tr>
<td>2nd incidence</td>
<td>75% of the initial dose</td>
<td>50% of the initial dose</td>
<td></td>
</tr>
<tr>
<td>3rd incidence</td>
<td>50% of the initial dose</td>
<td>Permanent withdrawal unless the continuation of the treatment is in the patient’s best interest.</td>
<td></td>
</tr>
<tr>
<td>4th incidence</td>
<td>Permanent withdrawal unless the continuation of the treatment is in the patient’s best interest.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**6.6.2.2 Dose modification of Cetuximab**

The dose modifications for Cetuximab are also described specific to the respective toxicity in chapter 6.6.6. Except in case of grade 3 or 4 dermal toxicity, the Cetuximab therapy is not delayed in the presence of chemotherapy-induced toxicities. Even if the following administrations of 5-FU or Irinotecan are delayed, the patient still receives the Cetuximab infusions every 7 days as planned.

However, it may be necessary to delay the Cetuximab infusion if the patient has fallen ill in the meantime (e.g. due to an infection). If the clinical investigator believes that the temporary suspension of the Cetuximab
therapy is justified, the interim medical condition must resolve within such a timeframe that no more than 2 successive infusions are delayed. After the temporary suspension of the Cetuximab therapy, it is continued with the defined dose. The higher initial dose is not repeated. If the therapy has to be delayed for more than 14 days, the treatment within the scope of the study is withdrawn. **Treatment with Cetuximab must be suspended as soon as a patient develops a grade 3 or 4 allergic reaction or hypersensitivity reaction.**

### 6.6.2.3 Dose modification of Bevacizumab

No recommendations for reducing the Bevacizumab doses exist. Toxicities induced by Bevacizumab generally do not coincide with chemotherapy-induced toxicities (exception: patients with pre-existing anticoagulation).

All grade 3 toxicities induced by Bevacizumab (except for proteinuria) require the suspension of the Bevacizumab therapy. If the symptoms are reversed to grade ≤1 within 4 weeks, the therapy is continued as planned. Omitted individual doses are not made up.

The Bevacizumab therapy is withdrawn permanently in connection with:

- any grade 4 toxicity (except asymptomatic thrombosis)
- development of arterial thromboembolic events
- hypertension not manageable with medication or grade 4 hypertension
- grade ≥3 hemorrhages
- second incidence of the same Bevacizumab-specific grade 3 toxicity
- any Bevacizumab-specific grade 3 toxicity, which is not reversed to grade 1 within 4 weeks
- suspected gastrointestinal perforation

See chapter 6.6.3.2 & 6.6.5 for additional information about specific toxicity-related therapy suspensions or withdrawal of the Bevacizumab therapy.
6.6.3 Conditions for the start of a new chemotherapy cycle

The following criteria must be met before every new cycle of the combination chemotherapy:

• no grade 2, 3, or 4 hematologic toxicity (NCI-CTCAE V3.0) with a neutrophil granulocyte count of >1500/μL or platelet count of > 100,000/μL in the hemogram,

• no grade 2, 3, or 4 stomatitis (NCI-CTCAE V3.0),

• no grade 2, 3, or 4 nausea and vomiting (NCI-CTCAE V3.0),

• no grade 2, 3 or 4 diarrhea (NCI-CTCAE V3.0) and no antidiarrheal therapy within the last 24 hours,

• no grade 3 or 4 allergic reaction to Irinotecan or FUFA,

• no grade 2 or 3 hand-foot syndrome (NCI-CTCAE V3.0),

• Bilirubin levels ≤ 1.5 x ULN,

• ALAT and ASAT levels ≤ 2.5 x ULN in patients without metastases of the liver, ALAT and ASAT levels ≤ 5 x ULN in patients with metastases of the liver,

• no cardiotoxicity induced by 5-FU,

• no evidence of pulmonary fibrosis,

• no grade 3 or 4 peripheral sensory neuropathy,

• creatinine levels ≤1.5 x upper limit of normal,

• no other NCI-CTCAE V3.0 grade 2, 3, or 4 non-hematologic toxicities, except grade 2 or 3 proteinuria, acneiform skin rash, nail diseases

• no treatment suspension with delayed administration of the cytostatic agents by more than three weeks with respect to the last cycle and

• ECOG performance status ≤2.

If the application of the cytostatic agents is delayed, the administration of Bevacizumab and Cetuximab, respectively is not delayed.

6.6.4 Conditions for the administration of Cetuximab

According to the inclusion criteria, the detection of wild-type KRAS in the tumor (primary tumor or metastasis) is a pre-requisite for the administration of Cetuximab. Patients who were enrolled in the studies before amendment 2 entered into effect and in whom the KRAS mutation was detected, should not receive Cetuximab any longer. These patients remain in the study (with FOLFIRI alone) until the next scheduled restaging is conducted. Patients whose disease is progressive at that time will be withdrawn from the study.
In the presence of SD or therapy response, it is at the clinical investigator’s discretion to continue treating the patients with FOLFIRI alone outside of the study. In any case, these patients would be followed within the scope of the follow-up care.

**The following criteria must be met** before every administration of **Cetuximab**:

- the dermal toxicity before every Cetuximab administration (e.g. acne, acneiform skin rash, nail diseases) must be grade <3;
- no grade 3 or 4 allergy, no repeated allergic reaction to Cetuximab;
- no delay of the Cetuximab administration by more than 14 days.

If any toxicity develops which requires the suspension of the treatment with a delay of the cytostatic therapy as well as Cetuximab by more than three weeks with respect to the currently scheduled applications, the study treatment is withdrawn.

### 6.6.5 Conditions for the administration of Bevacizumab

**The following criteria must be met** before every administration of **Bevacizumab**:

All patients treated with Bevacizumab are required to measure the proteinuria by means of a test strip within the last 48 hours before every administration. Bevacizumab is administered according to the following procedure:

- nephrotic syndrome (grade 4, NCI-CTCAE V3.0): permanent therapy withdrawal;
- normal blood pressure or hypertension controlled with drugs (see also chapter 6.6.6.10);
- no Bevacizumab-specific grade 3 toxicity;
- no reason for permanent therapy withdrawal (see chapter 6.6.2.3);
- no impaired wound healing;
- no scheduled elective surgery (see chapter 6.5.5).

See chapter 6.6.2.3 & 6.6.6 for more information about therapy suspensions or withdrawal of the Bevacizumab therapy.
6.6.6 Dose modification for specific toxicities

6.6.6.1 Anemia

Higher grade (non-hemolytic) anemia should be managed with blood transfusions or with the administration of erythropoietin. No dose modification of the chemotherapy/antibody therapy is required.

6.6.6.2 Neutropenia, thrombopenia

If grade 4 NCI-CTCAE thrombocytopenia or neutropenia develop, the cytostatic agent dose for the subsequent cycles is reduced to 75% of the starting dose. In case of re-occurrence, the dose is reduced to 50% and, if the symptoms persist, the cytostatic therapy is withdrawn.

6.6.6.3 Stomatitis

If grade ≥2 stomatitis develops, the 5-FU therapy should be suspended immediately until the start of the next cycle. The latter may only be initiated once these symptoms have returned to grade 1 or resolved completely. In this case, the dose is modified according to Tab. 4 (chapter 6.6.2.1).

6.6.6.4 Nausea/vomiting

Nausea/vomiting can be treated with Metoclopramide and 5-HT3 antagonists. These substances can also be given to the patient as prophylaxis. Dexamethasone can be added to this antiemetic therapy for pronounced symptoms.

If grade ≥2 nausea/vomiting develops, the dose can be modified according to Tab. 4 (chapter 6.6.2.1).

6.6.6.5 Diarrhea

Patients with severe diarrhea must be monitored closely and treated with fluids and electrolyte substitution in case of dehydration. Therapy with standard anti-diarrheal agents (e.g. Loperamide) can be considered starting from grade 1. This therapy is essential starting from grade two. The common Loperamide dose is 4 mg first, followed by 2 mg every 2 hours for at least 12 hours until the patient has been free of diarrhea for 12 hours (the max. daily Loperamide dose of 16 mg should not be exceeded).

If Irinotecan-related delayed-onset diarrhea develops, treatment must be initiated promptly. See chapter 6.3.3 for details.
6.6.6.6 Allergic reactions

The clinical investigator should initiate treatment procedures according to the best medical practice for any allergic or hypersensitivity reactions.

No dose modification is required for acute grade 1 or 2 allergic reactions to the cytostatic agents, if the clinical investigator believes that the treatment should be continued in the patient’s interest.

The treatment should be suspended immediately in connection with acute grade 3 or 4 allergic reactions which the clinical investigator believes are likely due to a cytostatic agent and adequate treatment should be provided. Patients should not be given the corresponding medication any more.

