CLINICAL STUDY REPORT

CETUXIMAB/FOLFIRI WITH OR WITHOUT OXALIPLATIN AND FOLFOXIRI WITH OR WITHOUT BEVACIZUMAB IN NEOADJUVANT TREATMENT OF NON-RESECTABLE COLORECTAL LIVER METASTASES

(CELIM2-STUDY)

Version 1.0, 14 July 2022

Trial Protocol Version 2, 17.07.2014
Including amendment 1 version 1.2, 12.04.2012 and amendment 2 version 2, 17.07.2014

Sponsor: **Technische Universität Dresden**

Sponsor code: TUD-CELIM2-050

EudraCT-number: 2011-003288-31
ClinicalTrials.gov Identifier: NCT01802645

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Name of Finished Product and Active Substance
Finished product: Erbitux active substance: cetuximab

1 Synopsis

Sponsor	**Technische Universität Dresden** 01062 Dresden
Study drug	Erbitux (Cetuximab)
Title of Study	Cetuximab/FOLFIRI with or without oxaliplatin and FOLFOXIRI with or without bevacizumab in neoadjuvant treatment of non-resectable colorectal liver metastases
Short Title	CELIM 2- study
Trial Protocol	Trial Protocol Version 2, 17.07.2014; amendment 1 version 1.2, 12.04.2012 and amendment 2 version 2, 17.07.2014
Study centre	Nine German centres recruited patients (University Hospital Dresden, University Hospital Würzburg, University Hospital Hamburg-Eppendorf, University Hospital Aachen, Klinikum Oldenburg, University Hospital Göttingen, University Hospital Frankfurt, Hämato-Onkologische Gemeinschaftspraxis Coesfeld, Rotes Kreuz Krankenhaus Kassel Gemeinnützige GmbH)
Publication (reference)	SmPC for cetuximab
Indication	Liver metastases of colorectal cancer
Study design	Open, randomized, multicenter trial
Studied period (years):	First enrolment: 2013 Last completed: 2020
Phase of development	II, non-confirmatory

Objectives	To evaluate the efficacy of four regimens in neoadjuvant treatment of non-resectable liver metastases:
	- in pts with [K]RAS wild type tumors:
	  o FOLFOXIRI/cetuximab or
	  o FOLFIRI/cetuximab
	- in pts with [K]RAS mutant tumors:
	  o FOLFOXIRI/bevacizumab or
	  o FOLFOXIRI

Endpoints of the trial	Primary: Response rate Secondary: Rate of patients with resection and a DFS of at least 6 months Further endpoints: DFS, PFS, OS, safety

Methodology	Patients with liver metastases of colorectal cancer were randomized according to their [K]RAS status to cetuximab plus doublet or triplet chemotherapy (wild type tumors) or triplet chemotherapy with or without bevacizumab (mutant tumors). Response and resectability were assess that did not belong to one of the "favourable" sub groups underwent screening and were randomised to chemotherapy with paclitaxel and carboplatin alone (max. 6 cycles, arm A) or to the same chemotherapy plus the EGFR antibody cetuximab until disease progression. The tumor was evaluated every 8 weeks by CT or MRI. The primary endpoint was progression free survival (PFS). An interims analysis was planned for tumor response.
Number of patients	planned sample size: 256 actually screened: 111 pts / randomised and analyzed: 92 pts
Diagnosis and main criteria for inclusion	- Non-resectable, histologically confirmed, synchronous or metachronous colorectal liver metastases. - Non-resectability will be documented by a local multidisciplinary tumor board with participation of a surgeon experienced in liver surgery. Patients can be enrolled if they o are technically non-resectable (locally determined by a multi-disciplinary team discussion based on remaining functional liver tissue after resection and / or o have ≥ 5 liver metastases and / or o are regarded as non-resectable for other reasons (description necessary) - Patients with simultaneous liver metastases are eligible, o if the primary tumor was resected at least 1 month prior to chemotherapy or o all of the following conditions apply: ▪ the primary tumor is clearly resectable, ▪ no radiation therapy is planned, ▪ liver resection is planned before resection of the primary or at the same operation as the resection of the primary, ▪ no two-stage liver resection is planned, and ▪ all efforts were made to exclude additional distant metastases. - WHO PS ≤ 1 - Written informed consent - No non-resectable, histologically confirmed, synchronous or metachronous colorectal liver metastases
Test product, dose and mode of administration	Cetuximab 400 mg/m² i.v. followed by weekly doses of 250 mg/m² plus standard chemotherapy
Duration of treatment	Up to 12 cycles of chemotherapy

<table>
<tr><td>Treatment schedules</td><td>Cetuximab/FOLFIRI: cetuximab as above, irinotecan 180 mg/m² , folinic acid 400 mg/m² , 5-FU 400 mg/m² (bolus), 5-FU 2400 mg/m² (46 h)
Cetuximab/FOLFOXIRI: cetuximab as above, irinotecan 125 mg/m², oxaliplatin 85 mg/m², folinic acid 400 mg/m², 5-FU 3200 mg/m² (46 h)
FOLFOXIRI: irinotecan 165 mg/m²,oxaliplatin 85 mg/m², folinic acid 400 mg/m², 5-FU 3200 mg/m² (46 h)
Bevacizumab/FOLFOXIRI: bevacizumab 5 mg/kg irinotecan 165 mg/m², oxaliplatin 85 mg/m², folinic acid 400 mg/m² (2 h), 5-FU 3200 mg/m² (46 h)
All chemotherapy was given i.v., every 2 weeks</td></tr>
<tr><td>Criteria for evaluation: Efficacy, Safety</td><td>RECIST 1.1 for tumor response, CTC-AE v 4.0 for adverse events, Clavien complications for resection</td></tr>
<tr><td>Statistical methods</td><td>The response rate was determined a proportion of all randomized patients, the median PFS and overall survival (OS) were estimated by the Kaplan Meier method.
The treatment arms were compared using the stratified log rank test or for proportion by chi square tests.</td></tr>
<tr><td>Summary – Conclusions: Efficacy Results, Safety Results, Conclusion</td><td>Efficacy:
<table>
<tr><th></th><th>Cetux/ FOLFOXIRI</th><th>Cetux/ FOLFIRI</th><th>Bev/ FOLFOXIRI</th><th>FOLFOXIRI</th><th>All patients</th></tr>
<tr><td></td><td>N=26</td><td>N=28</td><td>N=20</td><td>N=18</td><td>N=92</td></tr>
<tr><td>(K)RAS</td><td>wild type</td><td>wild type</td><td>mutant</td><td>mutant</td><td></td></tr>
<tr><td>CR + PR, number [95% CI]</td><td>23 (89%)
[70-98%]</td><td>23 (82%)
[63-94%]</td><td>14 (70%)
[46-88%]</td><td>13 (72%)
[46-90%]</td><td>73 (79%)
[70-87%]</td></tr>
<tr><td>Resections with DFS of ≥ 6 months, number [95% CI]</td><td>16 (62%)
[41-80%]</td><td>9 (32%)
[16-52%]</td><td>8 (40%)
[19-64%]</td><td>6 (33%)
[13-59%]</td><td>39 (42%)
[32-53%]</td></tr>
<tr><td>Overall survival, months [95% CI]</td><td>54.7
[32.1-77.4]</td><td>41.7
[36.4-47.1]</td><td>44.1
[13.0-75.2]</td><td>28.3
[22.1-34.4]</td><td>41.7
[33.7-49.8]</td></tr>
<tr><td>Progression free survival, months [95% CI]</td><td>16.8
[12.4-21.2]</td><td>16.1
[10.6-21.6]</td><td>15.1
[9.0-21.2]</td><td>17.5
[12.8-22.2]</td><td>16.1
[13.9-18.3]</td></tr>
<tr><td>Disease free survival, months [95% CI]</td><td>11.5
[9.1-14.0]</td><td>8.2
[0-17.6]</td><td>25.0
[0.6-49.4]</td><td>12.3
[2.4´-22.1]</td><td>11.7
[7.7-15.6]</td></tr>
</table>
Safety: There were no new safety signals detected.
Conclusion: All four regimens achieved high response and resection rates. With the limitation of the low patient numbers per arm, the response rate as well as the rate of patients resected and disease free for at least 6 months was highest in patients with [K]RAS wild type tumors and treated with</td></tr>
</table>

	cetuximab plus triplet chemotherapy and the triplet / antibody combinations had the numerically longer overall survival
Date of report	14 July 2022

2 Table of contents

2.1 Tables

2.2 Figures

3 General study information

3.1 Study background

3.1.1 Cetuximab

Cetuximab is a chimeric anti-EGFR antibody, approved for treatment of metastatic, RAS wild type colorectal cancer in combination with irinotecan based schedules, furthermore for squamous cell head and neck cancer in combination with radiotherapy for locally advanced carcinoma and in combination with platinum based chemotherapy for recurrent or metastatic disease. It is marketed in Germany by Merck-Serono GmbH. The approved dose is 400 mg/m² for first dose followed by weekly doses of 250 mg/m². The first approval was June 2004.

The sponsor (Technical University of Dresden) has no access to non-published data of cetuximab.

3.1.2 Colorectal cancer and liver metastases

Colorectal cancer is the third most common cause of cancer deaths in Germany with more than 25,000 deaths per year, [1] but colorectal liver metastases can be resected with curative intent. At time of diagnosis of metastatic disease, less than ¼ of patients have resectable disease. For patients with non-resectable liver metastases, chemotherapy provides an effective option to downsize the metastases. There is a clear relationship between the response rate and the number of patients resected for their metastases in clinical trials.

The first large series on resection of previously non-resectable liver metastases was reported after the combination therapies of two cytotoxic drugs (i.e. oxaliplatin / fluorouracil, FOLFOX, or irinotecan / fluorouracil, FOLFIRI) [2] were introduced into the clinical practice. An overview on published studies and retrospective reports revealed that the response rates correlate with the frequency of liver resections and generated the hypothesis that tumor response according to radiological criteria is a precondition for the resection of initially non-resectable liver metastases. [3]

For patients with [K]RAS wild type tumors, anti-EGFR antibodies (i.e. cetuximab) plus doublet chemotherapy (FOLFOX or FOLFIRI) provide high response rates are regarded as standard of care. [4], [5], [6] Cetuximab based doublet regimens have been shown to be associated with high rates of tumor response and high resectability. [7] Combinations of anti-EGFR antibodies plus triplet chemotherapy (oxaliplatin, irinotecan and fluorouracil, FOLFOXIRI) had demonstrated high response rate in non-randomized studies. [8] Therefore, we explored the combination of cetuximab / FOLFOXIRI vs. cetuximab / doublet chemotherapy in patients with colorectal liver metastases that are non-resectable at screening – or in whom the disease resection of liver metastases is uncertain due to the high number of liver metastases.

For patients with [K]RAS mutations, most effective therapy with regard to response rate is known to be FOLFOXIRI [9], [10] whereas it was uncertain whether bevacizumab contributes to improved response rates, better resectability or a longer disease free survival in the context of a neoadjuvant therapy of non-resectable metastases.

3.2 Investigators and sites

Patients were recruited at nine German sites. The study had been initiated at eight additional sites which had not enrolled patients Table 1.

Table 1: Study sites

Site no.	Site / city	Principal investigator	Patients
1	University Hospital Dresden	Prof. Dr. Folprecht	26
3	University Hospital Würzburg	Prof. Dr. Kunzmann	7
4	University Hospital Hamburg-Eppendorf	PD Dr. Stein	10
6	University Hospital Aachen	Prof. Dr. Neumann	4
7	Klinikum Oldenburg	Prof. Dr. Köhne	10
9	University Hospital Göttingen	Prof. Dr. Liersch	18
12	University Hospital Frankfurt	Prof. Dr. Bechstein	11
13	Hämato-Onkologische Gemeinschaftspraxis Coesfeld	Dr. Glados	4
17	Rotes Kreuz Krankenhaus Kassel Gemeinnützige GmbH	Dr. Kleiss	2
The following site have not recruited patients			
2	University Hospital Mainz	Prof. Dr. Möhler	
5	Charite Berlin	Prof. Seefeld	
10	Klinikum Landshut gemeinnützige GmbH	Prof. Dr. Löhe	
11	University Hospital Leipzig	Prof. Dr. Lordick	
14	Überörtliche Gemeinschaftspraxis; Schwerpunktpraxis Hämatologie/ Onkologie	Dr. Burstedde	
15	Klinikum Coburg GmbH	PD Dr. Lamberti	
16	Rems-Murr-Klinikum Winnenden	Prof. Dr. Schaich	

3.3 Type of study

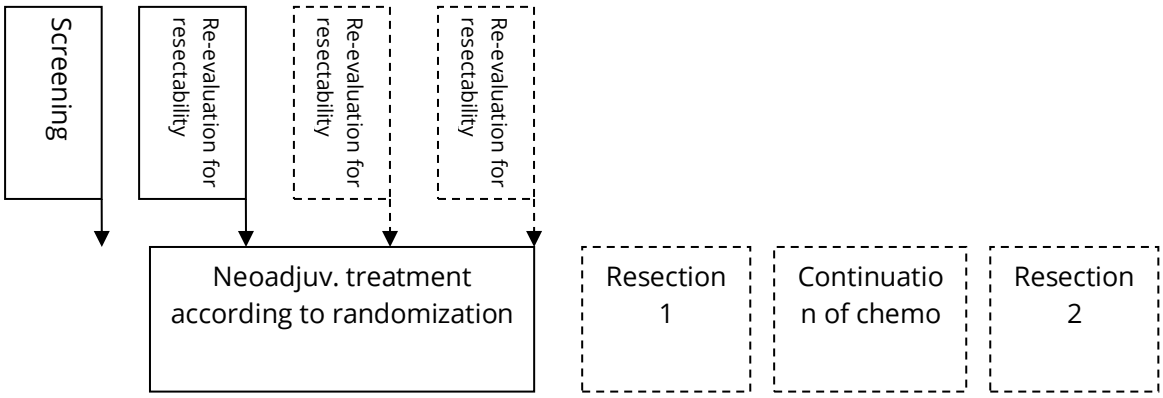
Open, multicentre, randomized phase II trial

3.4 Design and general treatment strategy

Patients with liver metastases from colorectal and without known extra-hepatic tumor disease were screened for this study. This included a KRAS exon 2 test (after the amendment KRAS/NRAS testing) according to local standard and the prescription information should be performed in a certified laboratory with the option of central testing, if a local certified laboratory was not available.

Patients received chemotherapy according to the allocation and were re-evaluated for resectability every 8 weeks for a maximum of 6 months. Resectable patients were resected and should receive an adjuvant treatment to complete 12 cycles. A second resection was allowed within the study. The timing of the second resection was determined by the local team. The second resection should be performed immediately (within 6 weeks) after the first resection or following continuation of the chemotherapy depending on the surgical conditions and the performance status of the patients after the first resection.

Figure 1: General overview on the treatment of a patient



3.5 Randomization

Patients were randomized using a web-based computer system that allowed randomization if the key basic characteristics are entered.

Patients with **KRAS- and NRAS-wild-type** tumors were randomized to receive:

- Cetuximab/FOLFIRI or
- Cetuximab/FOLFOXIRI

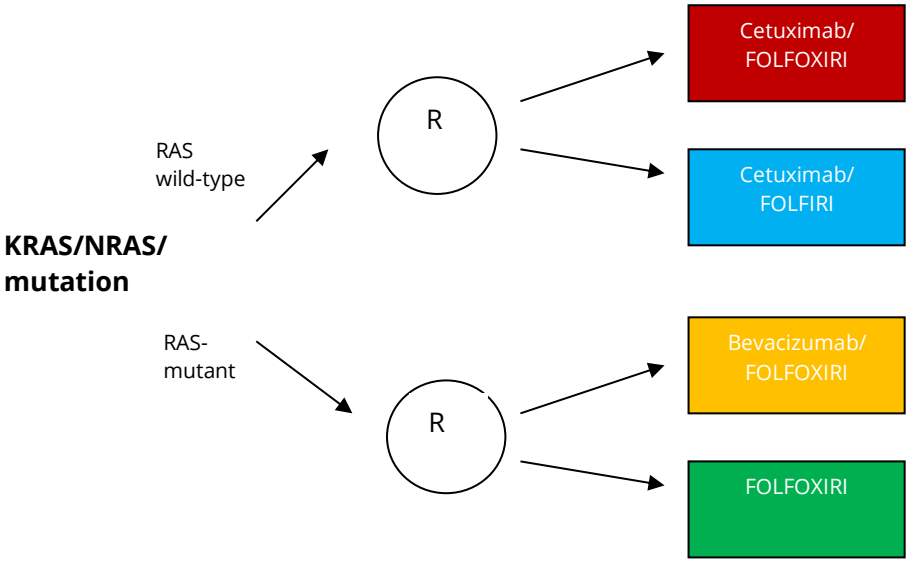
Patients with **KRAS- or NRAS- mutations** were randomized to receive:

- FOLFOXIRI or
- FOLFOXIRI/bevacizumab

The randomization was stratified according to:

- Number of metastases (< 5 vs. ≥ 5 metastases)
- Primary tumor *in situ*
- Centre

Figure 2: Treatment allocation



3.6 Schedule of visits

Table 2: Visit schedule

Procedures	**Scree-ning[a]**	**Every neoadjuvant cycle**		**Perioperative evaluation**	**Every adjuvant cycle**	**End of Study Visit**	**Follow-Up Visit[j]**
		every cycle d 1 and 8	after every four preoperative cycles		before each treatment and weekly		
Informed consent	X Prior to any study-specific procedure.						
Procedures	To be assessed and recorded in source documents and entered in CRF.						
Toxicities/AE assessments[c]	Reporting throughout every subsequent cycle to 30 days after last administration (End of Study Visit)						
Concomittant medication[p]	Reporting throughout every subsequent cycle to 30 days after last administration (End of Study Visit)						
Demographic data	X						
Tumor history[b]	X						
Concomitant diseases	X						
WHO Performance status	X		X			X	
Physical examination	X		X			X	
Height	X						