Based on previous experience with allergic reactions/hypersensitivity reactions to Cetuximab, the therapy guidelines illustrated in Table 5 may be applicable. Please also follow the specific recommendations for drug prophylaxis outlined in chapter 6.4.4!
Tab. 5  *Treatment adjustment for Cetuximab-related allergic/hypersensitivity reactions*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Allergic reactions/hypersensitivity reactions with a degree of severity according to NCI-CTCAE V3.0 criteria</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Temporary reddening or skin rash, drug-induced fever of &lt;38° C</td>
<td>Reduction of the Cetuximab infusion speed by 50%; close monitoring for deterioration of the symptoms.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The overall duration of the infusion of the weekly Cetuximab dose should not exceed 240 minutes.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Rash, reddening, urticaria, drug-induced fever of ≥38° C</td>
<td>Stop the Cetuximab infusion.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administer bronchodilators, oxygen etc. as medically indicated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume the infusion at a speed of 50% as soon as the allergic reaction/hypersensitivity reaction has reversed or receded to grade 1; close monitoring for deterioration of symptoms.</td>
</tr>
<tr>
<td>Grade 3 or grade 4</td>
<td>Grade 3: symptomatic bronchospasm requiring parenteral medication, with or without urticaria; hypersensitivity-related edema, angioedema, hypotension</td>
<td>Immediately stop the Cetuximab infusion and disconnect the patient from the infusion set.</td>
</tr>
<tr>
<td></td>
<td>Grade 4: anaphylaxis</td>
<td>Administration of Adrenaline, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressors, oxygen etc. as medically indicated. The patient’s treatment must be suspended immediately; no further Cetuximab therapy may be administered.</td>
</tr>
</tbody>
</table>

If the Cetuximab infusion speed was lowered because of an allergic reaction/hypersensitivity reaction, this slower speed must be maintained for all subsequent infusions. If a patient develops a second allergic reaction/hypersensitivity reaction under this slower infusion speed, the infusion must be stopped and no further Cetuximab therapy may be administered. The Cetuximab treatment must be discontinued as soon as a patient develops a grade 3 or 4 allergic reaction or hypersensitivity reaction.

No hypersensitivity reactions have yet been reported for Bevacizumab. If a grade 3 or 4 reaction develops which the clinical investigator believes is due to Bevacizumab, the administration should be withdrawn permanently.
6.6.6.7 Hand-foot syndrome

Hand-foot syndrome (palmoplantar erythrodysesthesia) is a type of dermal toxicity which is classified into three degrees of severity:

- **grade 1** minimal alterations of the skin or dermatitis (e.g. erythema) not accompanied by pain
- **grade 2** alterations of the skin (e.g. detachment of the skin, blistering, bleeding, edema) accompanied by pain, but without functional impairment
- **grade 3** ulcerative dermatitis or alterations of the skin accompanied by pain and functional impairment

If grade 2 or 3 develops, the 5-FU therapy should be suspended immediately until the next cycle starts. The latter may only be initiated once these symptoms have returned to grade 1 or resolved completely. In this case, the dose is modified according to Tab. 4 (chapter 6.6.2.1). With grade 3, Cetuximab should be temporarily suspended until the symptoms have returned to grade ≤2. Treatment with vitamin B6 is not necessary. The therapeutic or prophylactic use of a corticoid- or urea-containing ointment may be conducive.

### 6.6.6.8 Acne, acneiform skin rash, nail diseases

If the patient develops a grade 3 dermal reaction (acne, acneiform rash, nail diseases), the Cetuximab therapy can be delayed for up to 2 weeks without changing the dose (i.e. maximum interval between therapy administrations: 3 weeks). The clinical investigator should consider the concurrent medication with topical or oral antibiotics; topical corticosteroids are not recommended. The prescription of topical antibiotics (e.g. Benzoyl peroxide, Erythromycin) or the systemic administration of antibiotics (e.g. oral tetracyclines such as Doxycycline 100 mg) should be considered for the treatment of acne-like grade 1 or 2 skin rashes. Patients with grade ≥3 reactions should be seen by a dermatologist for assessment and treatment. The administration of an oral antihistamine is recommended for itchiness. The use of calming creams has proven useful for the relief of dry skin. Dry skin can be associated with fissures for which local bandages can be helpful. If the toxicity is reversed to grade ≤2 during the subsequent treatment period, the therapy can be resumed. If grade 3 dermal reactions re-occur for a second or third time, the Cetuximab therapy can be delayed one more time by up to 14 days, but the dose at the time of resumption must be reduced to 200 mg/m² and then to 150 mg/m². Any reductions in the Cetuximab dose must be maintained. The Cetuximab therapy must be suspended if 3 successive infusions are omitted or if grade 3 dermal reactions re-occur for the fourth time in
spite of an adequate dose reduction (see Figure 1). However, the therapy with the cytostatic agents within the scope of the study can be continued.

Figure 1: Treatment adjustment for Cetuximab-related dermal reactions

6.6.6.9 Elevated transaminase and alkaline phosphatase levels

After the first incidence of elevated ALAT or ASAT levels or grade 3 or 4 AP, which the clinical investigator believes is caused by Bevacizumab, the therapy with Bevacizumab should only be resumed after the symptoms have reversed to grade ≤1. The therapy with Bevacizumab should be discontinued after the second incidence.

6.6.6.10 Arterial hypertension

In the past, arterial hypertension was reported in all studies with Bevacizumab. Every incidence should be documented as an adverse event and antihypertensive therapy should be initiated as needed. The latter should be documented in the CRF.

Regular blood pressure measurements (before and after the administration) should be conducted for patients under Bevacizumab. Regular self-measurements are beneficial. The measurements are correctly taken while
seated and after 5 minutes of rest. Repeat the measurement if the initial systolic blood pressure is ≥140 mmHg and/or the diastolic blood pressure is ≥90 mmHg.

• Grade 1 hypertension: one-time, asymptomatic, transient (<24 hour) elevation of >20 mmHg (diastolic) or >150/100 mmHg with previously regular blood pressure values. No intervention is required.

• Grade 2 hypertension: repeat or persistent (≥24 hours) or symptomatic elevation of >20 mmHg (diastolic) or >150/100 mmHg with previously regular value. Monotherapy with an antihypertensive agent may be indicated. The therapy with cytostatic agents and Bevacizumab can be resumed once the blood pressure has returned to values of <150/100 mmHg.

• Grade 3 hypertension: if more than one antihypertensive agent or the intensification of the pre-existing therapy is required. The therapy is temporarily suspended for as long until the blood pressure has returned to regular values. The therapy within the scope of the study is withdrawn permanently if the hypertension is unmanageable.

• Grade 4 hypertension: life-threatening hypertension such as hypertensive crisis. The emergence of grade 4 hypertension requires the permanent withdrawal of the Bevacizumab therapy.

6.6.11 Cardiotoxicity

If a grade ≥2 cardiac adverse effect develops which the clinical investigator believes is due to the administration of 5-FU, the Fluoropyrimidine therapy should be withdrawn permanently. In this case, no further Irinotecan therapy is administered either. The continuation with the Cetuximab or Bevacizumab therapy within the scope of the study is possible.

6.6.12 Hemorrhages

All NCI-CTCAE V3.0 grade 3/4 hemorrhages require the permanent withdrawal of the Bevacizumab therapy.

6.6.13 Gastrointestinal perforation

Rare cases of gastrointestinal perforation were reported under Bevacizumab. Patients had generally been diagnosed with inflammatory processes. Special precaution is indicated if major abdominal pain develops under the therapy and the symptoms should be assessed promptly.

The Bevacizumab therapy is permanently withdrawn for patients with gastrointestinal perforation.

6.6.14 Impaired wound healing

For patients who develop impaired wound healing under Bevacizumab therapy, the Bevacizumab treatment should be temporarily suspended until the wound has healed completely. Likewise, the Bevacizumab therapy is temporarily suspended before elective surgery (see chapter 6.5.5).
6.6.6.15 Proteinuria

All patients treated with Bevacizumab are asked to measure the proteinuria by means of test strips within the last 48 hours before every administration. Bevacizumab is permanently withdrawn in the presence of nephrotic syndrome (NCI-CTCAE V3.0 grade 4).

6.6.6.16 Thromboses/embolisms

The therapy must be temporarily suspended or permanently withdrawn for patients who develop grade 3 or 4 thrombosis/embolism under Bevacizumab. The following procedure is required:

- Bevacizumab must be permanently withdrawn in the presence of arterial thromboembolic events.
- Grade 3 or asymptomatic grade 4 thrombosis: temporary suspension of the Bevacizumab therapy. If the duration of the anticoagulant therapy is ≤2 weeks, the Bevacizumab therapy is temporarily suspended until the end of the therapy. If the planned anticoagulant therapy is ≥2 weeks, the Bevacizumab therapy is only resumed after the 2 weeks under the existing anticoagulation if the following criteria are met:
  - The patient is receiving an unchanged dose of anticoagulant and, if Warfarin is used, the INR value is within the defined range of 2-3 before the Bevacizumab therapy is resumed
  - The patient may not have had any grade 3 or 4 hemorrhagic events since the start of the study
  - There may not be evidence of tumor growth in any of the major blood vessels in any of the patient’s previous CT scans
  - Symptomatic grade 4 thrombosis: permanent withdrawal of the Bevacizumab therapy.