Procedures	Scree-ning[a]	Every neoadjuvant cycle		Perioperative evaluation	Every adjuvant cycle	End of Study Visit	Follow-Up Visit[j]
		every cycle d 1 and 8	after every four preoperative cycles		before each treatment and weekly		
Weight, vital signs (blood pressure, heart rate, temperature)	X	d 1			d 1	X	
Treatment administration		d1 and 8[o]			d1 and 8[o]		
Evaluation of general operability acc. to local standards	X						
Blood count[d]	X	d 1 and 8			X	X	
Laboratory 1[e]	X	d1			X	X	
Laboratory 2[f]	X						
CEA	X		X			X	X
Blood for TR (2.4ml EDTA)	X						
Plasma for TR (2x 8ml, tubes provided)	X		X				
ras-/raf-mutational analysis[q] **Block shipment**	X						
Tumor assessment [MRI or CT][g]	X		X				
Optional: 18-FDG PET[h]	X						
Imaging[i]							X
EKG	X						
Randomization	X after *RAS*-analysis						
Dipstick urine analysis[j]		d1			d1		
Evaluation for resectability			X				
Perioperative Evaluation[k]				X			

a) Screening	All investigations should be performed within 3 weeks before randomization, except CT scan (4 weeks). To ensure comparability, the baseline scans and subsequent scans to assess response must be performed using identical technique.
b) Tumor history	including: date of diagnosis, histology, tumor site (within the colon; rectum) and clinical and TNM stage, previous treatment(s), previous surgery, documentation of the reason of non-resectability (technical resectability and number of metastases)
c) Toxicities/AEs	Toxicities will be recorded using NCI CTCAE Version 4.0.
d) Blood count	including hemoglobin, and leukocyte, platelet, neutrophil count
e) Standard laboratory 1	Before chemotherapy: biochemistry: sodium, potassium, magnesium, creatinine, alkaline phosphatase, total bilirubine, LDH, SGOT, SGPT; At screening and then only for patients on bevacizumab: dipstick urine analysis, 24 hour urine analysis if dipstick >1+)
f) Standard laboratory 2	Albumine Female patients (within ≤ 7 days before treatment start: gravidity test (not necessary if > 1 year postmenopausal or with conditions that exclude gravidity, i.e. hysterectomy)
g) Tumor assessment	Screening: Abdominopelvic and thoracic, contrast-enhanced helical CT scan including three-phasic contrast-enhanced CT scan of the liver (to be performed within 4 weeks before treatment start). The abdominopelvic CT scan can be substituted by MRI; in this case, all follow-up examinations must be performed by MRI (the same imaging method has to be performed at baseline and all further tumor measurements). During treatment: Abdominal helical CT scan (or MRI, if initial imaging with MRI) and chest imaging (CT or conventional x- ray) The CT (or MRI) should be sent - DICOM formatted, on CD or DVD – to the coordinating study office.
h) 18-FDG PET	An optional 18-FDG PET- examination will be performed at discretion of the local investigator. PET- examination is *optional* and performed at clinical decision of the local investigator. Participation at additional studies investigating the impact of PET or other imaging methods in staging or response evaluation is not excluded.
i) Imaging	Imaging (CT scan recommended for all patients and obligatory for patients without R0 resection, abdominal ultrasound and chest x-ray obligatory as minimal requirement for R0 resected patients)
j) Follow up	will be performed every 3 months in the first two years and thereafter every 6 months until 5 years after randomization until disease progression: Documentation of progression / survival status Documentation of subsequent procedures or treatment lines
k) Perioperative evaluation	Type of intervention, classified as segment resections, hemihepatectomia, extended hemihepatectomia, central resections, non-anatomical resections, explorative laparatomy and local ablations, or combinations of these methods Resection status as R0/R1/R2 for resections and – for ablations – as complete/incomplete according to imaging Perioperative morbidity according to Clavien et al. (see appendix **Fehler! Verweisquelle konnte nicht gefunden werden.**) Days of mechanical ventilation Bilirubine at days 3, 8, (if not normalized at day 8, on days 15, 22, 28) Report of surgery and pathology reports (patient name /date of birth and other identifiers replaced by patient numbers). Pathological specimen: tumor block of resected liver metastases and of non-metastatic liver tissue

	(to determine tumor regression and potential effects of normal liver tissue, i.e. sinusoidal obstruction, steatosis/steatohepatitis, in a central review process)
l Adjuvant therapy	Number of adjuvant cycles depending on neoadjuvant treatment No. of neoadjuvant cycles: 4 | 5 | 6 | 7 | 8 | 9 | ≥ 10 No. of adjuvant cycles: 8 | 7 | 6 | 5 | 4 | 3 | 0
m End of Study Visit	should be planned 30 days after last treatment
o	d 8 in patients with cetuximab, only
p	After screening, for treatment of adverse events, only
q	*ras/b-raf* analysis to be performed locally according to local standard in a certified laboratory. The test will be done centrally if there is no local certified laboratory available.. Block should be shipped following mutational analysis.

3.7 Treatment

The patients received the treatment as specified below. One cycle wass defined as one dose of chemotherapy and all cetuximab or bevacizumab doses until the next day of chemotherapy. Chemotherapy was given after cetuximab or bevacizumab, Irinotecan was admnistered before oxaliplatin, and oxaliplatin and folinic acid at the same time via separate lines.

3.7.1 Cetuximab / FOLFIRI

Cetuximab (1.0 h i.v.)†	**250 mg/m²**	weekly
Irinotecan (1.0 h i.v.)	**180 mg/m²**	d1, 15, ...
D,L Folinic acid (2.0 h i.v.)	**400 mg/m²**	d1, 15, ...
5-FU (Bolus i.v.)	**400 mg/m²**	d1, 15, ...
5-FU (46 h i.v.)	**2400 mg/m²**	d1, 15, ...

† first dose, only: 400 mg/m² (2.0h)

3.7.2 Cetuximab / FOLFOXIRI

Cetuximab (1.0 h i.v.)†	**250 mg/m²**	weekly
Irinotecan (1.0 h i.v.)	**125 mg/m²**	d1, 15, ...
Oxaliplatin (2.0 h i.v.)	**85 mg/m²**	d1, 15, ...
D,L Folinic acid (2.0 h i.v.)	**400 mg/m²**	d1, 15, ...
5-FU (46 h i.v.)	**3200 mg/m²**	d1, 15, ...

† first dose, only: 400 mg/m² (2.0h)

3.7.3 FOLFOXIRI

Irinotecan (1.0 h i.v.)	**165 mg/m²**	d1, 15, …
Oxaliplatin (2.0 h i.v.)	**85 mg/m²**	d1, 15, …
D,L Folinic acid (2.0 h i.v.)	**400 mg/m²**	d1, 15, …
5-FU (46 h i.v.)	**3200 mg/m²**	d1, 15, …

3.7.4 FOLFOXIRI / bevacizumab

Bevacizumab (90 min i.v.)†	**5 mg/kg**	d1, 15, …
Irinotecan (1.0 h i.v.)	**165 mg/m²**	d1, 15, …
Oxaliplatin (2.0 h i.v.)	**85 mg/m²**	d1, 15, …
D,L Folinic acid (2.0 h i.v.)	**400 mg/m²**	d1, 15, …
5-FU (46 h i.v.)	**3200 mg/m²**	d1, 15, …

† Infusion time could be reduced to 60 min at the second dose and 30 min at the third dose

3.7.5 Evaluation for response and resections

Patients were evaluated for response by the same imaging technique as at baseline every 8 weeks. The findings had to be discussed for resectability within two weeks after tumor assessment in a local multidisciplinary team.

Technically resectable patients should have been offered liver resection.

Treatment should be continued with neoadjuvant intent for a total maximum of six months (12 cycles).

3.7.6 Adjuvant treatment

After liver resection, adjuvant treatment was recommended with the same schedule as preoperatively, for a maximum pre- and postoperative treatment of 12 cycles. If less than three postoperative cycles remain, no postoperative treatment was planned.

3.7.7 Follow up

After resection, patients were planned to be followed up for 5 years after randomization. This included

- imaging and clinical investigation every three months for the first 2 years, then every six months (patients without tumor progression / recurrence)
- survival status and surgical (procedure, R-status) /medical treatment (drugs and periods) every three months for the first 2 years and then every six months (all patients)

3.8 Study protocol and amendments

The study started with the protocol version 1.2 (12 April 2012) that included the first amendment that was issued as answer to request during the submission process to the ethics committees and the health authorities..

The protocol was amended in 2014 with the amendment 2 to the protocol version 2 (17.07.2014). The version 2 is the reference for this reports.

Main reason for the amendment was the change of the approval status of cetuximab requiring the test not for KRAS exon 2, only, KRAS and NRAS exon 2-4 testing.

In addition, UGT1A1 adapted treatment not longer recommended as part of the study protocol due to the higher number of available safety data for FOLFOXIRI combinations and the lack of a general acceptance of UGT1A1 testing to adjust irinotecan doses.

A further change referred to the BRAF testing. Initially, BRAF mutations were centrally tested and BRAF mutant patients were excluded. After the amendment 2, BRAF mutational testing was optional and not centrally tested. Patients with known BRAF mutations could be randomized within the RAS mutant stratum according to decision of the investigator.

The leaner central procedures were implemented in order to facilitate the recruitment process and to increase the enrolment rate.

4 Methods

4.1 Randomisation

A central randomization was performed using a computer-generated list. Patients were stratified by the number of metastases (< 5 vs. ≥ 5 metastases), primary tumor in situ and centre.

Recruitment was competing without a maximal patient number per study site.

4.2 Data flow and software

Data were entered by the centres into the MACRO data base version 4. After checking for plausibility and source data verification by on-site monitoring, the date were exported and analyzed using SPSS (Statistical Package for the Social Sciences), version 25.0.

4.3 Response evaluation

Response was measured by CT (or MRI) scans every 8 weeks until disease progression and evaluated by RECIST 1.1. [11]

4.4 Definition of the variables

4.4.1 Primary end point

Response rate: Rate of patients with partial or complete remission according to RECIST 1.1 (nominator) out of the patients randomised into the treatment arm (denominator).

The arms within the two patient groups ([K]RAS wild type = treatment with cetuximab or [K]RAS mutation = treatment without cetuximab) were compared with the chi square test.

4.4.2 Secondary end points

Rate of resected patients with a disease free survival of at least 6 months: Rate of patients with resection and being alive and without progression of disease for six months or more measured

from last resection (nominator) out of the patients randomised into the treatment arm (denominator). The arms within the two patient groups ([K]RAS wild type = treatment with cetuximab or [K]RAS mutation = treatment without cetuximab) were compared with the chi square test.

Progression free survival: Time from randomization to the date of progression or death in the ITT population.

Disease free survival: Time from last resection to the date of progression or death in the resected patients population.

Overall survival: Time from randomization to death in the ITT population)

The arms within the two patient groups ([K]RAS wild type = treatment with cetuximab or [K]RAS mutation = treatment without cetuximab) were compared using the log rank test.

Toxicity: frequency in treatment groups according to NCI-CTC v4.0 in the safety population (patients randomised and having received at least one dose of the study treatment)

4.5 Sample size calculation

The response rate for FOLFIRI/cetuximab is estimated at 70% (π1).

Trials with FOLFOXIRI/cetuximab have achieved response rates of nearly 80% for the entire patient population (not selected for k-ras wild type). Trials with chemotherapy and cetuximab observed higher response rates in patients with liver limited disease than in the ITT population and in KRAS wild type than in KRAS mutant patients. Therefore, a response rate of 85% (π2) was expected for the experimental arm cetuximab/FOLFOXIRI.

With a beta error of 20 % and alpha error of 10 %, 69 patients are required per arm to reject the H0 hypothesis: π2- π1 ≤ 0.

Thus, 138 RAS wild type patients were planned to be randomized.

With an estimated response rate for FOLFOXIRI/bevacizumab of 78% (π_2) and a response rate for FOLFOXIRI of 60% (π_1), a power of 80% and an alpha of 10%, 59 evaluable patients were necessary per arm to reject the H_0 hypothesis: $\pi_2 - \pi_1 \leq 0$.

Therefore, 118 *ras* mutant patients have to be randomized and will be included in the ITT analysis.

The sample size was calculated with ADDPLAN, Cologne, Germany, version 5.0.3.

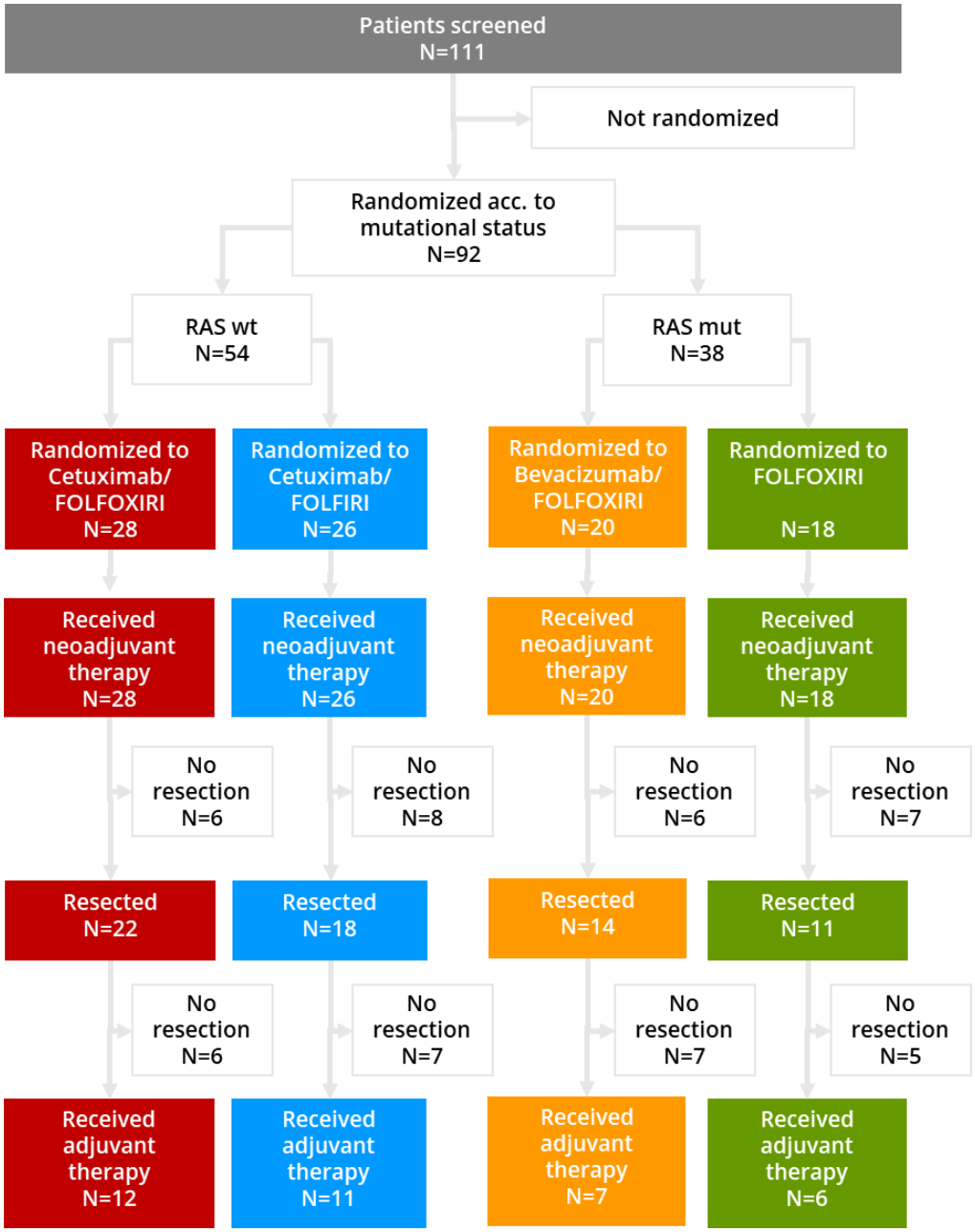
5 Patient flow

In total, 111 patients were screened for the CELIM2 study, of whom 92 patients were randomized between 22.4.2013 and 31.09.2018. The trial was closed for recruitment before the initially planned sample size was achieved due to the limited recruitment.

In the (K)RAS wild type cohort, 54 patients were randomized to cetuximab plus FOLFOXIRI (28 patients) or cetuximab / FOLFIRI (26 patients). In the (K)RAS mutant group, 38 patients were randomized to FOLFOXIRI with bevacizumab (20 patients) or without bevacizumab (18 patients).

The patient disposition it shown in Figure 3

Figure 3: CONSORT diagram



5.1 Treatment duration

5.1.1 Neoadjuvant Treatment

All randomized patients started neoadjuvant treatment. The median number of chemotherapy cycles was eight in all treatment arms (see Table 3 and Table 4).