For patients who develop a venous thromboembolic event during the course of the study or who are treated with oral anticoagulants, the INR must be determined at least every other day during the first week and then at least twice every week until stable INR values are achieved and at least once every three weeks once the weekly dose has been defined.

6.6.6.17 Respiratory symptoms

If any respiratory symptoms emerge or worsen during or after the treatment with Cetuximab, a detailed description is required and the clinical investigators are asked to use their best judgment to request diagnostic procedures that allow the establishment of a secure diagnosis (see chapter 6.4.5).
6.7 Number of therapy cycles/completion of the study treatment

The therapy is continued until one of the following events occurs:

• tumor progression

• observation of an unacceptable toxicity

• achievement of confirmed CR

• achievement of a status for surgical treatment according to an interdisciplinary consult and simultaneous status of objective remission (CR or PR) as well as the patient’s consent to undergo surgery (cp. chapter 6.4.7 & 6.5.5)

• the patient asks for withdrawal of the therapy

• required withdrawal of the therapy based on the assessment of the treating physician

The following additional events may result in the suspension of the individual study treatment:

• pregnancy or inadequate contraception (for female patients of child-bearing potential only)

• lost to follow-up

• death

NB.: based on the rules of “Good Clinical Practice” (GCP), it is necessary to include all patients enrolled in the clinical study in the analysis, even if it was impossible to conduct their treatment in accordance with the clinical study protocol. It is therefore essential to continue documenting the patients as detailed as possible even if the protocol was violated and to conduct at least the examinations intended in the final examination. The time of the withdrawal and, if known, the reason for the withdrawal should be documented in the case report form.

6.8 Concomitant medication/supportive measures

6.8.1 General information

Generally, patients should continue to take their previous medication as advised by the treating physician.
The concomitant therapy relevant to the study outcomes is recorded on the case report form.

6.8.2 Antiemetic therapy and prophylaxis

Adequate doses of 5-HT3 antagonists and corticosteroids as needed prior to the chemotherapy, if necessary in combination with Metoclopramide.

6.8.3 Treatment of diarrhea

Cp. chapter 6.3.3. and 6.6.6.5

6.8.4 Treatment for neutropenia

Patients with severe neutropenia have a high risk with respect to febrile neutropenia/infections, especially in the presence of simultaneous diarrhea. The dose of subsequent cycles should be reduced as soon as asymptomatic grade 4 neutropenia or febrile neutropenia (grade 3 to 4) is determined (see chapter 6.6.6.2).

The preventive oral or i.v. administration of antibiotics is not recommended for grade 4 neutropenias without fever (except in the presence of simultaneous diarrhea). However, the decision about the use of antibiotics shall be made in accordance with the respective study site’s common strategy. The preventive use of growth factors (e.g. G-CSF, GM-CSF) is not recommended. However, if the clinical investigator believes that they would be helpful, the prophylactic use should only be considered in the case of a history of prolonged neutropenia.

6.8.5 Hand-foot syndrome

The prophylactic intake of Pyridoxine (vitamin B6) across the board concomitantly with the chemotherapy is not recommended, because it may potentially reduce the therapeutic efficacy of the used cytostatic agents. For the same reason, the therapeutic use of Pyridoxine should only be considered for severe hand-foot syndrome and the indication must be established by the treating physician. The use of corticosteroid- or urea-containing fatty ointments as topical treatment may be helpful.
6.8.6 Arterial hypertension

The administration of common antihypertensive agents is indicated for the treatment of hypertensive crises.

6.9 EMERGENCY PROCEDURES

In case of emergency, the director of the clinical study may be contacted as follows:

Prof. Dr. V. Heinemann  
Medical Clinic III, Clinical Center Großhadern  
Ludwig-Maximilians University Munich  
Marchioninistr. 15  
81377 Munich  
Phone: 089 7095 -2208, -2250 or 089 7095 -0 (through radio)  
Fax: 089 7095 -5256

Serious adverse drug reactions (cp. chapter 7.7.6) observed within the scope of this study must be reported within 24 hours to

ClinAssess GmbH  
Birkenbergstr. 82  
51379 Leverkusen  
Phone: 02171 36 336 -0  
Fax: 02171 36 336 -55.

ClinAssess GmbH will promptly notify the director of the clinical study as well as the affected manufacturer. Serious adverse drug reactions in particular relate to fatal, life-threatening or otherwise permanently debilitating toxicities. A special documentation sheet for adverse reactions must be completed with the provision of additional details.

6.10 RANDOMIZATION/STRATIFICATION

Patients enrolled in the study are randomized at a ratio of 1:1 into arm A (FOLFIRI + Cetuximab) or arm B (FOLFIRI + Bevacizumab). They are stratified based on the following parameters, which must be indicated at the time of randomization:

• general status ECOG 0-1 vs. 2

• number of metastatic locations: 1 vs. >1

• white blood cell count <8000/μL vs. ≥8000/μL
• alkaline phosphatase $< 300 \text{ U/L}$ vs. $\geq 300 \text{ U/L}$.

Once a patient who meets the selection criteria is ready for enrolment in the study, contact the randomization center on weekdays between 08:00 a.m. and 06:00 p.m. and fax them the registration form or call them at:

ClinAssess GmbH  
Phone: 02171 36 336 -0  
Fax: 02171 36 336 -55

The following information is required for the registration:

• name/no. of the clinical center and the clinical investigator  
• name of the caller/person submitting the registration (if different from clinical investigator)  
• patient’s date of birth  
• stratification factors (see above)

The randomization center will then issue the subject identification number (the number used to identify the patient on all case report forms and in any other correspondence) and the therapy assignment.

6.11 SECOND-LINE THERAPY

The following recommendation is made with respect to the second-line therapy:

Arm A:  
FOLFOX (plus Bevacizumab, if necessary)

Arm B:  
Irinotecan + Cetuximab

The type of the therapy regimen as well as the quality and duration of the response are recorded within the scope of the follow-up documentation.
7 EXAMINATION METHODS AND EVALUATION CRITERIA

7.1 OVERVIEW/EXAMINATION SCHEDULE

<table>
<thead>
<tr>
<th>Examination Item</th>
<th>Before the therapy start (within 7 days)</th>
<th>Before each cycle</th>
<th>Restaging: after 6 and 12 weeks of treatment, and then always after 10 weeks of treatment</th>
<th>End of therapy</th>
<th>Follow-up every 3 months (until the subject dies or for a maximum of 5 years)</th>
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<tbody>
<tr>
<td>Declaration of consent</td>
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<td>Inclusion and exclusion criteria</td>
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<tr>
<td>Accompanying translational research project</td>
<td>one-time blood sampling</td>
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<tr>
<td>Medical history</td>
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<td>Height</td>
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<td>Vital signs (blood pressure, heart rate)</td>
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<td>ECOG performance status</td>
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<td>X</td>
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<td>X</td>
<td></td>
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<tr>
<td>ECG</td>
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<td></td>
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<td>Measurement of the reference lesion (RECIST)</td>
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<td>X</td>
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<td>X</td>
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<td>Bone scintigraphy/X-ray in case of suspected bone metastases</td>
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<td>X</td>
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<td></td>
</tr>
<tr>
<td>Brain CT in case of suspected CNS metastases</td>
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<td>X</td>
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<tr>
<td>Blood count</td>
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<td></td>
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<tr>
<td>Clinical chemistry</td>
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<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>INR</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEA and/or CA 19-9</td>
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<tr>
<td>Urine dipstick test</td>
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<td>X</td>
<td>X</td>
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<td></td>
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<tr>
<td>Pregnancy test (serum or urine) for women of child-bearing potential</td>
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<td></td>
<td></td>
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<td>Relevant concomitant therapy</td>
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<td></td>
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<td>Clinical symptoms/toxicity (NCI-CTCAE V3.0)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

1: within 14 days before the therapy start, additional chest CT in case of suspected lung metastases
2: white blood cells, red blood cells, platelets, hemoglobin, neutrophil granulocytes
3: bilirubin, creatinine, ALAT, ASAT, AP, INR, potassium, calcium, magnesium
4: in case of detected protein of ≥30mg or >1+ in the urine dipstick analysis: quantitative protein determination in the 24-hour urine sample
5: survival/disease status only
6: as long as no confirmed progression under/after 1st-line therapy has been documented
7: one-time blood sampling (for the timing of the examination see synopsis, number 7.1 and 7.2). The written consent (signature of the patient information and declaration of consent, version 2.0 dated 01-25-2011 and version 3.0 dated 04-20-2012, respectively) is required for the one-time blood sampling.
7.2 BASELINE DOCUMENTATION

Within 14 days before the therapy start:

- measurement of the reference lesions according to the RECIST criteria (CT scan of the abdomen/pelvis, chest X-ray in 2 planes if necessary, additional chest CT in case of suspected lung metastases), bone scintigraphy/X-ray in case of suspected bone metastases, brain CT in case of suspected CNS metastases

Within 7 days before the therapy start:

- written declaration of consent
- medical history
- comorbidities and medications
- physical examination including measurement of height, body weight and vital signs (blood pressure and heart rate)
- evaluation of the performance status (ECOG scale)
- ECG
- pre-existing symptoms (NCI-CTCAE V3.0)
- complete blood count (white blood cells, neutrophil granulocytes, platelets, red blood cells, hemoglobin)
- clinical chemistry (bilirubin, creatinine, ALAT, ASAT, alkaline phosphatase, potassium, calcium, magnesium)
- INR
- pregnancy test (serum or urine) for women of child-bearing potential
- urine dipstick analysis, 24-hour urine test for proteinuria of \( \geq 1^+ \) or \( \geq 30 \text{ mg/dL} \)

Accompanying translational research project

One-time collection of a 10 mL PAXgene blood DNA sample (corresponding tubes are provided by the LMU). Blood is collected from all patients enrolled in the study after amendment 3 entered into effect during the pre-treatment phase. For all patients who were already enrolled in the study before amendment 3 entered into effect, the blood sample is collected during the next scheduled visit. The written consent (signature of the patient information and declaration of consent, version 2.0 dated 01-25-2011) is required for the one-time blood collection.
7.3 Examinations during the study treatment

7.3.1 Examinations during chemotherapy and antibody therapy (before every cycle)

- physical examination, vital signs (blood pressure, heart rate) body weight
- complete blood count (white blood cells, neutrophil granulocytes, platelets, red blood cells, hemoglobin)
- clinical chemistry (bilirubin, creatinine, ALAT, ASAT, alkaline phosphatase, potassium, calcium, magnesium)
- documentation of clinical symptoms and toxicities (NCI-CTCAE V3.0), concurrent medication
- ECOG performance status
- urine dipstick analysis, 24-hour urine test for proteinuria of $>1\geq30$ mg/dL

7.3.2 Tumor assessment

The tumor is assessed according to the RECIST criteria after the completion of cycle 3 (after 6 weeks of treatment) and cycle 6 (after 12 weeks of treatment) and then after every 10 weeks of treatment (CT scan of the abdomen/pelvis, chest X-ray in 2 planes, if necessary, additional chest CT in case of suspected lung metastases).

Moreover, the other tumor manifestations as well as the tumor markers CEA and/or CA 19-9 are determined and documented.

7.4 Final examinations

The following examinations are conducted at the end of the treatment (i.e. when the tumor progresses or if the treatment is withdrawn prematurely):

- physical examination including ECOG performance status, body weight
- complete blood count (white blood cells, neutrophil granulocytes, platelets, red blood cells, hemoglobin)
- clinical chemistry (bilirubin, creatinine, ALAT, ASAT, alkaline phosphatase, potassium, calcium, magnesium)
- ECG
- documentation of clinical symptoms and toxicities (NCI-CTCAE V3.0)
- measurement of the reference lesion (CT scan of the abdomen/pelvis, chest X-ray in 2 planes, if necessary, additional chest CT in case of suspected lung metastases), bone scintigraphy/X-ray if necessary, in case of bone metastases and brain CT in case of CNS metastases
- determination and documentation of the remaining tumor manifestations

7.5 **FOLLOW-UP**

Cancer follow-up care is provided every 3 months after completion of the treatment (until the subject dies or for a maximum of 5 years):

- survival/disease status, ECOG performance status
- measurement of the reference lesion (RECIST) (CT scan of the abdomen/pelvis, chest X-ray in 2 planes, if necessary, additional chest CT in case of suspected lung metastases), determination and documentation of the remaining tumor manifestations as long as no confirmed progression has been documented under/after 1st-line therapy
- documentation of relevant protracted toxicity
- documentation of the follow-up therapy with quality and duration of response

7.6 **DOCUMENTATION OF THE THERAPEUTIC EFFECTIVENESS**

7.6.1 **Primary target criterion: tumor response**

The remission is assessed by means of the RECIST criteria\textsuperscript{55}. To evaluate the therapeutic success, the same examination methods used to diagnose the tumor spread at baseline are used to check the tumor spread. All measurable tumor manifestations identified as target lesions must be measured during each evaluation.

At least one measurable lesion must be present which can be measured properly in one plane and has a size of \( \geq 2 \text{ cm} \) (1 cm in the spiral CT scan). If several lesions are present, the sum of the longest diameters of the individual target lesions is used for the evaluation. All initially identified target lesions must always be evaluated.
The following are defined as non-target lesions: bone lesions, leptomeningeal metastases, pleural/pericardial effusion, ascites, inflammatory chest diseases, lymphangitis, cystic lesions and lesions not measurable by means of a CT or MRI scan as well as measurable manifestations not defined as target lesions, if any. All non-target lesions are described as the illness progresses and must not be measured.

**Complete remission (CR):** complete disappearance of all lesions for at least 4 weeks.

**Partial remission (PR):** more than 30% reduction in the overall diameter of the tumor for at least 4 weeks.

**Stable disease (SD):** neither partial remission nor progression of the tumor growth.

**Progressive disease (PD):** more than 20% increase in the diameter of the tumor or the total diameter of the tumor or at least one new lesion.

**Tab. 6 Evaluation of the overall response:**

<table>
<thead>
<tr>
<th>Overall response</th>
<th>Target lesion</th>
<th>Non-target lesion</th>
<th>New lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>CR</td>
<td>no</td>
</tr>
<tr>
<td>PR</td>
<td>CR</td>
<td>incomplete resp./SD</td>
<td>no</td>
</tr>
<tr>
<td>PR</td>
<td>PR</td>
<td>not PD</td>
<td>no</td>
</tr>
<tr>
<td>SD</td>
<td>SD</td>
<td>not PD</td>
<td>no</td>
</tr>
<tr>
<td>PD</td>
<td>PD</td>
<td>irrelevant</td>
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<tr>
<td>PD</td>
<td>irrelevant</td>
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</tr>
<tr>
<td>PD</td>
<td>irrelevant</td>
<td>irrelevant</td>
<td>yes</td>
</tr>
</tbody>
</table>

Within the scope of this clinical study protocol, the conduct of secondary resection of metastases with a curative intent requires the prior demonstration of objective remission (CR or PR). If it is impossible to
confirm the findings of remission before the surgery for lack of time, this patient is still deemed a success within the meaning of the primary target criterion, unless the surgical/pathological findings are diametrically opposed to this.

Central radiological review: the confirmation of the tumor response is validated with an independent, blinded, central review of the imaging results (radiologyConsulting GmbH, Am Arenzberg 40, 51381 Leverkusen). The currently applicable version of the RECIST 1.1 classification shall be used for this purpose.

7.6.2 Time-related efficacy parameters

Duration of full remission: calculated from the time of first confirmation of complete remission to progress.

Total duration of remission: calculated from the time of first confirmation of partial or complete remission to progress.

Progression-free survival (PFS): interval between randomization and progress or death, irrespective of the cause.

With respect to the duration of the remission and PFS, a renewed progression is present following interim remission, if the criterion defined above under “progressive disease (PD)” applies in relation to the best possible achieved interim status (“nadir”).

Time to failure of first-line strategy (TFS): the time from the start of the study therapy to the occurrence of one of the following endpoints (events) is defined as TFS: death, Capecitabine administration, Oxaliplatin administration, Cetuximab administration (arm B only), Bevacizumab administration (arm A only), Mitomycin administration. Consequently, the endpoint is only reached if a substance is prescribed that was not administered within the scope of the first-line therapy. The TFS is illustrated by means of Kaplan-Meier diagrams and specification of the median TFS times using the 95% confidence interval. The differences between the two therapy arms are calculated by means of the log-rank test. A statistically significant difference is achieved if p<0.05.

Overall survival (OS): interval between randomization and death due to any cause.
7.6.3 Qualitative efficacy parameter

**Remission depth:** the remission depth is calculated as change in percent of the tumor size measured according to the RECIST criteria compared to baseline in order to facilitate a more detailed illustration of the tumor response. The results of the central review of the imaging results should be used for this purpose and a so-called “waterfall analysis” should be conducted. In addition, the two groups should be compared by means of the Mann-Whitney U test to determine a potential statistical difference. A statistically significant difference is achieved if the calculated two-sided p-value is $0<0.05$.

7.6.4 Procedure for resectable metastases

Patients for whom the resectability of metastases becomes evident during the study therapy should undergo a surgical resection of the metastases. The EORTC study published by Nordlinger et al.\(^{56}\) demonstrated that patients with primary resectable metastases achieved a significantly longer progression-free survival if they received FOLFOX4 therapy 3 months before and after surgery. It is unclear to what extent this data is transferrable to patients with secondary resectable metastases and what the significance of chemotherapy is in this context. No conclusive recommendation for the continuation of the therapy can therefore be made for the treatment after the resection of the metastases in R0-resected patients.