Table 3: Median number of doses in neoadjuvant treatment per arm

	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI
	N=28	N=26	N=20	N=18
Cetuximab	16 (6-24)	15.5 (7-24)		
Bevacizumab			8 (1-12)	
Irinotecan	8 (3-12)	8 (3-12)	8 (1-12)	8 (1-12)
Oxaliplatin	8 (3-12)		8 (1-12)	8 (1-12)
Folinic acid	8 (3-12)	8 (3-12)	8 (1-12)	8 (1-12)
FU infusion	8 (3-12)	8 (3-12)	8 (1-12)	8 (1-12)
FU bolus		8 (1-12)		

Table 4: Number of doses in neoadjuvant treatment per arm

	No of doses	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI
		N=28	N=26	N=20	N=18
Cetuximab	6	1	0		
	7	2	1		
	8	3	5		
	9	0	1		
	10	1	2		
	11	1	2		
	12	0	1		
	14	1	0		
	15	0	2		
	16	5	2		
	17	2	1		
	18	1	2		
	19	0	1		
	20	1	2		
	22	2	0		
	23	4	3		
	24	2	3		
Median		16	15,5		
Bevacizumab	1			1	

	No of doses	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI
	2			2	
	4			1	
	5			1	
	6			2	
	8			5	
	9			1	
	10			1	
	11			1	
	12			4	
Median				8	
Irinotecan	1	0	0	2	1
	3	1	1	0	0
	4	4	6	1	3
	5	2	3	1	0
	6	2	1	1	0
	7	2	0	0	0
	8	6	4	6	6
	9	2	2	1	3
	10	0	2	1	0
	11	2	1	0	1
	12	5	8	7	4
Median		8	8	8	8
Oxaliplatin	1	0		2	1
	3	1		0	0
	4	4		1	3
	5	2		1	1
	6	2		1	0
	7	3		0	0
	8	7		6	5
	9	2		1	3
	10	1		1	1
	11	2		2	1
	12	2		5	3
Median		8		8	8
Folinic acid	1	0	0	2	1
	3	1	1	0	0
	4	4	6	1	3
	5	2	3	1	0
	6	2	1	1	0
	7	2	0	0	0
	8	6	4	6	6

	No of doses	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI
	9	2	2	1	3
	10	0	2	1	0
	11	2	1	0	1
	12	5	8	7	4
Median		8	8	8	8
FU infusion	1	0	0	2	1
	3	1	1	0	0
	4	4	6	1	3
	5	2	3	1	0
	6	2	1	1	0
	7	2	0	0	0
	8	6	4	6	6
	9	2	2	1	3
	10	0	2	1	0
	11	2	2	0	1
	12	5	7	7	4
Median		8	8	8	8
FU bolus	1		1		
	2		1		
	3		1		
	4		4		
	5		4		
	6		1		
	8		4		
	9		2		
	10		1		
	11		1		
	12		8		
Median			8		

5.1.2 Adjuvant Treatment

After resection, 36 patients started adjuvant therapy. The median number of adjuvant chemotherapy cycles was four in all treatment arms (see Table 5 and Table 6).

Table 5: Median number of doses in adjuvant treatment per arm

	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI
	N=12	N=11	N=7	N=6
Cetuximab	8 (6-17)	8,5 (1-16)		

Bevacizumab			4 (1-4)	
Irinotecan	4 (1-8)	4 (1-8)	4 (1-5)	4 (4-8)
Oxaliplatin	4.5 (1-8)		4 (1-2)	4 (0-5)
Folinic acid	4 (1-8)	4 (1-8)	4 (1-5)	4 (4-8)
FU infusion	4 (1-8)	4 (1-8)	4 (1-5)	4 (4-8)
FU bolus		4 (1-8)		

Table 6: Number of doses in adjuvant treatment per arm

	No of cycles	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI
		N=12	N=11	N=7	N=6
Cetuximab	1	0	1		
	4	0	1		
	6	1	0		
	8	4	3		
	9	0	1		
	10	1	0		
	12	1	0		
	14	0	2		
	15	0	1		
	16	1	1		
	17	1	0		
Median		8	8,5		
Bevacizumab	1			1	
	4			5	
Median				4	
Irinotecan	1	1	1	1	0
	3	2	0	0	0
	4	4	5	5	4
	5	2	0	1	0
	6	0	1	0	1
	7	1	1	0	0
	8	1	3	0	1
Median		4	4	4	4
Oxaliplatin	0	0		0	1
	1	1		1	0
	2	1		0	0
	3	1		1	0
	4	2		3	2
	5	2		0	1
	7	1		0	0
	8	2		0	0
Median		4,5		4	4

	No of cycles	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI
Folinic acid	1	1	1	1	0
	3	2	0	0	0
	4	4	5	5	4
	5	2	0	1	0
	6	0	1	0	1
	7	1	1	0	0
	8	2	3	0	1
Median		4	4	4	4
FU infusion	1	1	1	1	0
	3	2	0	0	0
	4	4	5	5	4
	5	2	0	1	0
	6	0	1	0	1
	7	1	1	0	0
	8	2	3	0	1
Median		4	4	4	4
FU bolus	1		2		
	4		5		
	7		1		
	8		3		
Median			4		

5.1.3 Reasons for end of treatment

The majority (56%) stopped treatment because of resection, planned end of treatment. In four patients (4%), the postoperative therapy was not re-introduced because the conditions for adjuvant therapy were not met. Twelve patients (13%) stopped treatment because of progressive disease. Intolerable toxicity, patients or investigators decision led in 13 patients (14%) to end of treatment, death in three patients (3%). In eleven patients, treatment was stopped for other reasons (Table 7).

Table 7: Reason for end of treatment

	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
	N=26	N=28	N=20	N=18	N=92
planned end of postoperative treatment	9 32%	12 46%	8 40%	4 22%	33 36%
planned end of treatment without resection (non-curative)	10	1	3	4	18

	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
	36%	4%	15%	22%	20%
postoperative treatment not started following resection	1 4%	2 8%	1 5%	0 0%	4 4%
progressive disease	2 7%	3 12%	1 5%	6 33%	12 13%
intolerable toxicity	1 4%	1 4%	2 10%	0 0%	4 4%
withdrawal of patients consent	2 7%	1 4%	0 0%	1 6%	4 4%
decision by investigator in best interest of patient	1 4%	0 0%	1 5%	1 6%	3 3%
patient died	0 0%	2 8%	1 5%	0 0%	3 3%
other	2 7%	4 15%	3 15%	2 11%	11 12%

5.2 Blinding

The study was not blinded.

6 Baseline characteristics

In total, 92 patients were randomized, 26 patients to cetuximab / FOLFOXIRI, 28 patients to cetuximab / FOLFIRI (54 patients with [K]RAS wild type) and 20 and 18 patients to FOLFOXIRI with or without bevacizumab ([K]RAS mutant tumors).

The median ager of patients was 59.5 years. Most patients (76%) had a very good performance WHO status 0. According to the incidence of colorectal cancer, the majority of patients was male (71%).

Nearly every second patient had the primary tumor *in situ* (42%), a small minority of 9% of patients had had a previous liver resection. The median number of liver metastases at enrolment was six.

The detailed baseline characteristics are in Table 8

Table 8: Baseline characteristics

	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
	N=26	N=28	N=20	N=18	N=92
(K)RAS	wild type	wild type	mutant	mutant	
Age, median **Age, range**	56.5 (39-70)	58 (42-76)	61 (38-78)	62 (34-74)	59.5 (34-78)
WHO PS 0	19 *(73%)*	21 *(75%)*	17 *(85%)*	13 *(72%)*	70 *(76%)*
WHO PS 1	7 *(27%)*	7 *(25%)*	3 *(15%)*	5 *(28%)*	22 *(24%)*
Female	6 *(23%)*	8 *(29%)*	5 *(25%)*	8 *(44%)*	27 *(29%)*
Male	20 *(77%)*	20 *(71%)*	15 *(75%)*	10 *(56%)*	65 *(71%)*
Tumor stage at diagnosis					
T1	0 *(0%)*	0 *(0%)*	1 *(5%)*	1 *(6%)*	2 *(2%)*
T2	4 *(15%)*	1 *(4%)*	2 *(10%)*	2 *(11%)*	9 *(10%)*
T3	17 *(65%)*	19 *(68%)*	12 *(60%)*	7 *(39%)*	55 *(60%)*
T4	2 *(8%)*	1 *(4%)*	1 *(5%)*	5 *(28%)*	9 *(10%)*
T unknown	3	7	4	3	17
N-stage at diagnosis					
N0	6 *(23%)*	5 *(18%)*	5 *(25%)*	4 *(22%)*	20 *(22%)*
N1	10 *(38%)*	13 *(46%)*	4 *(20%)*	6 *(33%)*	33 *(36%)*
N2	7	4	7	5	23

	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
	(27%)	*(14%)*	*(35%)*	*(28%)*	*(25%)*
N unknown	3 *(12%)*	6 *(21%)*	4 *(20%)*	3 *(17%)*	16 *(17%)*
M1	21 *(81%)*	25 *(89%)*	18 *(90%)*	15 *(83%)*	79 *(86%)*
M0 / unknown	5 *(19%)*	3 *(11%)*	2 *(10%)*	3 *(17%)*	13 *(14%)*
Previous therapy					
Primary tumor resected	17 *(65%)*	17 *(61%)*	8 *(40%)*	11 *(61%)*	53 *(58%)*
Primary tumor in situ	9 *(35%)*	11 *(39%)*	12 *(60%)*	7 *(39%)*	39 *(42%)*
Previous liver resection	3 *(12%)*	2 *(7%)*	4 *(20%)*	2 *(11%)*	8 *(9%)*
No previous liver resection	23 *(88%)*	26 *(93%)*	16 *(80%)*	16 *(89%)*	81 *(88%)*
Previous adjuvant therapy	4 *(15%)*	2 *(7%)*	1 *(5%)*	3 *(17%)*	10 *(11%)*
No previous adjuvant therapy	22 *(85%)*	26 *(93%)*	19 *(95%)*	15 *(83%)*	82 *(89%)*
Staging with PET-scan	2 *(8%)*	4 *(14%)*	0 *(0%)*	0 *(0%)*	6 *(7%)*
Staging without PET	24 *(92%)*	24 *(86%)*	20 *(100%)*	18 *(100%)*	86 *(93%)*
Median no of metastases at randomization	6	6	7	5	6
≤ 4 metastases	10 *(39%)*	9 *(32%)*	3 *(15%)*	4 *(22%)*	26 *(28%)*
> 4 metastases	16 *(61%)*	19 *(68%)*	17 *(85%)*	14 *(78%)*	66 *(72%)*
≤ 10 metastases	23 *(88%)*	20 *(71%)*	18 *(90%)*	14 *(78%)*	75 *(82%)*
> 10 metastases	3 *(12%)*	8 *(29%)*	2 *(10%)*	4 *(22%)*	17 *(18%)*
Thrombocytes ≤ 400 Gpt/L	24 *(92%)*	20 *(71%)*	15 *(75%)*	11 *(61%)*	70 *(76%)*
Thrombocytes > 400 Gpt/L	2 *(8%)*	8 *(29%)*	5 *(25%)*	7 *(39%)*	22 *(24%)*
Leukocytes ≤ 10 Gpt/L	24 *(92%)*	20 *(71%)*	15 *(75%)*	11 *(61%)*	70 *(76%)*
Leukocytes > 10 Gpt/L	2	8	5	7	22

	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
	(8%)	*(29%)*	*(25%)*	*(39%)*	*(24%)*
Median CEA at randomization	44	36	33	470	43
CEA ≤ 5	6 *(23%)*	4 *(14%)*	5 *(25%)*	4 *(22%)*	19 *(21%)*
CEA > 5	20 *(77%)*	24 *(86%)*	15 *(75%)*	14 *(78%)*	73 *(79%)*
CEA ≤ 10	9 *(35%)*	9 *(32%)*	6 *(30%)*	4 *(22%)*	28 *(30%)*
CEA > 10	17 *(65%)*	19 *(68%)*	14 *(70%)*	14 *(78%)*	64 *(70%)*
CEA ≤ 50	15 *(58%)*	16 *(57%)*	12 *(60%)*	8 *(44%)*	51 *(55%)*
CEA > 50	11 *(42%)*	12 *(43%)*	8 *(40%)*	10 *(56%)*	41 *(45%)*

7 Efficacy analysis

7.1 Primary Endpoint

The primary endpoint of the trial was the response rate according to RECIST. The response was locally evaluated.

In total, three patients (3%) achieved a complete response and 70 patient a partial response (76%) resulting in a overall response rate of 73 / 92 patients (79%, 95% CI: 70 – 87%).

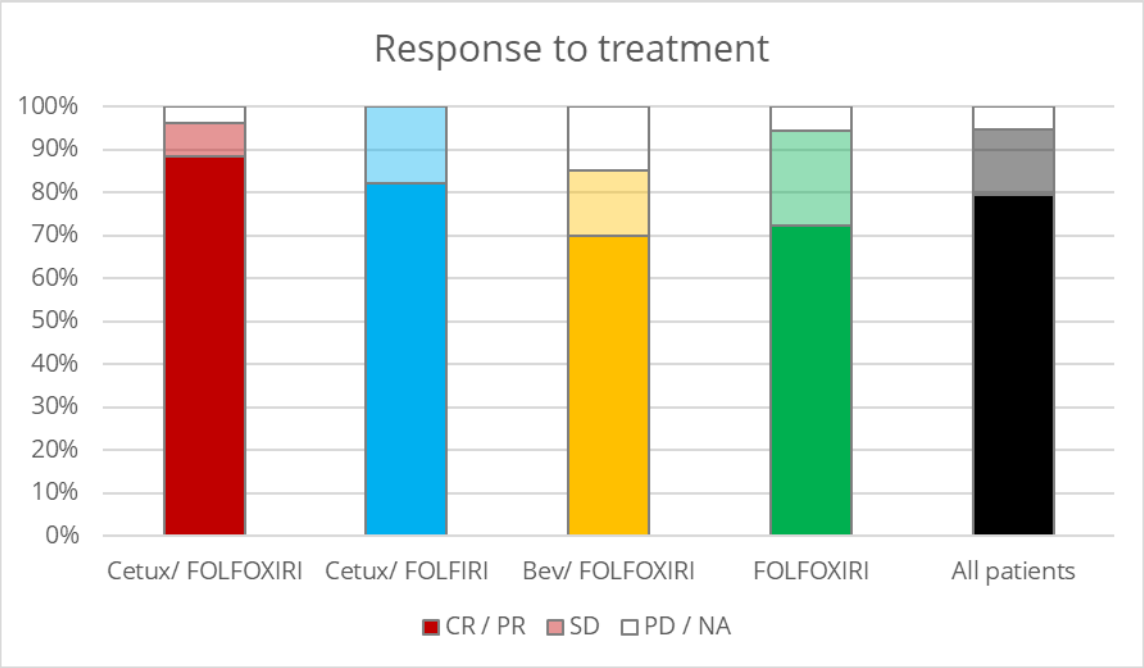
The response rates were numerically higher in both cetuximab arms in which [K]RAS wild type patients were randomized (89% and 82% for cetuximax with FOLFOXIRI or FOLFIRI) than in the arms with FOLFOXIRI +/- bevacizumab (70% and 72%), see Table 9 and Figure 4.

Fourteen patients (15%) had stable disease as best response to treatment. In five patient, progression was documented as best response or the response could not be evaluated.

Table 9: Response to treatment

	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
	N=26	N=28	N=20	N=18	N=92
(K)RAS	wild type	wild type	mutant	mutant	
Complete response (CR)	2 (8%)	0	0	1 (3%)	3 (3%)
Partial response (PR)	21 (81%)	23 (82%)	14 (70%)	12 (67)	70 (76%)
CR + PR, number, [95% CI]	**23 (89%)** [70-98%]	**23 (82%)** [63-94%]	**14 (70%)** [46-88%]	**13 (72%)** [46-90%]	**73 (79%)** [70-87%]
	46 (85%) Comparison between arms: P=0.71		**27 (71%)** Comparison between arms: P=1.0		
Stable disease (SD)	2 (8%)	5 (18%)	3 (15%)	4 (22%)	14 (15%)
Progressive disease (PD)	1 (6%)	0	2 (10%)	0	3 (3%)
Not available (NA)	0	0	1 (5%)	1 (6%)	2 (2%)

Figure 4: Response rates per arm



7.2 Secondary Endpoints of Efficacy

7.2.1 Number of resections

In 65 patients (71%) with initially non-resectable metastases / more than five metastases, resections were performed, in 41 patients more than one resection. The resection rates were numerically higher in the cetuximab arms (79% and 69%, [K]RAS wild type patients) than in the FOLFOXIRI ± bevacizumab arms (70% and 61%, [K]RAS mutant patients).

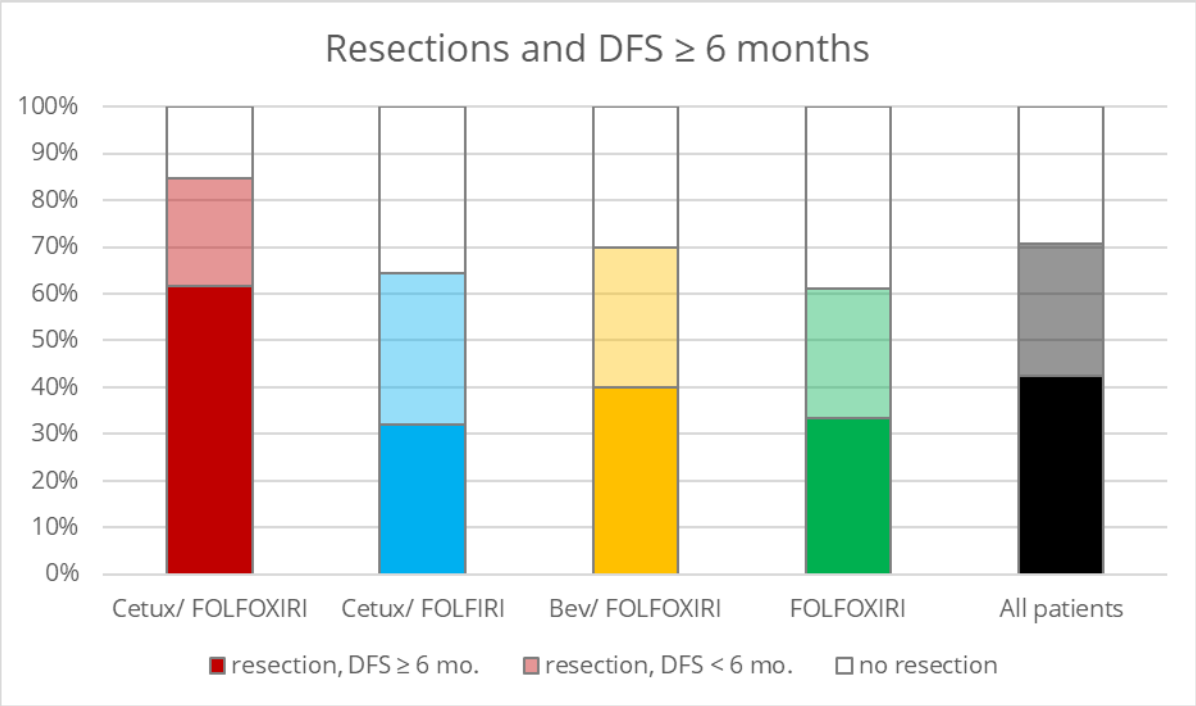
Out of the resected patients, 39 patients (42%) were at least 6 months disease free after resection. These rates were 62% with cetuximab / FOLFOXIRI, 32% with cetuximab / FOLFIRI, 40% with bevacizumab / FOLFOXIRI and 33% with FOLFOXIRI alone, Table 10 and Figure 5.