7.7 TOLERABILITY ASSESSMENT

7.7.1 General information

The clinical investigators are responsible for monitoring the safety of the patients enrolled in the study.

The toxicity is systematically evaluated at the end of each cycle. The ECOG performance status as well as the toxicity according to the NCI-CTCAE V3.0 criteria are recorded.

7.7.2 Laboratory tests
The following laboratory tests are conducted before the start of the study and before the start of each new cycle:

- hematological analyses (hemoglobin, platelets, white blood cells, neutrophil granulocytes, red blood cells)

- biochemical analyses (bilirubin, creatinine, ALAT, ASAT, AP)

Before the start of the study, a pregnancy test must be conducted for women of child-bearing potential.

Any clinically relevant abnormal laboratory test results must be documented on the corresponding page of the case report form and should be controlled as soon as possible.

The laboratory tasked with evaluating the tests must add a table containing the normal values (reference ranges) to the study binder before the start of the study and send a copy to the study center.
7.7.3 **Analysis of the EGFR-related signal transduction**

Due to the fact that Cetuximab specifically targets the EGF receptor, analyses of tumor specimens (primary tumor or metastases) are being conducted which are used to help define impairments of the EGFR-related signal transduction.

7.7.4 **Correlation analysis between defined single nucleotide polymorphisms and the response to antibody therapy of metastatic colorectal cancer within the scope of the FIRE-3 study**

The purpose of this accompanying translational research project is to examine the pharmacogenetic factors. They are necessary to predict the therapeutic efficacy in colon cancer patients before initiating the antibody therapy. In recent years, KRAS mutations were established as a negative predictor in connection with the EGF receptor antibodies (Cetuximab and Panitumumab). However, no predictors for the response of the anti-VEGF antibody Bevacizumab have yet been established.

Based on the blood sample analysis, the purpose is to establish a correlation between defined biomarkers such as single nucleotide polymorphisms (SNPs) of genes from the region of the angiogenesis or the VEGF pathway (e.g. FLT 1 gene (Chr. 13)) and the response to Bevacizumab (Avastin®) therapy or between genes from the region of the EGF receptor (e.g. VEGF Intron 1 CA repeat or F521K) and the response to Cetuximab (Erbitux®) therapy. The goal is to determine a risk stratification for future studies. These experiments are aimed at answering the following questions:

1. Is it possible to define predictive biomarkers (e.g. a correlation between the outcome and the allelic variant of SNPs in the VEGF receptor gene (FLT1)) within the respective therapy group (Cetuximab or Bevacizumab)?

2. Are patients with an unfavorable allelic variant benefitting from treatment within the study arm? Is the therapeutic benefit of this sub-group significant?

3. Can the predictive significance of a defined biomarker be demonstrated by the fact that no correlation is found between the outcome and the marker in the respective other arm (control group)?

One blood sample (approximately 10 mL) is required for the mentioned analyses.

7.7.5 **Physical examination, vital signs, weight**

A comprehensive physical examination, including weight and body height, is conducted at the time of the screening. The systolic and diastolic blood pressure (Riva Rocci) is measured with the patient is seated, after
at least 5 minutes of rest and if possible always on the same arm. The measuring times are specified in the flow chart and in chapter 7.2 to 7.4. The heart rate is measured at the same times (after at least 5 minutes of rest).

The physical examination is repeated during the course of the study at the times indicated in the flow charts and in chapter 7.2 to 7.5.

7.7.6 Adverse events (AEs)/toxicity

Adverse events and toxicities are recorded continuously and documented in the CRF after every therapy cycle.

Adverse events are any events that occur in a patient or subject enrolled in a clinical study after the administration of a medication even if they are not necessarily in a causal correlation with this treatment. Therefore, any adverse or unintended signs (including pathological laboratory test results), symptoms or any disease emerging in chronological correlation with the use of a medication can be deemed an adverse event (AE), irrespective of whether a causal correlation with the medication is assumed or not (see also: ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Pre-existing conditions that worsen over the course of a study must be reported as adverse events. They may become serious adverse events if one of the criteria below applies.

Based on regulatory provisions, events developing during the pre- and post-treatment phases of the studies should also be deemed adverse events. Accordingly, the monitoring of the safety and tolerability (i.e. the documentation of adverse events) starts when a patient is enrolled in the study (defined by the date when the declaration of consent is signed) and continues until after the end of the final study visit. Any events that emerge during the period from when the declaration of consent has been signed to the start of the administration of the study drug are therefore labeled AEs.

Every AE is classified according to the NCI-CTCAE V3.0 criteria and its severity evaluated. If no NCI category is provided for the event, it is described with free text and its severity evaluated as follows:

* Grade 1 - minor
  The event is noticeable, but well tolerated.
• **Grade 2** – moderate
  The event interferes with normal daily activities.

• **Grade 3** - severe
  The event completely interferes with the pursuit of normal activities.

• **Grade 4** – life-threatening

• **Grade 5** - fatal
  The event results in the patient’s death.

The clinical investigator is required to evaluate any laboratory test results that are outside of the regular range with respect to their clinical significance and to record them as adverse event/toxicity according to NCI-CTCAE V3.0 criteria, if they are relevant.

For every type of toxicity, it is documented whether a causal correlation with the cancer therapy is deemed likely/possible and, if so, which medication is the likely culprit. All adverse events associated with the study drug must be monitored until they resolve or stabilize.

**7.7.7 Serious adverse events**

This includes any adverse event which meets at least one of the following criteria in connection with any dose:

- lethal (causing death) event (note: death is the consequence rather than the event itself).

- life-threatening event (note: the term “life-threatening” refers to an event in connection with which the patient’s life was at risk at the time the event occurred, but not to an event which would have been able to cause death had it been more severe).

- required hospitalization or extension of a patient’s hospitalization.

- event causing permanent or considerable disability.

- congenital anomaly/birth defect.

- medically significant event or event requiring an intervention to prevent one of the consequences mentioned above.

“Life-threatening” means that the patient’s life was in immediate danger when the event occurred. An event that could have caused death had it been more severe does not qualify for this definition. “Required hospitalization” should be defined such that hospitalization was necessary to treat the adverse event.
Accordingly, hospitalization for the conduct of a therapeutic procedure according to the clinical study protocol or for scheduled elective surgery would not be deemed a serious adverse event. Likewise, elective hospitalization to simplify study procedures does not qualify as an SAE. 

As well, events (including death) and required procedures which are clearly and exclusively due to the progression of the underlying disease should not be documented as an SAE within the scope of this clinical study protocol (exception pursuant to section 12, subs. 4, GCP-O).

The documentation of SAEs includes the type of event, start, duration, characteristics/severity, causality as well as relevant information about the patient’s medical history. Signs of the illness, symptoms and altered laboratory test results connected with each other should be summarized into a single disease. If the clinical investigator believes that additional examinations are necessary, they should be labeled as such and documented on the case report form. A special case report form is available for the documentation.

An unexpected adverse event is an event that has never been reported in the past (with respect to the type, severity or incidence), neither in the current version of the information for clinical investigators (summary of product characteristics or investigator’s brochure) nor in the clinical study protocol. If the event is at the same time considered “serious”, it is referred to as SUSAR (“suspected unexpected serious adverse event”).

If a patient becomes pregnant during the course of the study, she must be withdrawn from the study. The sponsor must be notified by means of the therapy completion page on the CRF or the SAE reporting form.

For every serious adverse event, the following causality evaluation must be conducted for every medication:

- **no correlation**
  - the correlation appears to be extremely unlikely based on current knowledge.

- **possible correlation**
  - reasonably possible chronological correlation with the intake of the investigational drug
  - the AE has previously been described as an AE of the substance or can be expected
  - the AE could also be due to a number of other factors

- **probable correlation**
  - reasonably possible chronological correlation with the intake of the investigational drug
  - the AE has previously been described as an AE of the substance or can be expected
- regression or resolution of the AE after the investigational drug is discontinued or the dose is reduced
- it is impossible to reasonably explain the AE as a consequence of the patient’s clinical status

• confirmed correlation
  - reasonably possible chronological correlation with the intake of the investigational drug or achievement of effective levels in bodily fluids and tissues
  - the AE has previously been described as an AE of the substance or can be expected
  - regression or resolution of the AE after the investigational drug is discontinued (treatment-free interval) or the dose is reduced
  - re-emergence of the AE after re-exposure

7.7.8 Documentation and reporting of adverse, serious adverse or serious unexpected adverse events

The clinical investigator is required to report all serious adverse events within 24 hours by phone or fax to the following address:

ClinAssess GmbH
Birkenbergstr. 82
51379 Leverkusen
Phone: 02171 36 336 -0
Fax: 02171 36 336 -55

ClinAssess promptly forwards these reports to the director of the clinical study.

A report form has to be completed for all of these events and forwarded immediately to the specified address. Follow-up reports must be issued if the necessary information is not available at that point in time. In case of death, a copy of the autopsy report should be enclosed if possible.

The SAE is documented both on the corresponding pages of the case report form (CRF) as well as on the SAE page.