Table 10: Resections and disease free survival of more than six months per arm

	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
	N=26	N=28	N=20	N=18	N=92
(K)RAS	wild type	wild type	mutant	mutant	
Any resection, number, [95% CI]	**22 (79%)** [65-96%]	**18 (69%)** [44-81%]	**14 (70%)** [46-88%]	**11 (61%)** [36-83%]	**65 (71%)** [60-80%]
	40 (75%) Comparison between arms: P=0.12		**25 (65%)** Comparison between arms: P=0.73		
More than one resection:	14	13	8	6	41
2 resections	12	8	6	6	32
3 resections	2	4	2	0	8
4 resections	0	1	0	0	1
Resections with DFS of ≥ 6 months, number, [95% CI]	**16 (62%)** [41-80%]	**9 (32%)** [16-52%]	**8 (40%)** [19-64%]	**6 (33%)** [13-59%]	**39 (42%)** [32-53%]
	25 (46%) Comparison between arms: P=0.055		**14 (37%)** Comparison between arms: P=0.75		
Resections with a DFS of < 6 months	6	9	6	5	**26**
No resection	4	10	6	7	**27**

Arms were compared by chi square test.

Figure 5: Resections and disease free survival of more than six months per arm



7.2.2 Other efficacy endpoints

The randomized patients had a median overall survival of 41.7 months, Figure 6, with a trend towards a longer overall survival in the two cetuximab ([K]RAS wild type) arms (54.7 and 41.7 months) than in the two [K]RAS mutant arms (44.1 and 28.3 months), Figure 7 and Table 11.

The overall survival, progression free survival and disease free survival differences between the arms cetuximab/FOLFOXIRI vs. cetuximab/FOLFIRI (for [K]RAS wild type patients) and FOLFOXIRI / bevacizumab vs. FOLFOXIR for [K]RAS mutant patients) were not statistically significant.

Table 11: Overall, progression free and disesase free survival per arm

	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
	N=26	N=28	N=20	N=18	N=92
(K)RAS	wild type	wild type	mutant	mutant	
Overall survival, months, [95% CI] HR between arms	**54.7** [32.1-77.4]	**41.7** [36.4-47.1]	**44.1** [13.0-75.2]	**28.3** [22.1-34.4]	**41.7** [33.7-49.8]
	44.8 [29.3-60.3] Comparison between arms: HR=0,91 [0,41-1,99]		**31.2** [22.8-39.7] Comparison between arms: HR=0,90 [0,37-2,20]		
Progression free survival, Months, [95% CI] HR between arms	**16.8** [12.4-21.2]	**16.1** [10.6-21.6]	**15.1** [9.0-21.2]	**17.5** [12.8-22.2]	**16.1** [13.9-18.3]
	16.1 [14.1-18.1] Comparison between arms: HR=0,83 [0,46-1,52]		**17.5** [13.8-21.2] Comparison between arms: HR=0,78 [0,36-1,66]		
	N=22	N=18	N=14	N=11	N=65
Disease free survival, months [95% CI]	**11.5** [9.1-14.0]	**8.2** [0-17.6]	**25.0** [0.6-49.4]	**12.3** [2.4´-22.1]	**11.7** [7.7-15.6]
	11.5 [6.8-16.3] Comparison between arms: HR=1,02 [0,49-2,16]		**12.3** [4.8-19.8] Comparison between arms: HR= 0,85 [0,30-2,44]		

Arms were compare using the log rank test.

Figure 6: Overall survival in all patients

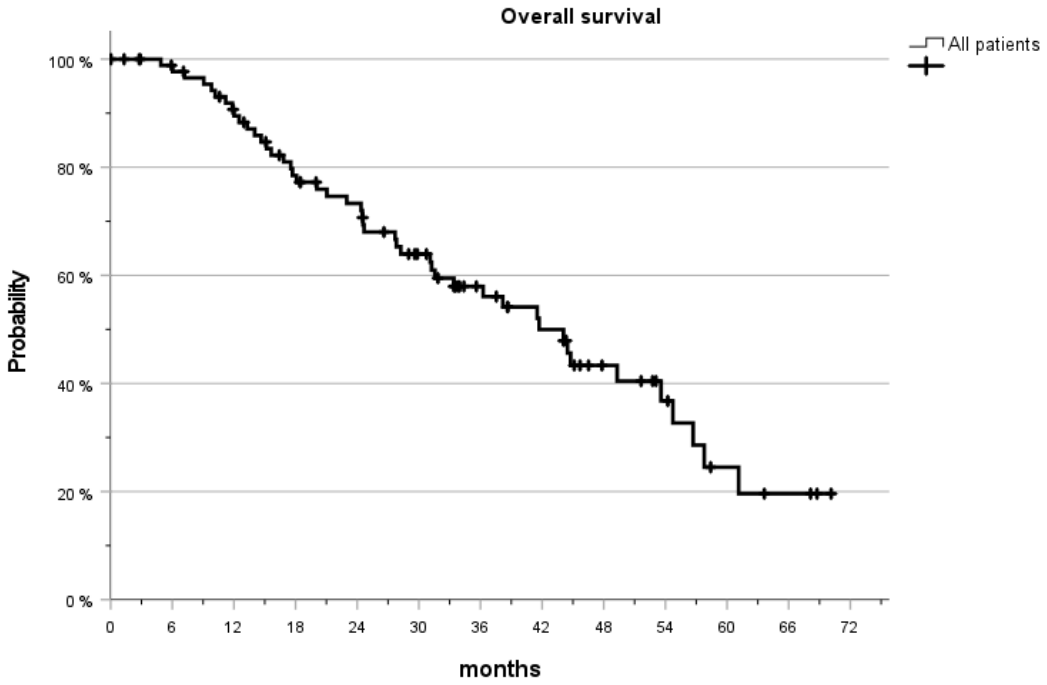
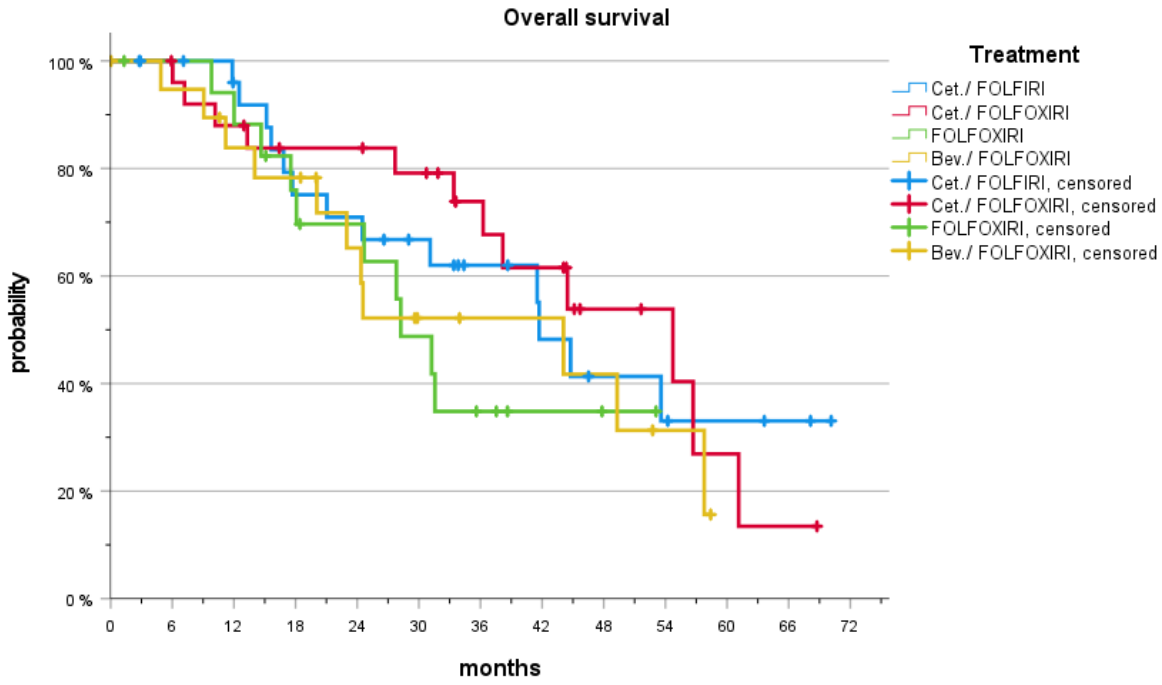


Figure 7: Overall survival per arm



The median progression free survival was 16.1 months (median, Figure 8) for all patients without differences between the treatment arms Figure 9 and Table 11.

Figure 8: Progression free survival in all patients

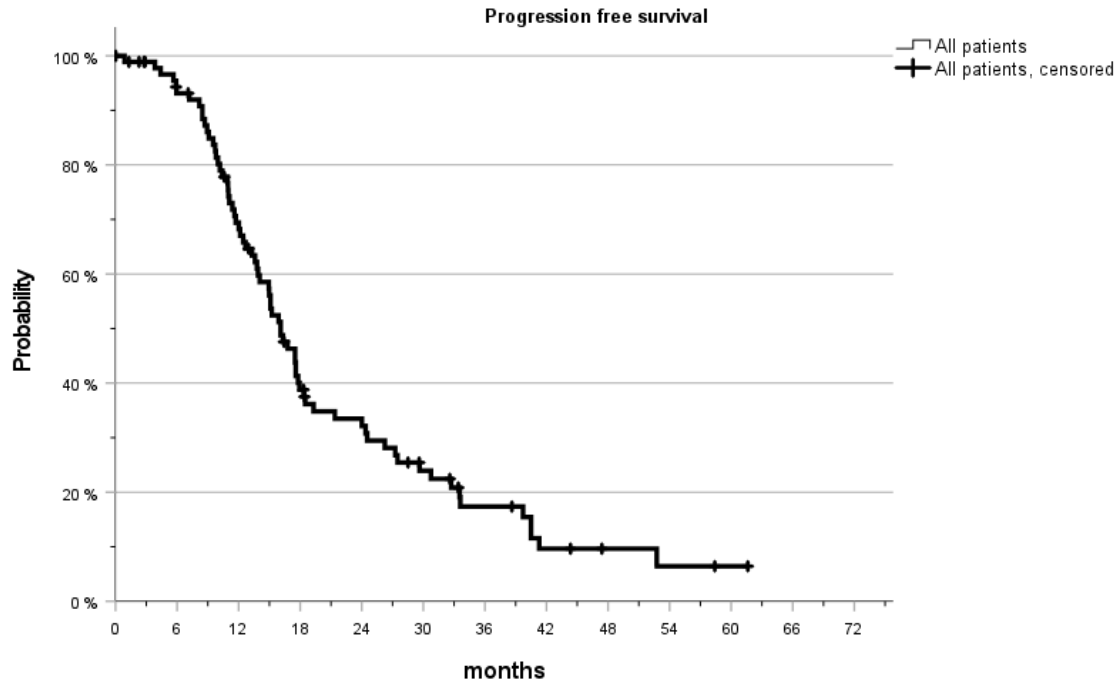
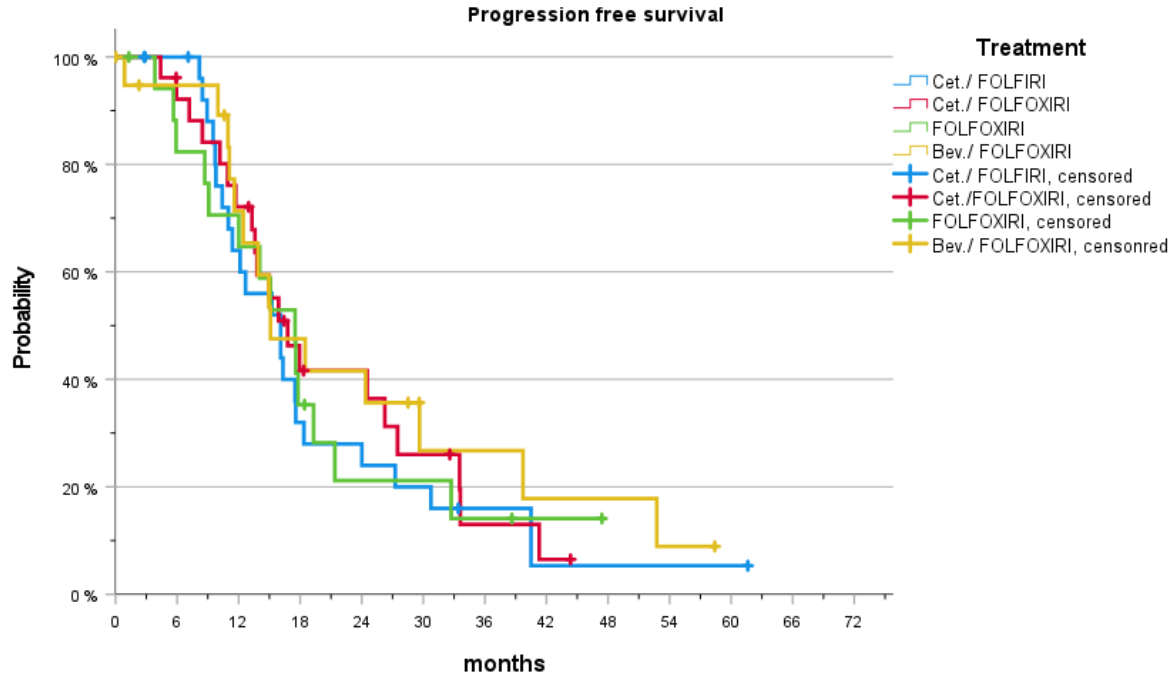


Figure 9: Progression free survival per arm



Resected patients had a median disease free survival of 11.7 months (Figure 10). The disease free survival in the four treatment arms was 11.5 and 8.2 months for the cetuximab ([K]RAS

wild type) arms and 25.0 and 12.3 months for the FOLFOXIRI ± bevacizumab ([K]RAS mutant) arms, respectively, Figure 11 and Table 11.

Figure 10: Disease free survival in all patients

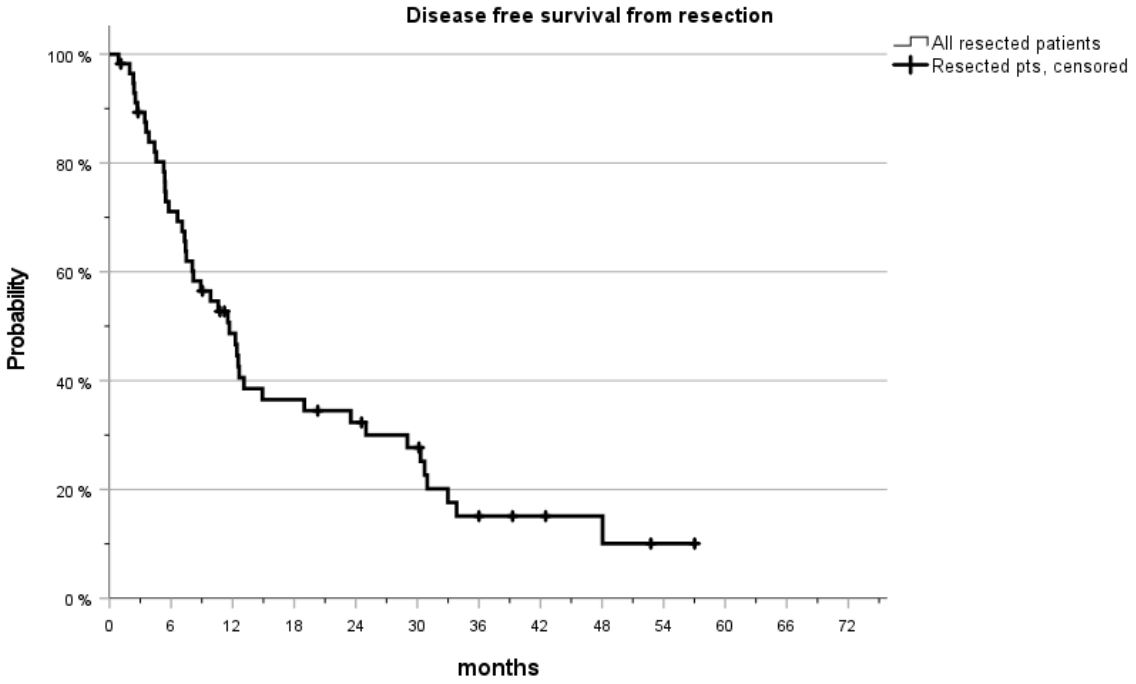
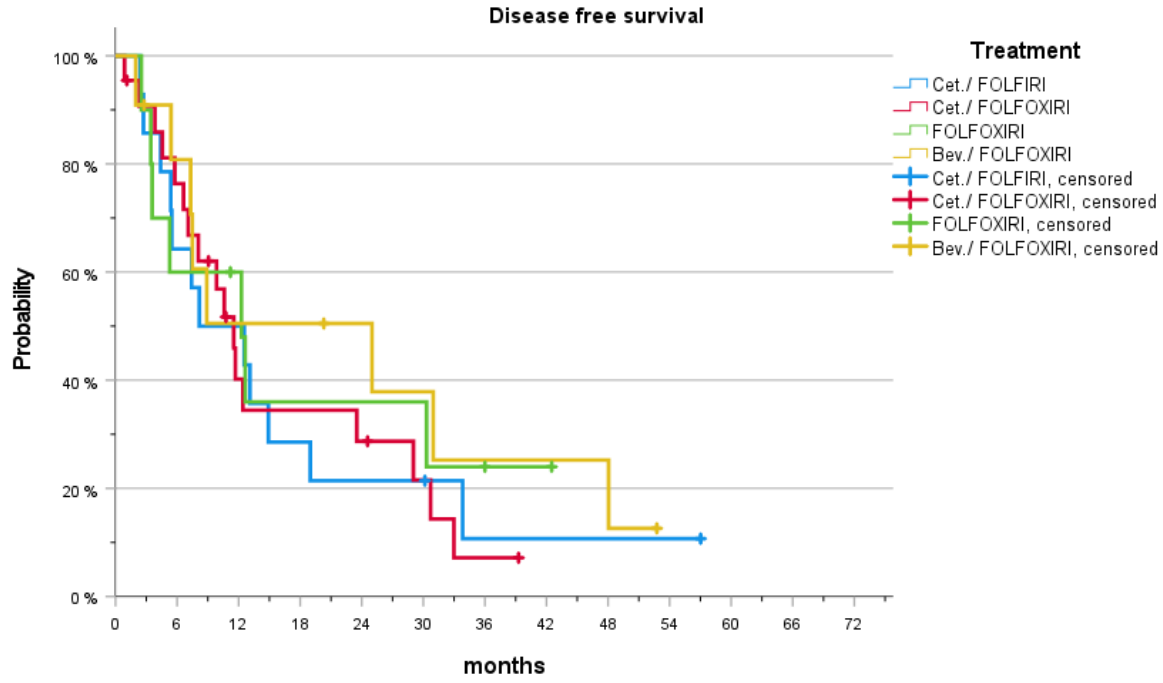
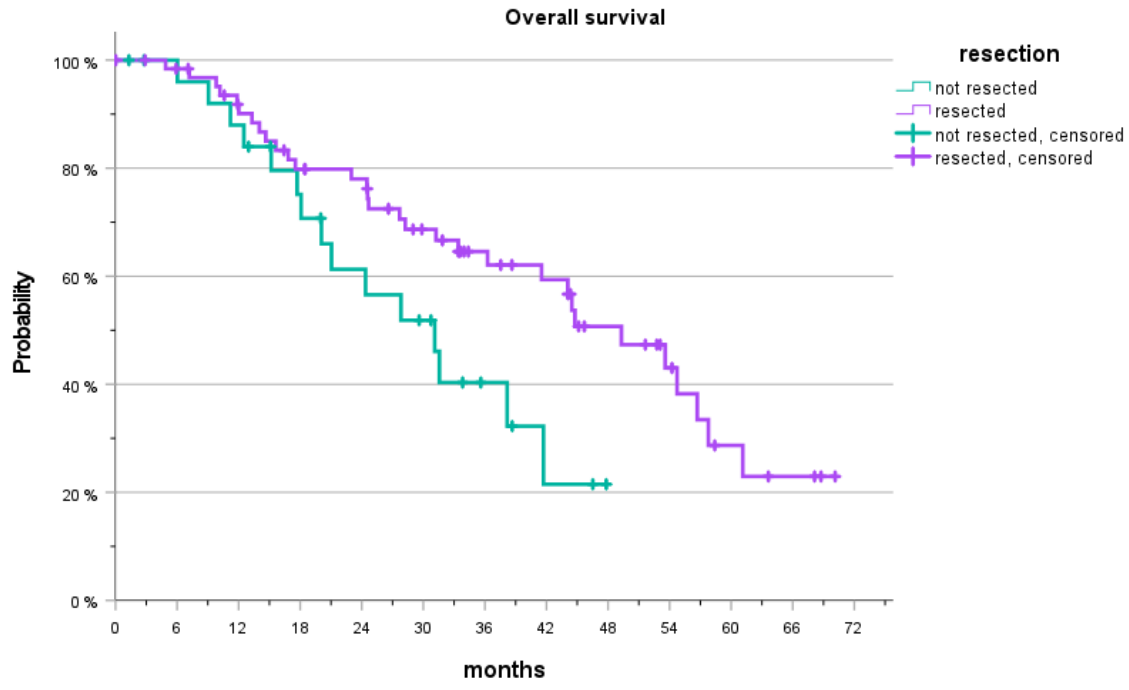