Non-serious adverse events are forwarded to the director of the clinical study as soon as possible after they have been documented on the CRF.

ClinAssess GmbH is in charge of the reporting of adverse drug effects regulated by law pursuant to section 12, subs. 6 as well as section 13, subs. 1 to 7 to the competent higher authority, BfArM (Federal Institute for
Drugs and Medical Devices) or PEI (Paul-Ehrlich Institute) as well as the ethics committee(s) on behalf of the sponsor, if necessary via the involved pharmaceutical manufacturers.

The sponsor is obligated to inform the participating clinical investigators about any suspected unexpected serious adverse reactions (SUSARs) pursuant to the formalities applicable in Germany (section 11, subs. 2 and 3 of the GCP-O). ClinAssess GmbH is again in charge of providing this information.

8 DATA MANAGEMENT AND STATISTICAL ASPECTS

8.1 DATA MANAGEMENT

The CRF data is entered in duplicate. The input mask as well as the database are developed specifically for this study. Both entries are compared by the data manager in charge. 100% of data is compared. Any inconsistencies are corrected by reviewing the original CRF.

Used software:

• client/server environment

• validated and documented Sybase/Power Builder Clinical Trial management system

• SAS 9.2

• DB visualizer

• Sybase Power Builder

• Oracle database
8.2 STATISTICS

8.2.1 Hypothesis

The primary target criterion of the continuation of this randomized study within the meaning of amendment no. 2 dated September 2008 which takes into account the new knowledge about the KRAS mutation as predictive factor for the efficacy, is to answer the following question: is it possible to achieve a greater efficacy with the use of the EGFR-targeted antibody Cetuximab compared to the reference therapy consisting of FOLFIRI/Bevacizumab in tumors with the wild-type KRAS mutation? The tumor response rate (OR = CR+PR) according to the RECIST criteria (cp. chapter 7.6.1 for the definition) serves as primary target criterion for this purpose. Therefore, the hypotheses to be analyzed are as follows:

\[ H_0: \text{OR (FOLFIRI/Cetuximab)} \leq \text{OR (FOLFIRI/Bevacizumab)} \]
\[ H_1: \text{OR (FOLFIRI/Cetuximab)} > \text{OR (FOLFIRI/Bevacizumab)} \]

OR = objective remission rate based on the RECIST criteria

Based on this formulation of the hypothesis, one-sided tests are conducted for the primary target criterion.

It is assumed that the therapy with Cetuximab is at least equal to the control arm with respect to the secondary target criterion progression-free survival.

Patients with mutated or unknown KRAS status who were randomized within the scope of the first phase of the study are not included in the primary analysis, although they are still accounted for within the scope of the descriptive analyses of the project.

8.2.2 Case number

Data of a phase III study investigating first-line treatment for metastatic colorectal cancer with Irinotecan/5-FU/Leucovorin/Bevacizumab published in 2004 is used as basis for the considerations concerning the case number. Accordingly, a response rate of approximately 50% is expected in the reference arm. The purpose is to demonstrate that the alternative administration of Cetuximab in a KRAS selected collective achieves a significantly higher response rate (62%). For this purpose, a case number of \( n = 284 \) patients eligible for evaluation with wild-type KRAS mutation is required per therapy arm (i.e. a total of 568). The case number calculation is based on the following framework conditions:
• The risk of incorrectly claiming the therapeutic superiority of the Cetuximab treatment in its absence (α error) is 2.5%.

• The success rate of determining an actual benefit achieved with the administration of Cetuximab as being significant is 80% (power, 1-β error).

The table below illustrates the required case number (excluding drop-outs) for a number of differences in efficacy to be demonstrated.

**Tab. 7  Case number calculations**

<table>
<thead>
<tr>
<th>Remission rate (Cetuximab)</th>
<th>Remission rate (Bevacizumab)</th>
<th>α error (one-sided)</th>
<th>Power</th>
<th>Number of patients per arm</th>
<th>Total number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design alternatives:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65%</td>
<td>50%</td>
<td>2.5%</td>
<td>80%</td>
<td>183</td>
<td>366</td>
</tr>
<tr>
<td>62%</td>
<td>50%</td>
<td>2.5%</td>
<td>80%</td>
<td>284</td>
<td>568</td>
</tr>
<tr>
<td>60%</td>
<td>50%</td>
<td>2.5%</td>
<td>80%</td>
<td>408</td>
<td>816</td>
</tr>
</tbody>
</table>

The listed patient numbers refer to a fixed case number design. They are only meant to serve as guidance for the size of the required case number, because a group sequential design is used in the proposed study which allows interim evaluations and if necessary a premature withdrawal of the study in case of demonstrated superiority to the defined extent (cp. 8.2.5). Accordingly, the expected required case number can be considerably lower, depending on the recruitment speed, number and time of interim evaluations as well as the actual difference between the groups. In the worst case, the maximum case number to be enrolled within the scope of the sequential design can be slightly higher than described above.

After the now completed subsequent typification of the KRAS mutation status of patients enrolled in the study before amendment II entered into effect, the number of patients with KRAS mutation or unknown KRAS mutation status (which is presumed to be a KRAS mutation) was determined to be 144. Patients with demonstrated wild-type KRAS status randomized within the scope of the first phase of the study (before amendment II entered into effect) are part of the collective of the “intention-to-treat” analysis. Consequently, at least 712 patients should be recruited for the study.
Based on an interim assessment of the available data, it is known that 15 randomized patients have not started with the study therapy for a number of reasons (“screening failures”). In addition, the “drop-out” rate (“early drop-out” and “non-eligible”) is presumed to be 10% based on the interim assessment. With respect to the total number of patients to be recruited, this means:

\[
\begin{align*}
568 & \quad \text{patients eligible for the evaluation with wild-type KRAS (284 patients per arm)} \\
144 & \quad \text{patients enrolled before amendment II entered into effect with KRAS mutation or unknown KRAS status} \\
15 & \quad \text{known “screening failures”} \\
\hline
727 & \quad \text{total} \\
73 & \quad \text{corresponds to a 10% “drop-out” rate} \\
\hline
800 & \quad \text{total number of patients to be recruited}
\end{align*}
\]

8.2.3 Patient evaluation categories

Patients for whom a major violation of the inclusion criteria is determined (“non-eligible”), are excluded from the statistical analysis. These cases are only described as case reports. Which patients with serious protocol violations should be part of this category will be decided prospectively before the conduct of the analysis in a “blind review”. Additional details in this respect are documented in a statistical analysis plan.

All other patients are included in the evaluation of the primary target criterion within the meaning of an “intention-to-treat analysis”. Only those patients who have completed at least 3 cycles of the planned combination therapy according to the clinical study protocol and for whom at least one imaging examination after the baseline is available for evaluation are included in a second analysis (“according-to-protocol”).

All patients who received at least one application of chemotherapy or immunotherapy are eligible for evaluation with respect to toxicity.

8.2.4 Statistical methods

A confirmatory analysis is used for the primary study criterion, where a global level of $\alpha = 0.025$ (one-sided) should be maintained. This means that a one-sided $p$-value of $<0.025$ is considered statistically significant.

A descriptive analysis is used for all other parameters, with the specification of incidence rates, means, medians, value ranges and confidence intervals. Explicit $p$-values are indicated for explorative statistical tests possibly conducted for the comparison of the therapy arms or sub-groups. Normally, the significance level is not adjusted in view of a multiplicity of the analysis, and therefore, the $p$-values reflect an $\alpha$ error related to
the individual comparison rather than the entire experiment. Two-sided tests are used unless otherwise specified. The statistical methods listed below are usually suitable for the data and distributions expected with these types of studies. The suitability is assessed after the data has been registered. If necessary, the selection of the method is modified accordingly, with a critical discussion of the respective outcomes.

The demographic and prognostic baseline data is reviewed for homogeneity between the treatment groups. In case of a major difference in the prognostically relevant variables, the statistical analysis is modified to achieve the best possible comparability of the groups. Adjusted and non-adjusted analyses are critically discussed in the comparison.

Remission, toxicity and survival or progression-free survival rates at certain points in time are calculated by means of exact confidence intervals and possibly compared by means of the Fisher’s exact test (primary target criterion), the chi-squared test or the Mantel-Haenszel test (or the COCHRANE-ARMITAGE test for trend, respectively) or with the corresponding stratified variants, depending on the type of occurrence and scope.

Continuously defined measurement data (e.g. tumor markers) is evaluated with the Wilcoxon test, comparisons between different registration times with the Wilcoxon test for paired samples.

Event-related data including the relapse-free and overall survival is illustrated according to the life table method by KAPLAN and MEIER and compared with the log-rank test. If the assumption of the “proportional hazard” which the Peto log-rank test is based upon is not met, GEHAN’s generalization of the Wilcoxon rank sum test for censored data is used, specifically in the version modified by PETO et al. and PRENTICE. The stratification as well as other prognostic layers as necessary are taken into account in the process.

The methods mentioned above are used analogously for the univariate analysis of prognostic factors (including the KRAS status). Suitable regression models are used for the conduct of the multivariate analysis, if applicable: logistic regression (primary target criterion), proportional hazard regression model.

### 8.2.5 Interim evaluation
Interim evaluations and hence possibly the premature withdrawal of the randomization should be considered for ethical reasons in connection with long-term studies investigating chronic diseases\textsuperscript{64}. The interim evaluations are based on the group sequential design using the ‘α error spending function’ according to LANDEMETS\textsuperscript{65}. In the process, the guideline for withdrawal limits formulated by O’BRIEN and FLEMING\textsuperscript{66} (1979) is defined as ‘use function’. The design allows the withdrawal because of early demonstrated superiority of the experimental arm (rejection of $H_0$) during interim evaluations with respect to the therapeutic efficacy. The premature withdrawal because of the exclusion of a benefit in the postulated extent (rejection of $H_1$) is not considered, because even a smaller difference with respect to its clinical relevance might potentially be worth being discussed.

The withdrawal limits are calculated during the respective interim evaluation to maintain the total percentage of type I errors at 5%. On the one hand, this design allows the conduct of any number of interim evaluations irrespective of time-related requirements and recruitment numbers. Secondly, this approach results in a general reduction of the study duration and case number actually required to make a conclusion compared to the design with a fixed case number (cp. 8.2.2), especially if the therapeutic difference is greater than expected. The scope of the “savings” largely depends on the actual scope of the difference in efficacy as well as the frequency and timing of the interim evaluations. At least 25 additional patients must be eligible for assessment with respect to the primary target criterion between two successive interim analyses.

The final statistical evaluation of the study and the compilation of the biometric report as part of the integrated clinical and statistical research report are done immediately after all duly completed, corrected and amended case report forms are available.

9 \textbf{DOCUMENTATION OF RESULTS AND QUALITY ASSURANCE}

9.1 \textbf{CONDUCT OF THE DOCUMENTATION AND DATA FLOW}

All patient-related data is recorded in pseudonymized format. Every patient is unmistakably identified with a patient number assigned at the time of recruitment. The clinical investigator keeps a confidential patient list in which the characteristics are linked with the full name of the patient (and the number of the medical chart, address of the general practitioner, etc. as applicable). The clinical investigator or a person appointed by him/her (co-investigator) enters all data collected during the study in the corresponding case report forms (CRFs). These
forms are provided by the study center and explained to the clinical investigator by the monitor. Data from patients who have already undergone the pre-examinations required for the inclusion in the clinical study according to information provided on the declaration of consent, but who are not eligible for enrolment because of exclusion criteria or other reasons, is also recorded. The data must be complete and plausible.

- Please use a blue or black ball point pen to ensure that all copies are clearly legible.

- Please only write one letter or number in each open top box. Data in closed boxes is documented with a check mark.

- All fields (except those relating to an open question) must be filled in. If a specific test was not performed or if any information is not definitively available, please write “not done”, “not applicable” etc. (not done = ND, not applicable, not available = NA, unknown = UK)

- If the exact determination of a date is impossible, please enter it as follows: - - 08 01 .

- Possibly required corrections in the case report forms must be done by the clinical investigator or a person assigned by him/her. Corrections must strictly be made in accordance with the GCP guidelines, i.e.

  - the version to be corrected is crossed out in such a way that it remains legible

  - the applicable version is clearly written above or next to the first version

  - the clinical investigator dates and initials the correction (or other entries) and adds the reason for the change, if applicable.

<table>
<thead>
<tr>
<th>Version to be corrected:</th>
<th>Corrected version:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Month</td>
<td>Day</td>
</tr>
</tbody>
</table>

- please write clearly and in printed letters.

The clinical investigator is obligated to complete the case report forms promptly and completely, generally within 2 weeks after establishing the findings. After completion, the forms should be signed by the clinical investigator as needed and handed to the monitor during his/her visit. The clinical investigator keeps a
carbon copy/copy. The monitor reviews the entries for completeness and plausibility. In case of questions, necessary corrections and/or additions which are not addressed directly during the monitor’s visit, the form or a copy of the respective page and/or a data correction form will be sent or handed to the clinical investigator for clarification/addition/correction. They must be processed within 4 weeks at the latest.

After the study center or monitor has completed the data verification, they forward the original forms to the center for biostatistics. If any uncertainties emerge during the data entry there for which an answer is required, the monitor will contact the clinical investigator.

9.2 SAFEKEEPING OF THE STUDY DOCUMENTS

The original of all central study documents including the case report forms are kept at the study center (by the director of the study or sponsor) for at least 10 years after the compilation of the final report. The clinical investigator/director of the study site keeps the created administrative documents (correspondence with the ethics committee, regulatory authority, director of the study, study center), the patient identification list, the signed declarations of consent, copies of the case report forms and the general study documentation (protocol, amendments) for the period mentioned above. Original data of the study subjects (patient records) shall be kept in accordance with the archiving period applicable at the study sites, but not less than 10 years.

9.3 QUALITY CONTROL AND QUALITY ASSURANCE

9.3.1 Standardization

The evaluation criteria are uniform for all sites. The internationally established TNM system is used to describe the tumor stage. Every site must provide normal ranges for the laboratory test results. Every laboratory is routinely validated by means of the interlaboratory comparison. The toxicity is documented based on the NCI-CTCAE V3.0 evaluation criteria.

A kick-start meeting is organized to instruct the clinical investigators and study co-ordinators. During this meeting, all sections of the protocol are described and an explanation on how to complete the clinical case report forms is provided. In addition, the methods for the conduct of the study are illustrated.
9.3.2 Monitoring/source data verification

The monitoring of the study is primarily conducted on site, i.e. in the form of visits from clinical research associates and additionally as needed with telephone or written contacts as well as within the scope of study meetings. The visitation frequency during the ongoing study depends on the recruitment at the site as well as the scope of existing problems, if any. The monitor is granted access to the study documents and medical records as set forth in the investigator’s agreement.

The following points must be reviewed regularly to ensure the quality of the study:

• compliance with the recruitment rate
• compliance with the selection criteria
• compliance with the treatment as outlined in the protocol
• compliance with the examination and evaluation deadlines
• availability of the declarations of consent
• completeness of the study documents

To verify the data quality, a formal review of all characteristics and properties documented in the case report forms for completeness and plausibility is conducted first, followed by the verification of the correct transfer of data contained in the medical records to the case report forms (source data verification). The latter is conducted by means of a random sampling schedule, with a 100% verification of the essential study parameters.

9.3.3 Audits

In the event of an audit by a regulatory authority or a CRO, the clinical investigator is required to provide unrestricted access to all study-related documents. The director of the study or the sponsor should be informed promptly about the date of a regulatory audit at an individual study site to allow them to initiate supportive measures as necessary. The audited clinical investigator or organizational unit of the study is informed about the outcome of the audit.

10 Protocol changes and additions (amendment)
To ensure comparable conditions for all study subjects and a proper future evaluation, no change of the agreed study conditions outlined in the study protocol is intended.

Exceptional changes that become necessary during the study sequence are implemented by the director of the clinical study in co-ordination with the other persons who are significantly involved in the compilation of the protocol. Any change of this kind must be made in writing including the specification of the reasons and signed by everyone who had signed the study protocol. This document is known as an amendment and becomes an integral component of the study protocol. The amendment must be added to every circulating copy of the study protocol.

The patient’s renewed written consent is required for any changes that might potentially affect the patient’s health-related interests. (The same applies to patients already enrolled in the study, if they are affected by this change). In these cases or if other relevant criteria are met, a re-application to the competent superior federal authority and the ethics committee with lead responsibility is required. The director of the study or the sponsor decides based on the criteria listed in section 10, subs. 1 GCP-O whether or not this is necessary and initiates the procedures pursuant to section 10, subsection 2 to 4 GCP-O as necessary. An addition to the study protocol is required for purely administrative or technical changes of the study protocol which have no bearing on the patient’s health-related interests. In this case, only the notification of the competent ethics committee is required.

11 ETHICAL AND LEGAL PRINCIPLES

11.1 GENERAL TERMS AND COVENANTS

The study is conducted in accordance with or based on the applicable legislative requirements, the German Medicines Act (AMG 1976 and amendments), the principles for the proper conduct of clinical trials with medicines (Federal Gazette no. 243 dated 12-30-1987), the ICH Harmonized Tripartite Guideline for Good Clinical Practice, valid since 01-17-1997, the “Regulation governing the use of good clinical practice for the conduct of clinical trials with medicines for use in humans” dated August 9, 2004 and in accordance with the principles of the Declaration of Helsinki (1964 as well as revisions dated 1975, 1983, 1989, 1996, 2000, 2003 and 2004). The director of the clinical study has two years of demonstrated experience with the conduct of clinical trials with medicines. The university where the director of the clinical study works is the sponsor of the study within the meaning of the GCP regulations, i.e. this therapy optimization study is a so-called
“investigator-initiated trial”. The sponsor or the person assigned by the sponsor maintains the “trial master file” based on chapter 8 of the ICH E6 “Note for Guidance on Good Clinical Practice”.