Figure 11: Disease free survival per arm



The overall survival was better if the patient was resected during the study (median 49.3 months, [95% CI: 38.8-59.8 mo.] than in patients in whom a resection was not performed (median 31.1 months, [95% CI; 21.7-40.6 mo.], HR 0.50 [95% CI: 0.26-0.95]; Figure 12).

Figure 12: Overall survival according to resection



8 Safety

8.1 Toxicity of neoadjuvant chemotherapy

In general, 66% of all patients had adverse events grade≥3 CTC. There was no significant difference between the four treatment arms.

Relevant differences were observed for toxicities that are known to be typical side effects of the drugs like skin related toxicities and allergic reactions for cetuximab and polyneuropathy for oxaliplatin (triplet regimens). So, [akne like] rash grade ≥ 3 was observed in 12 / 54 patients treated with cetuximab (22%) and in 1 / 38 patients treated without the EGFR antibody (3%), 2/54 patients with cetuximab had allergic reactions grade ≥ 3 compared to none patients without. Polyneuropathy was observed in 7/64 patients treated with FOLFOXIRI [oxaliplatin] containing schedules (11%) but not in the 28 patients treated without oxaliplatin.

The details of the grade ≥ 3 and all grade toxicities are displayed in Table 12 and Table 13.

Table 12: Frequency of grade ≥ 3 toxicities during neoadjuvant treatment per arm

	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
	N=26	N=28	N=20	N=18	N=92
Any toxicity	19	16	13	13	**61**
	(68%)	(62%)	(65%)	(72%)	(66%)
Neutropenia	10	8	8	10	**36**
	(36%)	(31%)	(40%)	(56%)	(39%)
Febrile Neutropenia	1	0	0	0	**1**
	(4%)	(0%)	(0%)	(0%)	(1%)
Leukopenia	5	4	4	4	**17**
	(18%)	(15%)	(20%)	(22%)	(18%)
Thrombopenia	2	0	2	2	**6**
	(7%)	(0%)	(10%)	(11%)	(7%)
Anemia	0	1	1	4	**6**
	(0%)	(4%)	(5%)	(22%)	(7%)
Rash	4	8	0	1	**13**
	(15%)	(31%)	(0%)	(6%)	(14%)
Paronychia	0	1	1	0	**2**
	(0%)	(4%)	(5%)	(0%)	(2%)

	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
Allergic reaction	1	1	0	0	**2**
	(4%)	(4%)	(0%)	(0%)	(2%)
Fatigue	0	0	0	2	**2**
	(0%)	(0%)	(0%)	(11%)	(2%)
PNP	3	0	2	2	**7**
	(11%)	(0%)	(10%)	(11%)	(8%)
Diarrhea	5	4	4	5	**18**
	(18%)	(15%)	(20%)	(28%)	(20%)
Stomatitis	1	0	1	0	**2**
	(4%)	(0%)	(5%)	(0%)	(2%)
Nausea	1	0	2	0	**3**
	(4%)	(0%)	(10%)	(0%)	(3%)
Vomiting	1	0	1	1	**3**
	(4%)	(0%)	(5%)	(6%)	(3%)
Thromboembolic events	1	1	1	1	4
	4%	4%	5%	6%	4%
Hypokalaemia	2	0	0	0	2
	8%	0%	0%	0%	2%
Syncope	0	2	1	0	3
	0%	7%	5%	0%	3%

Table 13: Frequency of toxicities of special interest during neoadjuvant treatment per arm

Toxicity	Maximal grade	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
		N=28	N=26	N=20	N=18	N=92
Any toxicity	1	0	2	3	0	**5**
	2	7	10	4	3	**24**
	3	13	13	9	10	**45**
	4	6	3	4	3	**16**
Neutropenia	1	5	1	1	0	**7**
	2	5	8	6	3	**22**
	3	5	6	4	7	**22**
	4	5	2	4	3	**14**
Leukopenia	1	4	4	4	1	**13**
	2	7	7	6	9	**29**
	3	4	3	4	3	**14**
	4	1	1	0	1	**3**
Thrombopenia	1	3	1	3	1	**8**

Toxicity	Maximal grade	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
	2	2	0	1	1	**4**
	3	1	0	1	2	**4**
	4	1	0	1	0	**2**
Anemia	1	5	3	4	1	**13**
	2	6	2	2	3	**13**
	3	0	1	1	4	**6**
Rash	1	6	6	0	2	**14**
	2	13	11	10	0	**24**
	3	4	8	0	1	**13**
Paronychia	1	1	0	0	0	**1**
	2	3	4	0	0	**7**
	3	0	1	1	0	**2**
Allergic reaction	1	1	1	1	0	**3**
	2	2	1	0	0	**3**
	3	1	1	0	0	**2**
Fatigue	1	11	5	7	3	**26**
	2	4	2	3	2	**11**
	3	0	0	0	2	**2**
Hand-foot-syndrome	1	2	2	1	0	**5**
	2	1	0	0	1	**2**
Sensoric polyneuropathy	1	3	3	7	2	**15**
	2	4	1	3	5	**13**
	3	3	0	2	2	**7**
Diarrhea	1	6	5	4	5	**20**
	2	8	4	4	4	**20**
	3	5	2	4	4	**15**
	4	0	2	0	1	**3**
Stomatitis	1	3	2	2	1	**8**
	2	4	2	2	1	**9**
	3	1	0	1	0	**2**
Other Mucositis	1	1	3	1	0	**5**
	2	4	2	1	0	**7**
Nausea	1	7	3	5	1	**16**
	2	3	1	4	7	**15**
	3	1	0	2	0	**3**
Vomiting	1	3	2	1	0	**6**
	2	1	1	2	1	**5**
	3	1	0	1	1	**3**

8.2 Toxicity of Adjuvant Chemotherapy

In total, 36 patients had received adjuvant therapy (6-12 patients per arm). The rate of grade ≥ 3 toxicity was similar to the rate in neoadjuvant therapy (56%). Four out of the 25 patients treated with oxaliplatin containing protocols experienced neuropathy grade ≥ 3 (and no patients treated without oxaliplatin), and three out of the 25 patients in the cetuximab arms had rash, two allergic reactions (Table 14 and Table 15). Both adverse events were not observed in the anti-EGFR free arms. Neuropathy, rash and allergic reactions are known side effects of oxaliplatin or cetuximab.

Table 14: Frequency of grade ≥ 3 toxicities during adjuvant treatment per arm

Toxicity grade ≥ 3	**Cetux/ FOLFOXIRI**	**Cetux/ FOLFIRI**	**Bev/ FOLFOXIRI**	**FOLFOXIRI**	**All patients**
	N=12	N=11	N=7	N=6	N=36
Any toxicity	8	7	4	1	**20**
	(67%)	(64%)	(57%)	(17%)	(56%)
Neutropenia	3	4	1	1	**9**
	(25%)	(36%)	(14%)	(17%)	(25%)
Leukopenia	1	0	0	1	**2**
	(8%)	(0%)	(0%)	(17%)	(6%)
Rash	1	2	0	0	**3**
	(8%)	(18%)	(0%)	(0%)	(8%)
Allegic reaction	0	2	0	0	**2**
	(0%)	(18%)	(0%)	(0%)	(6%)
Hand-foot-syndrome	1	0	0	0	**1**
	(8%)	(0%)	(0%)	(0%)	(3%)
Sensoric polyneuropathy	3	0	3	1	**7**
	(25%)	(0%)	(43%)	(17%)	(19%)
Diarrhea	1	0	0	0	**1**
	(8%)	(0%)	(0%)	(0%)	(3%)
Stomatitis	1	0	0	0	1
	(8%)	(0%)	(0%)	(0%)	(3%)
Nausea	1	1	0	0	**2**
	(8%)	(9%)	(0%)	(0%)	(6%)
Vomiting	1	0	0	0	**1**
	(8%)	(0%)	(0%)	(0%)	(3%)

Table 15: Frequency of toxicities of special interest during adjuvant treatment per arm

Toxicity	Maximal grade	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
		N=12	N=11	N=7	N=6	N=36
Any toxicity	1	0	0	1	1	**2**
	2	3	3	2	4	**12**
	3	7	7	4	1	**19**
	4	1	0	0	0	**1**
Neutropenia	1	0	1	1	0	**2**
	2	0	1	1	1	**3**
	3	3	4	1	1	**9**
Leukopenia	1	0	2	4	0	**6**
	2	1	4	0	1	**6**
	3	1	0	0	1	**2**
Thrombopenia	1	1	1	1	0	**3**
Anemia	1	3	2	2	0	**7**
	2	1	1	2	1	**5**
Rash	1	2	1	0	0	**3**
	2	3	5	0	0	**8**
	3	1	2	0	0	**3**
Paronychia	2	1	2	0	0	**3**
Allegic reaction	2	0	2	0	0	**2**
	3	0	2	0	0	**2**
Fatigue	1	3	2	3	0	**8**
	2	3	0	0	0	**3**
Hand-foot-syndrome	1	1	0	0	0	**1**
	2	1	0	0	0	**1**
	3	1	0	0	0	**1**
Sensoric polyneuropathy	1	3	0	2	2	**7**
	2	4	0	0	1	**5**
	3	3	0	3	1	**7**
Diarrhea	1	2	2	1	0	**5**
	2	3	2	1	1	**7**
	3	1	0	0	0	**1**
Stomatitis	1	1	1	2	0	**4**
	4	1	0	0	0	**1**
Nausea	1	3	0	1	1	**5**
	2	1	0	1	1	**3**
	3	1	1	0	0	**2**
Vomiting	1	1	1	1	0	**3**
	2	1	0	1	0	**2**

Toxicity	Maximal grade	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
	3	1	0	0	0	**1**

8.3 Complications of Resection

Out of the 65% patients who were resected, one patient died because of postoperatively liver failure related to low remnant functional liver tissue (1.5%; arm bevacizumab / FOLFOXIR).

The postoperative complication according to the Clavien classification are displayed in Table 16 and have not demonstrated differences between the arms.

Table 16: Complications of surgical resection per arm

Complication	Clavien grade	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
Any resection		N=22	N=18	N=14	N=11	**N=65**
Cardial	I	1	0	0	0	**1**
	IV	0	0	0	1	**1**
Respiratory	I	1	0	0		**1**
	II	1	1	2		**4**
Gastrointestinal	I	0	0	2	1	**3**
	II	0	1	0	0	**1**
	IIIa	1	0	0	0	**1**
	IIIb	0	0	1	0	**1**
Other	II	0	0	1	0	**1**
	IIIb	1	0	0	0	**1**
	V	0	0	1	0	**1**

8.4 Serious adverse events

In total, there were 55 serious adverse events reported in the CELIM2 study without differences between the arms (Table 17). One patient (arm Bevacizumab / FOLFOXIRI) died postoperatively from hepatic failure (most probably because of low remnant liver tissue after resection). One patient in the arm FOLFOXIRI/cetuximab had four SAEs and died from cholangitis, another patient in the FOLFOXIRI/cetuximab arm died because of tumor cachexia and a pelvic abscess.

Table 17: Frequency of serious adverse events

	Cetux/ FOLFOXIRI	Cetux/ FOLFIRI	Bev/ FOLFOXIRI	FOLFOXIRI	All patients
	N=26	N=28	N=20	N=18	N=92
Number of SAE's	16	14	12	13	55
	(57%)	(54%)	(60%)	(72%)	(60%)

9 Discussion

The trial has confirmed high response rates and high with all four regimens with numerically higher response rates for RAS wild type patients (treated with cetuximab) and within this group for the patients treated with cetuximab / FOLFOXIRI.

The overall survival (41.7 months) was longer than in other studies for patients with metastatic colorectal cancer, [4], [12], [13], [14] especially in the patients who were resected during the study (median: 49.3 months). The resection rate in the study in one of highest reported in clinical trials with metastatic colorectal cancer reflecting the patient population and the strong multidisciplinary cooperation within the study. Out of the resected patients, 39 patients (60%) had a disease free survival time of 6 months or more after the last resection, representing 42% of the entire study population. These data underline that a focus of future research should be to identify which patients benefit most from multidisciplinary treatment and who might have an early recurrence even if resected.

The overall survival for patients who were not resected (median: 31.1 months) is in the range of patients treated with metastatic colorectal cancer. [4], [12], [13], [14] Due to the lower number of patients than initially planned, it is difficult to draw firm conclusions.

There were no safety signals detected during the study. The frequency of adverse events is comparable to previous studies. Beside the typical toxicities of cetuximab (skin toxicity and allergic reaction) [15] and oxaliplatin (neuropathy), [16] there were no differences between the arms observed. The postoperative mortality of 1.5% is lower than historically for liver resections. [17]

10 Summary - Conclusions

10.1 Efficacy Results

The trial has confirmed high response rates and high with all four regimens with numerically higher response rates for RAS wild type patients (treated with cetuximab) and within this group for the patients treated with cetuximab / FOLFOXIRI. The overall survival (41.7 months) was longer compared to historically controls for patients with metastatic colorectal cancer, especially in the patients who were resected during the study (median: 49.3 months). The resection rate in the study in one of highest reported in clinical trials with metastatic colorectal cancer reflecting the patient population and the strong multidisciplinary cooperation within the study. Out of the resected patients, 39 patients (60%) had a disease free survival time of 6 months or more after the last resection, representing 42% of the entire study population. These data underline that a focus of future research should be to identify which patients benefit most from multidisciplinary treatment and who might have an early recurrence even if resected.

10.2 Safety Results

There were no safety signals detected during the study. The frequency of adverse events is comparable to previous studies. Beside the typical toxicities of cetuximab (skin toxicity and allergic reaction) and oxaliplatin (neuropathy), there were no differences between the arms observed. The postoperative mortality of 1.5% is lower than historically for liver resections.

10.3 Conclusion

The study confirmed high response rates in patients with colorectal liver metastases and high resection rates in the setting of a close multidisciplinary cooperation. The overall survival was longer in patients resected for liver metastases.

No new safety signals were detected.

11 Publications

Key data of the study were shown as a poster presentation at the Convention of the American Society of Clinical Oncology 2020 (virtual meeting due to COVID-19):

Gunnar Folprecht, Marika Mende, Torsten Liersch, Wolf Otto Bechstein, Claus-Henning Kohne, Alexander Stein, Volker Kunzmann, Michael Ghadimi, Ulf Peter Neumann, Sven Nilsson, Alexander Koenig, Ursula Pession, Achim Troja, Manfred Glados, Mathias Kleiss, Ulrike Ubbelohde, and Juergen Weitz: Cetuximab/irinotecan/5-FU +/-oxaliplatin or FOLFOXIRI +/- bevacizumab in patients with colorectal cancer and nonresectable liver metastases (AIO CELIM2-study). Journal of Clinical Oncology 2020 38:15_suppl, 4024-4024, DOI: 10.1200/JCO.2020.38.15_suppl.4024

12 Signatures

14.07.2022

Date

Professor Dr. Gunnar Folprecht,
University Hospital Carl Gustav Carus, Dresden, Germany

13 Appendix: References

[1] RKI, "Bericht zum Krebsgeschehen in Deutschland 2016," *Bericht zum Krebsgeschehen Deutschl. 2016. Zent. für Krebsregisterdaten im Robert Koch-Institut (Hrsg). Berlin*, pp. 16–77, 2016, doi: 10.17886/rkipubl-2016-014.

[2] R. Adam *et al.*, "Rescue Surgery for Unresectable Colorectal Liver Metastases Downstaged by Chemotherapy," *Trans. … Meet. Am. Surg. Assoc.*, vol. CXXII, no. NA;, pp. 242–256, 2004, doi: 10.1097/01.sla.0000141198.92114.f6.

[3] G. Folprecht, A. Grothey, S. Alberts, H. R. Raab, and C. H. Köhne, "Neoadjuvant treatment of unresectable colorectal liver metastases: Correlation between tumour response and resection rates," *Ann. Oncol.*, vol. 16, no. 8, pp. 1311–1319, 2005.

[4] E. Van Cutsem *et al.*, "Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status.," *J. Clin. Oncol.*, vol. 29, no. 15, pp. 2011–2019, 2011, doi: 10.1200/JCO.2010.33.5091.

[5] K. F. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, "Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer," *N. Engl. J. Med.*, vol. 350, no. 23, pp. 2335–2342, 2004.

[6] L. B. Saltz *et al.*, "Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study," *J. Clin. Oncol.*, vol. 26, no. 12, pp. 2013–2019, 2008, doi: 10.1200/JCO.2007.14.9930.

[7] G. Folprecht *et al.*, "Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial," *Lancet Oncol.*, vol. 11, no. 1, pp. 38–47, 2010, doi: 10.1016/S1470-2045(09)70330-4.

[8] G. Folprecht, S. Hamann, K. Schütte, T. Trarbach, J. Stoehlmacher-Williams, and G. Ehninger, "Dose escalating study of cetuximab and 5-FU/folinic acid (FA)/oxaliplatin/irinotecan (FOLFOXIRI) in first line therapy of patients with metastatic colorectal cancer.," *BMC Cancer*, vol. 14, p. 521, 2014, [Online]. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4223588&tool=pmcentrez&rendertype=abstract

[9] A. Falcone *et al.*, "Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: The gruppo oncologico nor," *J. Clin. Oncol.*, vol. 25, no. 13, pp. 1670–1676, 2007, doi: 10.1200/JCO.2006.09.0928.

[10] T. Gruenberger *et al.*, "Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: The OLIVIA multinational randomised phase II trial," *Ann. Oncol.*, vol. 26, no. 4, pp. 702–708, 2015, doi: 10.1093/annonc/mdu580.

[11] E. A. Eisenhauer *et al.*, "New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)," *Eur. J. Cancer*, vol. 45, no. 2, pp. 228–247, 2009, doi: 10.1016/j.ejca.2008.10.026.

[12] A. P. Venook *et al.*, "Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With *KRAS* Wild-Type Advanced or Metastatic Colorectal Cancer," *Jama*, vol. 317, no. 23, p. 2392, 2017, doi: 10.1001/jama.2017.7105.

[13] C. Cremolini *et al.*, "FOLFOXIRI or FOLFOXIRI plus bevacizumab as first-line treatment of metastatic colorectal cancer: A propensity score-adjusted analysis from two randomized clinical trials," *Ann. Oncol.*, vol. 27, no. 5, pp. 843–849, 2016, doi: 10.1093/annonc/mdw052.

[14] C. Cremolini *et al.*, "Individual Patient Data Meta-Analysis of FOLFOXIRI Plus Bevacizumab Versus Doublets Plus Bevacizumab as Initial Therapy of Unresectable Metastatic Colorectal Cancer," *J. Clin. Oncol.*, p. JCO.20.01225, 2020, doi: 10.1200/jco.20.01225.

[15] D. Jonker *et al.*, "Cetuximab for the treatment of colorectal cancer," *N. Engl. J. Med.*, vol. 357, no. 20, 2007, doi: 10.1056/NEJMOA071834.

[16] F. Maindrault-Goebel *et al.*, "Oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX6). GERCOR," *Eur. J. Cancer*, vol. 35, no. 9, pp. 1338–1342, Sep. 1999, doi: 10.1016/S0959-8049(99)00149-5.

[17] O. Farges, N. Goutte, N. Bendersky, and B. Falissard, "Incidence and risks of liver resection: an all-inclusive French nationwide study," *Ann. Surg.*, vol. 256, no. 5, pp. 697–705, Nov. 2012, doi: 10.1097/SLA.0B013E31827241D5.

14 List of Abbreviations

AE	adverse event
AMG	Arzneimittelgesetz
AR	adverse reaction
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease free survival
eCRF	Electronic Case Report Form
EGFR	Epithelial growth factor receptor
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FOLFIRI	**Fol**inic acid, 5-**F**U, **iri**notecan (doublet) chemotherapy regimen)
FOLFOX	**Fol**inic acid, 5-**FU**, **ox**aliplatin (doublet) chemotherapy regimen)
FOLFOXIRI	**Fol**inic acid, 5-**F**U, **ox**aliplatin, **iri**notecan (triplet) chemotherapy regimen)
FPFV	First patient first visit
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ISF	Investigator Site File
ITT	Intention to treat
KKS	Koordinierungszentrum für Klinische Studien
LPLV	Last patient last visit
NA	not applicable
ND	not done
OS	Overall survival
PEI	Paul-Ehrlich-Institut
PFS	Progression free survival
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAS	Safety Analysis Set
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPSS	Statistical Package for the Social Sciences
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UAR	Unexpected Adverse Reaction

15 Appendix: Serious adverse events

Table 18: Line listing of SAEs

SAE-Nr.	Arm	Pat. No	Site	Gender	Age	Event	Grade/ intensity	Related to Bevacizumab	Related to Irinotecan	Related to Oxaliplatin	Related to Cetuximab	Related to FA	Related to 5-FU	seriousness criteria	onset date	date of resolution	outcome of SAE	SUSAR?	changes of benefit-risk	changes of trial conduction
1	FOLFOXIRI	01-003	01 (Dresden)	m	69	port infection	3	0	0	0	0	0	0	Hospitali-zation	25.04.2013	26.04.2013	recovered/ resolved	no	no	no
2	FOLFOXIRI	01-003	01 (Dresden)	m	69	Ileus	4	0	0	0	0	0	0	Hospitali-zation	28.04.2013	06.05.2013	recovered/ resolved	no	no	no
3	FOLFOXIRI/ Bevacizumab	07-002	07 (Olden-burg)	m	57	infected pilonidalsinus	3	0	1	1	0	1	1	Hospitali-zation	23.12.2013	26.12.2013	recovering	no	no	no
4	FOLFOXIRI/ Bevacizumab	07-002	07 (Olden-burg)	m	58	pleural effusion (exclusion of broncho-pneumonia)	3	0	0	0	0	0	0	Hospitali-zation	10.02.2014	20.02.2014	recovered/ resolved	no	no	no
5	FOLFOXIRI/ Cetuximab	03-003	03 (Würz-burg)	m	61	febrile neutropenia	3	0	3	3	1	0	3	Hospitali-zation	26.04.2014	02.05.2014	recovered/ resolved	no	no	no

SAE-Nr.	Arm	Pat. No	Site	Gender	Age	Event	Grade/ intensity	Related to Bevacizumab	Related to Irinotecan	Related to Oxaliplatin	Related to Cetuximab	Related to FA	Related to 5-FU	seriousness criteria	onset date	date of resolution	outcome of SAE	SUSAR?	changes of benefit-risk	changes of trial conduction
6	FOLFIRI/ Cetuximab	01-010	01 (Dresden)	w	71	urinary tract infection (with fever)	3	0	1	0	1	1	1	Hospitali-zation	26.08.2014	04.09.2014	recovered/ resolved	no	no	no
7	FOLFOXIRI/ Cetuximab	01-009	01 (Dresden)	m	58	suspicion of abscess of surgical (initial): perihepatic bilioma and pleural effusion right	3	0	0	0	0	0	0	Hospitali-zation	27.09.2014	10.10.2014	recovered/ resolved	no	no	no
8	FOLFIRI/ Cetuximab	01-010	01 (Dresden)	w	71	abdominal wound dehiscence after hemihepatectomy	3	0	0	0	0	0	0	Prolon-gation	28.09.2014	11.12.2014	recovered/ resolved	no	no	no
9	FOLFOXIRI	01-013	01 (Dresden)	w	50	diarrhea/ neutropenia	4	0	4	4	0	3	4	Hospitali-zation	16.10.2014	22.10.2014	recovered/ resolved	no	no	no
10	FOLFOXIRI	01-013	01 (Dresden)	w	50	fever of unknown origin	1	0	0	0	0	0	0	Hospitali-zation	24.10.2014	07.11.2014	recovered/ resolved	no	no	no
11	FOLFOXIRI/ Cetuximab	03-003	03 (Würz-burg)	m	61	liver insufficiency grade B	2	0	0	0	0	0	0	Prolon-gation	08.10.2014	18.10.2014	recovered/ resolved	no	no	no
12	FOLFOXIRI/ Cetuximab	03-003	03 (Würz-burg)	m	61	cholangitis	2	0	0	0	0	0	0	Hospitali-zation	21.10.2014	01.11.2014	recovered/ resolved	no	no	no
13	FOLFOXIRI/ Cetuximab	03-003	03 (Würz-burg)	m	61	cholangitis	2	0	0	0	0	0	0	Hospitali-zation	05.11.2014	03.12.2014	fatal	no	no	no
14	FOLFOXFIRI/ Cetuximab	01-009	01 (Dresden)	m	58	Bilioma and pleural effusion downgraded because beyond time window	3	0	0	0	0	0	0	Hospitali-zation	27.09.2014	10.10.2014	recovered/ resolved	no	no	no

SAE-Nr.	Arm	Pat. No	Site	Gender	Age	Event	Grade/ intensity	Related to Bevacizumab	Related to Irinotecan	Related to Oxaliplatin	Related to Cetuximab	Related to FA	Related to 5-FU	seriousness criteria	onset date	date of resolution	outcome of SAE	SUSAR?	changes of benefit-risk	changes of trial conduction
15	FOLFOXIRI	03-005	03 (Würzburg)	w	66	tumor pain (initial term: worsening general condition) + nausea 2° + fatigue 2°	2	5	2	2	5	2	2	Hospitalization	29.11.2014	03.12.2014	recovered/ resolved	no	no	no
16	FOLFOXIRI/ Cetuximab	01-014	01 (Dresden)	m	62	Cerebral embolism (initial term: hemiparesis right arm with speech disorder)	3 (initial: 4)	0	0	0	0	0	0	Hospitalization	16.03.2015	23.03.2015		no	no	no
17	FOLFOXIRI/ Cetuximab	03-007	03 (Würzburg)	w	65	Diarrhea	2	5	5	2	1	0	3	Hospitalization	22.03.2015	03.04.2015	recovered/ resolved	no	no	no
18	FOLFIRI/ Cetuximab	01-015	01 (Dresden)	w	67	Diarrhea	4	0	4	0	3	2	4	Hospitalization	11.04.2015	16.04.2015	recovered	no	no	no
19	FOLFIRI/ Cetuximab	01-015	01 (Dresden)	w	67	suspected TIA (transient ischemic attack) with symptom of speech disorder downgraded, because no hospitalization	0	0	0	0	0	0	0	Hospitalization	23.04.2015		not recovered / not followed up	no	no	no
20	FOLFOXIRI/ Cetuximab	09-001	09 (Göttingen)	m	58	indistinct lower GI-bleeding	1	0	1	1	1	1	1	Hospitalization	12.06.2015	13.06.2015	recovered/ resolved	no	no	no
21	FOLFOXIRI/ Bevacizumab	07-008	07 (Oldenburg)	m	61	Fever & Infection because of Leukopenia	3	0	4	4	0	0	3	Hospitalization	04.07.2015	13.07.2015	recovered/ resolved	no	no	no
22	FOLFOXIRI/ Cetuximab	09-001	09 (Göttingen)	m	58	Vomiting due to suspected viral infection of the GI tract	2	0	3	3	3	0	3	Hospitalization	16.07.2015	21.07.2015	recovered/ resolved	no	no	no

SAE-Nr.	Arm	Pat. No	Site	Gender	Age	Event	Grade/ intensity	Related to Bevacizumab	Related to Irinotecan	Related to Oxaliplatin	Related to Cetuximab	Related to FA	Related to 5-FU	seriousness criteria	onset date	date of resolution	outcome of SAE	SUSAR?	changes of benefit-risk	changes of trial conduction
						(aggravated by prior chemotherapy)														
23	FOLFIRI/ Cetuximab	07-007	07 (Olden-burg)	m	47	occlusion of nephrostomy catheter	0	0	0	0	0	0	0	Hospitali-zation	27.07.2015	28.07.2015	recovered/ resolved	no	no	no
24	FOLFOXIRI/ Cetuximab	09-001	09 (Göttingen)	m	59	diarrhea, differential diagnosis mucositis	2	0	3	3	3	3	3	Hospitali-zation	22.08.2015	24.08.2015	recovered/ resolved	no	no	no
25	FOLFIRI/ Cetuximab	09-003	09 (Göttingen)	f	61	pulmonary embolism	3	0	1	0	1	1	1	Hospitali-zation	19.01.2016	20.01.2016	recovered/ resolved	no	no	no
26	FOLFOXIRI/ Cetuximab	04-004	04 (Olden-burg)	m	42	fever in neutropenia and infection caused by Enterococcus faecalis	3	0	3	3	2	1	3	Hospitali-zation	23.01.2016	28.01.2016	recovered/ resolved	no	no	no
27	FOLFOXIRI	12-006	12 (Frank-furt)	m	57	Nausea & Vomiting	3 & 2	0	4	4	0	0	4	Hospitali-zation	10.02.2016	12.02.2016	recovered/ resolved	no	no	no
28	FOLFIRI/ Cetuximab	13-002	13 (Coesfeld)	m	54	hyperglycemia	4	0	0	0	0	0	0	Hospitali-zation	11.03.2016	17.03.2016	recovered/ resolved	no	no	no
29	FOLFOXIRI	09-009	09 (Göttingen)	m	78	ileus	4	1	1	1	1	1	1	Hospitali-zation	09.04.2016	03.05.2016	recovered/ resolved	no	no	no
30	FOLFIRI/ Cetuximab	09-004	09 (Göttingen)	m	43	allergic reaction (rash 3°, dry mucosa, difficulty in swallowing, Back pain, chest pain)	3	0	0	0	4	0	0	other medically important condition	18.04.2016	18.04.2016	recovered/ resolved	no	no	no

SAE-Nr.	Arm	Pat. No	Site	Gender	Age	Event	Grade/ intensity	Related to Bevacizumab	Related to Irinotecan	Related to Oxaliplatin	Related to Cetuximab	Related to FA	Related to 5-FU	seriousness criteria	onset date	date of resolution	outcome of SAE	SUSAR?	changes of benefit-risk	changes of trial conduction
31	FOLFOXIRI/ Bevacizumab	12-006	12 (Frankfurt)	f	57	rectal bleeding		0	0	0	0	0	0	Hospitalization	26.04.2016	28.04.2016	recovered/ resolved	no	no	no
32	FOLFOXIRI/ Bevacizumab	09-012	09 (Göttingen)	m	61	urinary tract infection (fever)	2	1	1	1	0	1	1	Hospitalization	07.06.2016	10.06.2016	recovered/ resolved	no	no	no
33	FOLFOXIRI/ Cetuximab	09-010	09 (Göttingen)	m	57	diarrhea	3	0	3	0	0	0	2	Hospitalization	13.06.2016	24.06.2016	recovered/ resolved	no	no	no
34	FOLFOXIRI/ Cetuximab	09-010	09 (Göttingen)	m	58	port a cath infection, urinary tract infection, anemia, pleural effusion, anasarca	3	0	3	0	2	3	3	Hospitalization	06.07.2016	12.07.2016	recovered/ resolved	no	no	no
35	FOLFOXIRI/ Cetuximab	13-001	13 (Coesfeld)	m	70	reduced general condition with exsiccosis, mucositis	2	0	0	0	2	0	0	Hospitalization	07.07.2016	12.07.2016	recovered/ resolved	no	no	no
36	FOLFIRI/ Cetuximab	09-014	09 (Göttingen)	m	76	hypotension, diarrhea	2	0	3	0	1	0	3	Hospitalization	13.07.2016	14.07.2016	recovered/ resolved	no	no	no
37	FOLFOXIRI/ Bevacizumab	12-009	12 (Frankfurt)	f	66	vomiting 3° (and renal failure, nausea, neutropenia, leukopenia)	3	1	4	4	0	0	4	Hospitalization	22.08.2016	31.08.2016	recovered/ resolved	no	no	no
38	FOLFIRI/ Cetuximab	09-010	09 (Göttingen)	m	58	urinary tract infection (exciccosis, acute renal failure)	3	0	3	0	3	3	3	Hospitalization	29.08.2016	06.09.2016	recovered/ resolved	no	no	no
39	FOLFIRI/ Cetuximab	09-014	09 (Göttingen)	m	76	sinus tachycardia	2	1	1	1	1	1	1	Hospitalization	03.09.2016	04.09.2016	recovered/ resolved	no	no	no