11.2 DECLARATION OF HELSINKI

The study is conducted in accordance with the Declaration of Helsinki, adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964; amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; amended by the 35th World Medical Assembly, Venice, Italy, October 1983, Hong Kong, September 1989, in October 1996 in Somerset West, East Africa, 2000 in Edinburgh, Scotland, amended by the 54th World Medical Assembly, Washington 2002 and the 56th World Medical Assembly, Tokyo 2004.

11.3 PATIENT COUNSELING AND DECLARATION OF CONSENT

Before enrolment in the clinical study, every patient is told that participation in the study is voluntary and that he/she may withdraw from the study any time without stating the reasons and without any disadvantages. However, if adverse drug reactions are the reason for the withdrawal, the patient is asked to inform the clinical investigator thereof.

The patient is counseled by the treating physician about the investigational medication and the possible adverse accessory symptoms. At the same time, the nature, significance, scope, expected benefits, possible risks of the study and alternative treatments are explained to him/her. The patient briefing also includes the information about the existing insurance coverage and the duties of the insured. The patient is given plenty of time and the opportunity to ask any questions. In addition, a form entitled “Patient information” is handed out to the patient which contains the essential information one more time in written format.

The patient’s written consent must be obtained before the start of the study. The patient must personally sign and date the declaration of consent. By doing so, he/she declares his/her voluntary participation in the study and his/her intention to follow the study requirements and the instructions given by the clinical investigator during the course of the study as well as to answer any questions he/she is asked during the course of the clinical study diligently.

The declaration of consent is issued in duplicate. It is intended that one copy is kept by the clinical investigator and the other copy is given to the patient. The declaration of consent is only valid after it has
been duly signed and the patient can be enrolled in the study provided he/she meets the inclusion and exclusion criteria.

By signing the declaration of consent, the patient at the same time confirms that he/she agrees with the documentation and disclosure of medical data in pseudonymized format to the sponsor or the director of the study within the scope of the clinical study, as well as additionally with the inspection of the personal data by the supervisory authority or authorized representatives of the sponsor to verify the proper conduct of the clinical study.

By signing the respective case report form, the clinical investigator bindingly confirms that an individual patient briefing was conducted and that a signed declaration of consent has been obtained from the patient.

11.4 DATA PRIVACY AND PROFESSIONAL SECRECY

All findings collected during the course of the clinical study are archived on electronic data carriers and handled strictly confidentially.

Organizational procedures are in place to protect this data aimed at preventing the disclosure to unauthorized third parties. For instance, patients are only identified by their initials and the individual subject number during the entire documentation and evaluation phase, while the full name is not visible. The applicable provisions of the country-specific data privacy laws are fully complied with.

The clinical investigator is responsible for keeping adequate information about every patient (name, date of birth, gender, declaration of informed consent, patient identification within the study) (to be able to identify a patient based on his/her study no. in case of emergency).

Persons authorized by the sponsor as well as representatives of domestic and foreign authorities are granted access to the personal medical records in the office of the study doctor to verify the data. All data remains confidential and is subject to patient-doctor confidentiality. In accordance with the GCP guidelines, these documents must be archived for at least 10 years.

11.5 DUTIES PERTAINING TO THE APPLICATION AND REPORTING

Before the start of the study, the sponsor submits a duly completed application pursuant to section 7, subs. 1, 2, 4 to 6 GCP-O to the Federal Institute for Drugs and Medical Devices (BfArM) or the Paul-Ehrlich Institute, respectively. At the same time, an application is sent to the ethics committee with jurisdiction over the director of the clinical study pursuant to section 7, subs. 1, 2, 3, 5 and 6 GCP-O as well as to any other...
“local” ethics committees formed in accordance with the national laws with jurisdiction over the respective individual study sites pursuant to section 7, subs. 1 GCP-O. In representation of the individual sites, the sponsor additionally notifies the competent regional authorities about the individual clinical investigators pursuant to section 67 of the Medicines Act and section 12, subs. 1 GCP-O.

The sponsor informs the competent higher federal authority (at the same time as the competent ethics committee, cp. chapter 11.7) about the progress of the study both with respect of the safety aspects (pursuant to section 13 GCP-O, subs. 1 to 6) as well as about the completion of the study and its outcomes (pursuant to section 13 GCP-O, subs. 8 and 9).

11.6 SUBJECT INSURANCE

Insurance pursuant to section 40, subs. 1 no. 8 and subs. 3 AMG is taken out for all patients enrolled in the study with

HDI-Gerling Industrie Versicherung AG, Gangerhoferstr. 39, 80339 Munich
Insurance policy no. 70-005891524-6 (valid before amendment 2 entered into effect)
Insurance policy no. 39-130537-03014/390 (valid after amendment 2 entered into effect).

The patient is provided with the relevant information.

Any damage to health which may be a consequence of participation in the clinical study must be reported promptly to the address mentioned above to ensure that the insurance coverage is not voided. The duty to report rests with the patient. The insured is required to take any reasonable steps to help identify the cause and scope of the damage and to reduce this damage.

In the event of death, the duty to report rests with the legal successor (heir). The death must be reported within 48 hours. If any damage to health within the scope of this study is not reported, the insurance benefits expire. This also applies if the patient fails to follow the doctor’s instructions, e.g. by taking medications not permitted during the study without informing the clinical investigator.
For the duration of this study, the patient may only receive other medical treatment with the clinical investigator’s prior consent. In addition, he/she is required to promptly inform the treating physician about any adverse events as well as any additional medications he/she is taking. The clinical investigator is always available to answer any questions the patient may have. The patient has the right to view the insurance terms and conditions kept by the clinical investigator any time.

11.7 Ethics Committee

Before the start of the study, the clinical study protocol and any other required documents (cp. chapter 11.5) are submitted to the ethics committee with jurisdiction over the director of the study for evaluation. The study may only be started after the positive vote from the ethics committee has been received. The competent ethics committee is promptly notified of any changes to the study protocol (cp. chapter 10) as well as any suspected unexpected serious adverse drug reactions pursuant to section 13, subs. 2 and 3 GCP-O. As well, the ethics committee is provided with a report about all suspected SAEs and the safety of the affected persons pursuant to section 13, subs. 6 GCP-O once every year and upon request for the duration of the study. Any recommendations and remarks from the ethics committee are incorporated into the study protocol. Moreover, the sponsor informs the competent ethics committee (at the same time as the competent higher federal authority, cp. chapter 11.5) about the progress of the study both with respect to the safety aspects (pursuant to section 13 GCP-O, subs. 1 to 6) as well as about the completion of the study and its outcomes (pursuant to section 13, GCP-O, subs. 8 and 9).

The clinical investigators are not permitted to take part in the decision of the ethics committee. A list of the committee members as well as the by-laws of the ethics committee are requested.

11.8 Details about the Investigational Drug for the Clinical Investigators

The clinical investigators are fully informed about the pre-clinical and clinical knowledge with respect to the investigational drug by means of the latest versions of information for clinical investigators (investigator’s brochure/product information), to the extent the respective medication has not yet been approved for sale in Germany and hence no summary of product characteristics/instructions for use are available. If any new knowledge emerges, an updated version of the investigator’s brochure/product information is handed out or the existing version amended.
11.9 **FINANCING**

The sponsor is in charge of securing the financing of the study. In this study, the investigational medication (Cetuximab) is provided free of charge to the sponsor by the Company Merck KGaA, Darmstadt. After amendment 2 has entered into effect, Cetuximab is no longer provided as a free investigational medication, because the drug has meanwhile been approved for use in the first-line therapy.

11.10 **STUDY WITHDRAWAL BY THE SPONSOR OR PRINCIPAL INVESTIGATOR**

The director of the clinical study or the sponsor has the right to withdraw or end the study at any time for an individual patient as well as the entire study for plausible medical and/or administrative reasons or for reasons under the Medicines Act (including inadequate patient recruitment), especially in connection with high incidence rates of adverse events, taking into account the benefit-to-risk ratio.

12 **PROCEDURE IN CASE OF PUBLICATION**

A publication under the primary authorship of the site in charge of managing the study is prepared once the biometric evaluation or the clinical biostatistical evaluation report is complete. Any other involved sites where at least 5 patients were recruited are entitled to name one co-author each, provided the publisher permits this. The order of the co-authors is based on the number of patients cared for in this study. Other persons with a considerable involvement in the planning, conduct and evaluation of the study are offered to be named as an author.

All co-authors are given the opportunity to provide feedback within a reasonable period before the manuscript/abstract is submitted for publication.

The involved study sites have the right to publish the data generated at their site. The director of the clinical study must be informed about any data to be presented in verbal lectures and receives copies of any manuscripts containing data obtained from the study. This condition is exclusively meant to inform the director of the clinical study and does not imply the entitlement to editorial work or restriction of the content of publications and lectures.
13 **Literature**


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