SAE-Nr.	Arm	Pat. No	Site	Gender	Age	Event	Grade/ intensity	Related to Bevacizumab	Related to Irinotecan	Related to Oxaliplatin	Related to Cetuximab	Related to FA	Related to 5-FU	seriousness criteria	onset date	date of resolution	outcome of SAE	SUSAR?	changes of benefit-risk	changes of trial conduction
40	FOLFOXIRI	07-014	07 (Olden-burg)	f	72	intermittend AV-block	3	0	1	1	0	1	2	Prolon-gation	08.09.2016	13.09.2016	recovered/ resolved	no	no	no
41	FOLFIRI/ Cetuximab	09-014	09 (Göttingen)	m	76	sinus tachycardia	2	0	1	0	1	1	1	Hospitali-zation	18.09.2016	19.09.2016	recovered/ resolved	no	no	no
42	FOLFOXIRI/ Bevacizumab	06-002	06 (Aachen)	m	71	post-op liver failure with hepatic encephalopathy	3	1	2	2	0	1	1	Hospitali-zation	27.10.2016	30.10.2016	fatal	YES	no	no
43	FOLFIRI/ Cetuximab	17-001	17 (Kassel)	m	58	diarrhea	4	0	3	0	3	3	3	Hospitali-zation	16.01.2017	19.01.2017	recovered/ resolved	no	no	no
44	FOLFOXIRI	04-009	04 (Hamburg)	m	77	fever, broncho-pulmonary infection	2	1	3	3	0	2	3	Hospitali-zation	30.01.2017	31.01.2017	recovered/ resolved	no	no	no
45	FOLFIRI/ Cetuximab	12-011	12 (Frankfurt)	m	72	subileus	2	0	0	0	0	0	0	Hospitali-zation	17.02.2017	18.02.2017	recovered/ resolved	no	no	no
46	FOLFIRI/ Cetuximab	17-001	17 (Kassel)	m	58	Deaf right arm	3	0	0	0	0	0	0	Hospitali-zation	15.03.2017	24.03.2017	recovered/ resolved	no	no	no
47	FOLFOXIRI/ Bevacizumab	09-017	09 (Göttingen)	m	61	Infect of uncertain origin (CRP increased), Inappetence, exsiccosis	3	0	2	2	0	0	2	Hospitali-zation	24.03.2017	05.04.2017	rescovered / resolved	no	no	no
48	FOLFOXIRI/ Bevacizumab	09-016	09 (Göttingen)	m	67	vertigo, diarrhea	2	0	3	2	0	0	0	Hospitali-zation	02.04.2017	03.04.2017	recovered/ resolved	no	no	no

SAE-Nr.	Arm	Pat. No	Site	Gender	Age	Event	Grade/ intensity	Related to Bevacizumab	Related to Irinotecan	Related to Oxaliplatin	Related to Cetuximab	Related to FA	Related to 5-FU	seriousness criteria	onset date	date of resolution	outcome of SAE	SUSAR?	changes of benefit-risk	changes of trial conduction
49	FOLFOXIRI/ Bevacizumab	09-017	09 (Göttingen)	m	61	bowel perforation	4	3	1	1	0	5	1	Hospitali-zation	22.04.2017		recovered/ resolved	no	no	no
50	FOLFOXIRI/ Bevacizumab	01-027	01 (Dresden)	m	62	abdominal pain	2	1	2	2	0	2	2	Hospitali-zation	23.07.2017		not recovered / not resolved	no	no	no
51	FOLFOXIRI	06-003	06 (Aachen)	f	57	deterioration of general condition due to tumor cachexia and abscess in the sacral region	3	0	2	2	0	2	2	Hospitali-zation	01.08.2017	24.08.2017	fatal	YES	no	No
52	FOLFOXIRI	12-012	12 (Frankfurt)	m	44	febrile neutropenia	4	0	2	2	0	2	2	hospitali zation	09.12.2017	18.12.2017	recovered/ resolved	no	no	no
53	FOLFOXIRI/ Bevacizumab	12-012	12 (Frankfurt)	m	44	subileus	4	1	1	1	0	1	1	hospitali zation	06.01.2018	25.01.2018	recovered/ resolved	no	no	no
54	FOLFOXIRI	12-15	12 (Frankfurt)	m	64	First diagnozed diabetes mellitus	mo der ate	0	0	0	0	0	0	hospitali zation	30.07.2018	02.08.2018	recovered/ resolved	no	no	no
55	FOLFOXIRI/ Cetuximab	09-018	09 (Göttingen)	m	71	wound infection	sev ere	0	1	1	1	1	1	hospitali zation	10.10.2018	25.10.2018	recovered/ resolved	no	no	no
56	FOLFOXIRI	07-016	07 (Oldenburg)	m	55	Thrombosis v. subclavia left	mo der ate	0	0	0	0	0	0	medically importan t condition	14.11.2018	27.11.2018	recovered/ resolved	no	no	no

SAE-Nr.	Arm	Pat. No	Site	Gender	Age	Event	Grade/ intensity	Related to Bevacizumab	Related to Irinotecan	Related to Oxaliplatin	Related to Cetuximab	Related to FA	Related to 5-FU	seriousness criteria	onset date	date of resolution	outcome of SAE	SUSAR?	changes of benefit-risk	changes of trial conduction
57	FOLFOXIRI/ Cetuximab	01-03 1	01 (Dresden)	m	53	fever of unknown origin	3	0	1	1	1	1	1	hospitalization	19.11.2018	23.11.2018	recovered/ resolved	no	no	no

16 Appendix: Study protocol

Clinical study protocol

CELIM 2- study:
Cetuximab/FOLFIRI with or without oxaliplatin and FOLFOXIRI with or without bevacizumab in neoadjuvant treatment of non-resectable colorectal liver metastases

Open, randomized, multicenter phase II trial with cetuximab /5-FU/FA/irinotecan or cetuximab/5-FU/FA /irinotecan/oxaliplatin in ras wild type patients or with irinotecan/oxaliplatin/5-FU/FA with or without bevacizumab in ras mutant patients as neoadjuvant treatment in patients with non- resectable colorectal liver metastases.

Sponsor:
Technical University Dresden, Germany

Sponsor study code: TUD-CELIM2-050
EUDRACT No. 2011-003288-31

1 Content

2 Study coordination

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2.7 Financing

The study is supported by an unrestricted educational grant of Merck Pharma GmbH, Germany.

2.8 Protocol signatures

I agree to conduct the study in accordance with this clinical trial protocol and in compliance with Good Clinical Practice and all applicable regulatory requirements.

Study Title:

CELIM 2- study: Cetuximab/FOLFIRI with or without oxaliplatin and FOLFOXIRI with or without bevacizumab in neoadjuvant treatment of non-resectable colorectal liver metastases

(Open, randomized, multicenter phase II trial with cetuximab /5-FU/FA/irinotecan or cetuximab/5-FU/FA /irinotecan/oxaliplatin in ras wild type patients or with irinotecan/oxaliplatin/5-FU/FA with or without bevacizumab in ras mutant patients as neoadjuvant treatment in patients with non- resectable colorectal liver metastases.)

Sponsor study code: TUD-CELIM2-050

EUDRACT No. 2011-003288-31

17.02.2014

Date

Coordinating physician / on behalf of the sponsor

Date

Principal investigator

3 Study overview

Title	**CELIM 2- study: Cetuximab/FOLFIRI with or without oxaliplatin and FOLFOXIRI with or without bevacizumab in neoadjuvant treatment of non-resectable colorectal liver metastases**
Objective	The aim of this study is to investigate the following schedules for efficacy with regard to response rate in neoadjuvant treatment of patients with non-resectable liver metastases: - Cetuximab/FOLFOXIRI and cetuximab/FOLFIRI in patients with *ras* wild type tumours and - Bevacizumab/FOLFOXIRI and FOLFOXIRI in patients with *ras* mutant tumours.
Sponsor	Technical University Dresden, 01062 Dresden, Germany
Study codes	TUD-CELIM2-050
Primary endpoint	Rate of patients with partial or complete response according to modified RECIST criteria (definition see chapter 12.2.1, ITT- population)
Secondary endpoint	Rate of patients who had a R0 resection of all lesions and are disease free for at least 6 months (definition see chapter 12.2.4, ITT- population)
Other endpoints	- Resection rate, defined as patients with microscopically complete (R0) resection (ITT- population) - Rate of liver resection with macroscopically tumour free margins and/or RFA (all patients with R0 or R1 resection and/or complete RFA of all lesion, ITT- population) - Progression free survival (Kaplan-Meier-estimation, ITT- population) - Disease free survival after resection (Kaplan-Meier-estimation, resected patients) - Overall survival (Kaplan-Meier-estimation, ITT- population) - Toxicity (safety population) - Pathological response in resected tumour tissue - Evaluation of molecular predictive markers for response (i.e. other mutations in EGFR pathway, EGFR ligands) and toxicity
Study design	Patients with liver metastases from colorectal and without known extrahepatic metastases will be screened for this study including *ras* status (b-raf status according to local standard). Patients receive chemotherapy according to the allocation (see chapter 7.2.2) and are re-evaluated for resectability (chapter 9.8) every 8 weeks for a maximum of 6 months. Resectable patients will be resected and receive an adjuvant treatment to complete 12 cycles (details in chapter 9.10). In certain circumstances, a second resection is allowed within the study (details in chapter 9.10.2 and chapter 6.1). Patients will be randomized using a web-based computer system that allows randomization if the key basic characteristics are entered. Patients with ***ras* wild-type** tumours will be randomized to receive: - Cetuximab/FOLFIRI or - Cetuximab/FOLFOXIRI Patients with ***ras* mutations** will be randomized to receive: - FOLFOXIRI or - FOLFOXIRI/bevacizumab Chemotherapy doses are adjusted to the risk of toxicity in all treatment arms. Stratification will be performed according to: - Number of metastases (< 5 vs. ≥ 5 metastases) - Primary tumour *in situ* - Centre

	Treatment regimens For dose reductions and conditions to continue please refer to the full protocol. All drugs are used within the label and approved doses. B-raf mutations are determined according to local standard. If a b-raf mutation is known before randomization, the investigator can consider the patient as ras wildtype OR as ras mutant patient. *Cetuximab/FOLFIRI :* Cetuximab 400 mg/m² (first dose, 2 h), then 250 mg/m² (1 h) weekly Irinotecan 180 mg/m², *d-l* Folinic acid 400 mg/m² (2 h), 5-FU 400 mg/m² (Bolus), 5-FU 2400 mg/m² (46 h) every 2 weeks *Cetuximab/FOLFOXIRI:* Cetuximab 400 mg/m² (first dose, 2 h), then 250 mg/m² (1 h) weekly Irinotecan 125 mg/m² , Oxaliplatin 85 mg/m² (2 h), *d-l* Folinic acid 400 mg/m² (2 h), 5-FU 3200 mg/m² (46 h) every 2 weeks *FOLFOXIRI:* Irinotecan 165 mg/m², Oxaliplatin 85 mg/m² (2 h), *d-l* Folinic acid 400 mg/m² (2 h), 5-FU 3200 mg/m² (46 h) every 2 weeks *Bevacizumab/FOLFOXIRI:* Bevacizumab 5 mg/kg (90 – 30 min i.v.), Irinotecan 165 mg/m², Oxaliplatin 85 mg/m² (2 h), *d-l* Folinic acid 400 mg/m² (2 h), 5-FU 3200 mg/m² (46 h) every 2 weeks **Evaluation for response and resections** Patients are evaluated for response by the same imaging technique as at baseline every 8 weeks. The findings will be discussed for resectability within two weeks after tumour assessment in a local multidisciplinary team. Technically resectable patients should be offered liver resection. The treatment will continue until liver resection or for a maximum of six months (12 cycles). **Adjuvant treatment** After liver resection, an adjuvant treatment is recommended with the same schedule as preoperatively, for a maximum combined pre- and postoperative treatment of 12 cycles. If less than three postoperative cycles remain, no postoperative treatment will be started (see chapter 9.10). **Follow up** After resection, patients will be followed up for 5 years after randomization. This includes - imaging and clinical investigation every three months for the first 2 years, then every six months (patients without tumour progression / recurrence) - survival status and surgical/medical treatment every three months for the first 2 years and then every six months (all patients)
Inclusion criteria	Patients can be enrolled, if all of these conditions apply: 1) Non-resectable, histologically confirmed, synchronous or metachronous colorectal liver metastases. 2) Non-resectability will be documented by a local multidisciplinary tumour board with participation of a surgeon experienced in liver surgery. Patients can be enrolled if they a) are technically non-resectable (locally determined by a multi-

	disciplinary team discussion based on remaining functional liver tissue after resection, i.e. i) involvement of both portal veins, all hepatic veins, portal vein of the liver lobe and hepatic veins draining the segments of the other liver lobe, or ii) other reasons for less than 30% remaining functional liver tissue after resection) and / or b) have ≥ 5 liver metastases and / or c) are regarded as non-resectable for other reasons (description necessary) 3) Patients with simultaneous liver metastases are eligible, a) if the primary tumour was resected at least 1 month prior to chemotherapy or b) all of the following conditions apply: i) the primary tumour is clearly resectable, ii) no radiation therapy is planned, iii) liver resection is planned before resection of the primary or at the same operation as the resection of the primary, iv) no two-stage liver resection is planned, and v) all efforts were made to exclude additional distant metastases. 4) WHO PS ≤ 1 5) Written informed consent 6) Adequate bone marrow function, liver function (neutrophils > 1.5 x 10^9/l; platelets > 100 x 10^9/l; haemoglobin > 5.0 mmol/l (8.0 g/dl); bilirubin ≤ ULN or ≤ 1.5 x ULN and not increasing more than 25 % within the last 4 weeks; SGOT and SGPT < 5 x UNL) 7) Age ≥ 18 years
Exclusion criteria	1) Any evidence of extrahepatic metastases, distant lymph node metastases and primary tumour recurrence 2) (deleted) 3) Prior systemic anti-tumour therapy with anti- EGFR-, anti-angiogenetic drugs or with chemotherapy (except adjuvant chemotherapy with an interval of ≥ 6 months or in combination with radiation as radio sensitizer) 4) Radiotherapy or major abdominal or thoracic surgery (excluding diagnostic interventions or venous port implantation) ≤ 4 weeks before study entry 5) Renal insufficiency with serum creatinine ≥ 1.5 x UNL. If serum creatinine is between 1.0 and 1.5 x UNL, the creatinine clearance according to the Cockroft-Gault formula should be ≥ 60 ml/min 6) Hypertension with an arterial blood pressure > 150/90 mmHg 7) Severe or uncontrolled cardiovascular disease (congestive heart failure NYHA III or IV, unstable angina pectoris, history of myocardial infarction within the last 12 months, significant arrhythmias) 8) Known proteinuria > 1 g/day (to be tested if proteinuria more than 1+ in the urinary dipstick analysis) 9) Peripheral neuropathy > CTC grade I 10) Concurrent systemic immune therapy, chemotherapy, hormone therapy, or patients receiving immune suppressive treatment (i.e. for transplantation, severe rheumatologic disease) 11) Participation in clinical trials with investigational agents within 30 days before start of the treatment in study 12) Active treatment of a) peptic ulcers or bleeding erosive esophagitis / gastritis within 3 months before study b) pulmonary embolism, severe or unstable angina pectoris or myocardial infarction, stroke or transient ischemic attack within 12 months before study c) deep vein thrombosis within 4 weeks before study

	13) Inflammatory bowel disease 14) History of other malignancies, from which the patient is not 5 years disease free, with the exception of colorectal cancer, or adequately treated basal cell or squamous cell carcinoma of skin or in-situ cervical cancer within 5 years before study 15) History of brain metastases 16) History of severe psychiatric illness 17) Active drug- or alcohol abuse 18) Known hepatitis B or C or HIV infection 19) Breast- feeding or pregnant women 20) Lack of effective contraception (for male and female patients) 21) Known intolerance to one of the following drugs: cetuximab, bevacizumab, oxaliplatin, irinotecan, 5-FU, folinic acid
Sample size	138 randomized *ras/b-raf* wild type patients, 118 randomized *ras* mutant) For sample size calculation, see chapter 5.3
Recruitment	Jan 2013 – March 2017

Procedures	**Screening**[a]	**Every neoadjuvant cycle**		**Perioperative evaluation**	**Every adjuvant cycle**	**End of Study Visit**	**Follow-Up Visit**[j]
		every cycle d 1 and 8	after every four preoperative cycles		before each treatment and weekly		
Informed consent	X Prior to any study-specific procedure.						
Procedures	To be assessed and recorded in source documents and entered in CRF.						
Toxicities/AE assessments[c]	Reporting throughout every subsequent cycle to 30 days after last administration (End of Study Visit)						
Concomittant medication[p]	Reporting throughout every subsequent cycle to 30 days after last administration (End of Study Visit)						
Demographic data	X						
Tumour history[b]	X						
Concomitant diseases	X						
WHO Performance status	X		X			X	
Physical examination	X		X			X	
Height	X						
Weight, vital signs (blood pressure, heart rate, temperature)	X	d 1			d 1	X	
Treatment administration		d1 and 8°			d1 and 8°		
Evaluation of general operability acc. to local standards	X						
Blood count[d]	X	d 1 and 8			X	X	
Laboratory 1[e]	X	d1			X	X	
Laboratory 2[f]	X						
CEA	X		X			X	X
Blood for TR (2.4ml EDTA)	X						
Plasma for TR (2x 8ml, tubes provided)	X		X				
ras-/raf- mutational analysis[q] **Block shipment**	X						
Tumour assessment [MRI or CT][g]	X		X				
Optional: 18-FDG PET[h]	X						
Imaging[i]							X
EKG	X						
Randomization	X after *ras*-analysis						
Dipstick urine analysis[j]		d1			d1		
Evaluation for resectability			X				
Perioperative Evaluation[k]				X			

a) Screening	All investigations should be performed within 3 weeks before randomization, except CT scan (4 weeks). To ensure comparability, the baseline scans and subsequent scans to assess response must be performed using identical technique.
b) Tumour history	including: date of diagnosis, histology, tumour site (within the colon; rectum) and clinical and TNM stage, previous treatment(s), previous surgery, documentation of the reason of non-resectability (technical resectability and number of metastases)
c) Toxicities/AEs	Toxicities will be recorded using NCI CTCAE Version 4.0.
d) Blood count	including hemoglobin, and leukocyte, platelet, neutrophil count
e) Standard laboratory 1	Before chemotherapy: biochemistry: sodium, potassium, magnesium, creatinine, alkaline phosphatase, total bilirubine, LDH, SGOT, SGPT; At screening and then only for patients on bevacizumab: dipstick urine analysis, 24 hour urine analysis if dipstick >1+)
f) Standard laboratory 2	Albumine Female patients (within ≤ 7 days before treatment start: gravidity test (not necessary if > 1 year postmenopausal or with conditions that exclude gravidity, i.e. hysterectomy)
g) Tumour assessment	Screening: Abdominopelvic and thoracic, contrast-enhanced helical CT scan including three-phasic contrast-enhanced CT scan of the liver (to be performed within 4 weeks before treatment start). The abdominopelvic CT scan can be substituted by MRI; in this case, all follow-up examinations must be performed by MRI (the same imaging method has to be performed at baseline and all further tumour measurements). During treatment: Abdominal helical CT scan (or MRI, if initial imaging with MRI) and chest imaging (CT or conventional x- ray) The CT (or MRI) should be sent - DICOM formatted, on CD or DVD – to the coordinating study office.
h) 18-FDG PET	An optional 18-FDG PET- examination will be performed at discretion of the local investigator. PET- examination is *optional* and performed at clinical decision of the local investigator. Participation at additional studies investigating the impact of PET or other imaging methods in staging or response evaluation is not excluded.
i) Imaging	Imaging (CT scan recommended for all patients and obligatory for patients without R0 resection, abdominal ultrasound and chest x-ray obligatory as minimal requirement for R0 resected patients)
j) Follow up	will be performed every 3 months in the first two years and thereafter every 6 months until 5 years after randomization until disease progression: Documentation of progression / survival status Documentation of subsequent procedures or treatment lines
k) Perioperative evaluation	Type of intervention, classified as segment resections, hemihepatectomia, extended hemihepatectomia, central resections, non-anatomical resections, explorative laparatomy and local ablations, or combinations of these methods Resection status as R0/R1/R2 for resections and – for ablations – as complete/incomplete according to imaging Perioperative morbidity according to Clavien et al. (see appendix 20) Days of mechanical ventilation Bilirubine at days 3, 8, (if not normalized at day 8, on days 15, 22, 28) Report of surgery and pathology reports (patient name /date of birth and other identifiers replaced by patient numbers). Pathological specimen: tumour block of resected liver metastases and of non-metastatic liver tissue (to determine tumour regression and potential effects of normal liver tissue, i.e. sinusoidal obstruction, steatosis/steatohepatitis, in a central review process)
l Adjuvant therapy	Number of adjuvant cycles depending on neoadjuvant treatment

No. of neoadjuvant cycles	4	5	6	7	8	9	≥ 10
No. of adjuvant cycles	8	7	6	5	4	3	0

m End of Study Visit	should be planned 30 days after last treatment
o	d 8 in patients with cetuximab, only
p	After screening, for treatment of adverse events, only
q	*ras/b-raf* analysis to be performed locally according to local standard in a certified laboratory. The test will be done centrally if there is no local certified laboratory available.. Block should be shipped following mutational analysis.

4 Background

4.1 Current status of chemotherapy for non-resectable liver metastases

4.1.1 First line treatment in patients with metastatic colorectal cancer

Colorectal liver metastases can be resected with curative intent, but at time of diagnosis of metastatic disease, less than ¼ of patients have resectable disease. For patients with non-resectable liver metastases, chemotherapy provides an effective option to downsize the metastases.

The first large series on resection of previously non-resectable liver metastases was reported after the combination therapies of two cytotoxic drugs (i.e. oxaliplatin / fluorouracil, FOLFOX, or irinotecan / fluorouracil, FOLFIRI) were introduced into the clinical practice.[2-4] An overview on published studies and retrospective reports revealed that the response rates correlate with the frequency of liver resections [5] and generated the hypothesis that tumour response according to radiological criteria is a precondition for the resection of initially non-resectable liver metastases.

More recently, tumour response was showed to be increased if two drug regimens such as FOLFOX or FOLFIRI are combined with a third drug with direct antitumour effect.

Table 1: Randomized studies with chemotherapy and EGFR antibodies (k-ras wildtype patients)

Schedule	n	Response rate	Progression free time	Overall survival
First line therapy				
Cetuximab+FOLFIRI [6]	316	59%***	9.9 mo.**	23.5 mo.**
FOLFIRI	350	40%	8.4 mo.	20.0 mo.
HR (95% CI)			0.70 (0.56–0.87)	0.80 (0.67-0.95)
Cetuximab+FOLFOX [7]	82	57%**	8.3 mo.**	22.8 mo.
FOLFOX	97	34%	7.2 mo.	18.5 mo.
HR (95% CI)			0.57 (0.38–0.86)	0.86 (0.60–1.22)
Cetuximab+oxaliplatin based [8]	362	59%*	8.6 mo	17.0 mo.
Oxaliplatin based chemotherapy	367	50%	8.6 mo	17.9 mo.
HR (95% CI)			0.96 (0.84–1.09)	1.04.(0.90–1.20)
FOLFOX+panitumumab[9]	325	55%	9.6 mo*	23.9 mo.
FOLFOX	331	48%	8.0 mo	19.7 mo.
HR (95% CI)			0.80 (0.66–0.97)	0.83 (0.67–1.02)
Pretreated patients				
Cetuximab+supportive care[10]	117	12.8%***	3.7 mo***	9.5 mo***
Supportive care	113	0%	1.9 mo	4.8 mo
HR (95% CI)			0.40 (0.30–0.54)	0.55 (0.41–0.74)
Panitumumab+ supportive care [11]	124	17%***	2.8 Mo.***	8.1 mo
Supportive care	119	0%	1.7 mo.	7.6 mo
HR (95% CI)			0.45 (0.34–0.59)	0.99 (0.75-1.29)†

†Cross-over allowed for patients with tumour progression; * $p<0.05$; ** $p<0.01$; *** $p<0.001$

4.1.2 Combination with antibodies

Cetuximab is an antibody against the epidermal growth factor rector (EGFR) and was initially approved for treatment of patients with tumour progression during or immediately after irinotecan-based chemotherapy. [12] Initially phase II studies have shown high response rates when cetuximab was combined with irinotecan or oxaliplatin based therapy. [13-16] Later analyses have shown that the absence of mutations in the EGFR downstream effector molecule k-ras is a precondition for the efficacy of cetuximab and other anti-EGFR antibodies. [10, 11, 17] In patients without k-ras mutations, cetuximab has consistently been shown to increase the response rates. [6-8]

In contrast to EGFR antibodies, the incremental effect of bevacizumab regarding the response rates was less pronounced or even absent (Table 2).

Table 2 Selected randomized studies with bevacizumab for treatment of metastatic colorectal cancer

Schedule	n	Response rate	Progression free time	Overall survival
First line therapy				
Bevacizumab/bolus-5-FU/FA /irinotecan [18]	402	44.8 %**	10.6 mo. ***	20.3 mo.***
Bolus-5-FU/ FA /irinotecan (IFL)	411	34.8%	6.2 mo	15.6 mo.
HR (95% CI)			0.54	0.66
Bevacizumab/oxaliplatin/fluoropyrimidine	699	47%	9.4 mo**	21.3 mo
Oxaliplatin/fluoropyrimidine	701	49%	8.0 mo	19.9 mo
HR (95% CI)			0.83 (0.72–0.95)	0.89 (0.76–1.03)
Bevacizumab+5-FU/FA	108	26%	9.2 mo***	16.6 mo
5-FU/FA	116	15%	5.5 mo	12.9 mo
HR (95% CI)			0.50 (0.34–0.73)	0.79 (0.56–1.10)
Pre-treated patients				
Bevacizumab (10 mg/kg)+FOLFOX	286	22.7%***	7.3 mo***	12.9 mo*
FOLFOX	291	8.6%	4.7	10.8
Bevacizumab (10 mg/kg)	243	3.3%	2.7	10.2
			HR 0.61	HR 0.75

* $p<0.05$; ** $p<0.01$; *** $p<0.001$

4.1.3 Combination of three cytotoxic drugs

Compared to two drug cytotoxic regimens such as FOLFOX or FOLFIRI, the response rates and further efficacy parameters can be increased by additional treatment with oxaliplatin (FOLFOXIRI) compared to FOLFIRI alone in the Italian trial using higher doses of oxaliplatin and irinotecan [19] than the Greek trial. [20] In the Italian trial, the higher response rates translated to significantly more patients resected with FOLFOXIRI (15% vs. 6%, Table 3).[19]

Table 3: Trials with combination of three cytotoxic drug

Schedule	n	Response rate	Progression free time	Overall survival
First line randomized trials				
FOLFOXIRI [19]	122	60 %***	9.8 mo. ***	22.6 mo.*
(85 mg/m² oxaliplatin, 165 mg/m² irinotecan)				
FOLFIRI	122	34 %	6.9 mo.	16.7 mo.
HR (95% CI)			0.63	0.70
			(0.47-0.81)	(0.50-0.96)
FOLFOXIRI[20]	138	43%	8.4 mo	21.5 mo
(65 mg/m² oxaliplatin, 150 mg/m² irinotecan)				
FOLFIRI	147	34%	6.9 mo	19.5 mo

4.2 Data from CELIM trial [21, 22]

In the CELIM trial, patients with unresectable colorectal liver metastases and without extra-hepatic metastases were enrolled. These criteria were chosen as the opposite definition from the EORTC 40983 trial investigating perioperative treatment in patients with resectable colorectal liver metastases. Expected resectability after response to chemotherapy was not considered an inclusion criterion.

Patients were randomized to receive FOLFOX/cetuximab or FOLFIRI/cetuximab, and re-evaluated for resectability after four months. Resectable patients were offered resection. Non-resectable patients received further systemic treatment and were reevaluated every 2 months. Between December 2004 and March 2008, 114 patients were enrolled from 17 centres in Germany and Austria; three patients receiving FOLFOX6 alone (early closed arm) were excluded from the analysis. Of 111 patients randomised to receive cetuximab plus FOLFOX6 or cetuximab plus FOLFIRI, two did not receive treatment. Therefore, 109 patients were treated and evaluable for toxicity (safety population). Fifty three patients in each treatment arm were evaluable for tumour response.

Table 4: Response rates from CELIM trial

	All patients	**Treatment groups**		**Tumour *k-ras* mutation status**	
		FOLFOX6+ cetuximab	**FOLFIRI+ cetuximab**	***k-ras* wt**	***k-ras* mt**
	(N=106)	(N=53)	(N=53)	(N=67)	(N=27)
Response	66 (62%)	36 (68%)	30 (57%)	47 (70%)	11 (41%)
95% CI	52–72%	54–80%	42–70%	58–81%	22–61%
Odds ratio		1.62		3.42	
95% CI		0.74-3·59		1.35-8.66	
p-value		0.23		0.0080	
SD	31 (29%)	15 (28%)	16 (30%)	14 (21%)	13 (48%)
PD	9 (8%)	2 (4%)	7 (13%)	6 (9%)	3 (11%)

Objective tumour response was observed in 66/106 patients (62% [95% CI: 52-72%]), with a statistically non-significant difference of 11% [95% CI: -8 – 30%, p=0·23] between FOLFOX/cetuximab (68% [95% CI: 54-80%]) and FOLFIRI/cetuximab (57% [95% CI: 42-70%]). Twenty-nine patients had stable disease (29%), 9 patients progressive disease (9%, Table 4). In a retrospective analysis, tumour response was higher in patients with *k-ras* wild-type tumours (70% [95% CI: 58-81%]) compared with patients with *k-ras* tumour mutations (41% [95% CI: 22-61%]). This difference of 29% [95% CI: 7–52%] was statistically significant (p=0.0080). In the *k-ras* wild type population, the response rates were similar by numbers for cetuximab/FOLFOX6 and cetuximab/FOLFIRI (Table 5, unpublished data).

Table 5: CELIM: Response rates in *k-ras* wild type or mutant pts according to treatment arm

Confirmed response rates	**FOLFOX/ cetuximab**	**FOLFIRI/ cetuximab**
k-ras wild type	24/33 (73%)	23/34 (68%)
k-ras mutant	7/14 (50%)	4/13 (31%)

Furthermore, tumour response occurred in 46/64 patients whose tumours were wild-type for both the *k-ras* and *b-raf* genes (72% [95% CI: 59-82%]) compared with 12/30 patients whose tumours harboured a mutation in either gene (40% [95% CI: 23-59%], p=0.0030).

Tumour response was similar in EGFR-detectable and EGFR-undetectable tumours.

Table 6: Response rates of CELIM trial according to tumour characteristics

	Tumour *ras/raf* mutation status		**Tumour EGFR status**	
	k-ras and b-raf wt	***k-ras or b-raf* mt**	**EGFR detectable**	**EGFR undetectable**
	(N=64)	(N=30)	(N=77)	(N=29)
CR plus PR	46 (72%)	12 (40%)	46 (60%)	20 (69%)
95% CI	59–82%	23–59%	48–71%	49–85%
Odds ratio	3.83		0.67	
95% CI	1.54-9.54		0.27-1.66	
p-value	0.0030		0.38	
SD	12 (19%)	15 (50%)	25 (32%)	6 (21%)
PD	6 (9%)	3 (10%)	6 (8%)	3 (10%)

R0 resections were achieved in 36/106 patients (34% [95% CI: 25-44%]), 20/53 (38%) with FOLFOX/cetuximab and 16/53 (30%) FOLFIRI/cetuximab (Table 7). Any R0/R1 resection and/or RFA were performed in 49/106 patients (46%). R0-resections were performed in 19/48 patients (40% [95% CI: 26-55%]) enrolled with the inclusion criterion of ≥5 liver metastases, and in 16/57 patients (28% [95% CI: 17-42%]) with the criterion of technically unresectable metastases. The median time to resection and/or exploration was 5.1 months (Q1-Q3 4.4-5.9, range 2.5-14.7 months, Figure 2), and the median number of treatment cycles before intervention was 8 (range 3 – 41). With three exceptions, all interventions were performed within eight months of randomization.

Table 7: Resection rates in the CELIM trial

	FOLFOX6 plus cetuximab (N=53)	**FOLFIRI plus cetuximab (N=53)**	**All patients (N=106)**
R0 resections	20 (38%)	16 (30%)	36 (34%)
95% CI	25-52%	18-44%	25-44%
R1 resection or resection plus RFA	1 (2%)	4 (8%)	5 (5%)
RFA	5 (9%)	3 (6%)	8 (8%)
R0/R1 resection/ RFA	26 (49%)	23 (43%)	49 (46%)
95%CI	35-63%	30-58%	36-56%
R2 resection	1 (2%)	3 (6%)	4 (4%)
Exploratory laparotomy	3 (6%)	1 (2%)	4 (4%)

Surgeons from the participating centres reviewed the CT/MRI images. For that purpose, they were blinded to the time point of imaging (before / after chemotherapy) and to the clinical information of the patients . Following review, 41/68 patients (60%) were judged as resectable after chemotherapy compared with 22/68 patients (32%)

at baseline. This difference was statistically significant ($p<0.001$), leading to additional 19/68 patients (28%) considered resectable after treatment. In a regression analysis, the outcome of chemotherapy (confirmed response) had a statistically significant influence on change of resectability ($p<0.05$); however, the number of metastases, prior liver resection, the treatment arm, or technical unresectability of metastases did not significantly influence the changes in resectability status.

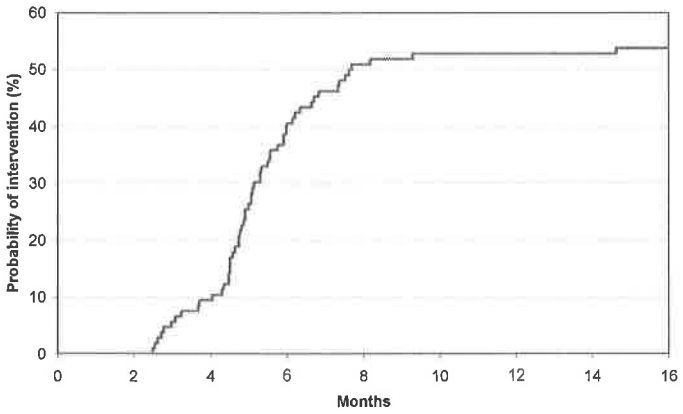


Figure 1: Time from the randomization to resection in the CELIM trial

4.3 Data for patients with liver limited disease in the registration trials

A recent subgroup analysis of the Data from the CRYSTAL (FOLFIRI ± cetuximab) and OPUS (FOLFOX ± cetuximab) trial have confirmed the increased efficacy of the combination especially with regard to the response rate and the resection rate.[23] These trials reproduced the high response rates in patients with liver metastases, only (Table 8).

Table 8: Efficacy of cetuximab in patients with liver limited disease in first line trials for patients with metastatic colorectal cancer[23]

	n	Response rate	Rate of R0-Resections
All patients			
„CRYSTAL"-trial			
FOLFIRI+Cetuximab	316	57%	5.1
FOLFIRI	350	40%	2.0
		p=0.0025	p=0.03
„OPUS"- trial			
FOLFOX+Cetuximab	82	57%	7.3
FOLFOX	97	34%	3.1
		p=0.0027	
Patients with liver limited disease			
„CRYSTAL"-trial			
FOLFIRI+Cetuximab	69	70%	13
FOLFIRI	72	44%	5.6
„OPUS"- trial			
FOLFOX+Cetuximab	25	76%	16
FOLFOX	23	39%	4.3

4.4 Strategies to increase treatment efficacy

Based on these results, FOLFIRI/cetuximab can be regarded as a standard regimen for patients with k-ras and b-raf wild type tumours, and FOLFOXIRI as probably one of the most active regimens in all patients, if the response rate (and resection) is the treatment aim. Both regimens have shown significant higher response rates and resection rates than FOLFIRI alone.

To increase resection rates, adding oxaliplatin to FOLFIRI / cetuximab would be a rational approach in patients without mutations in the k-ras / b-raf pathway, whilst incorporating bevacizumab into a FOLFOXIRI regimen might increase efficacy in all other patients. Both strategies still need to be explored in a randomized setting and will be tested in the relevant subgroups in this study.

4.5 Studies with FOLFOXIRI/cetuximab

4.5.1 Phase I COFI trial[24]

The recent phase I COFI trial was performed in two German centers (University Hospital Carl Gustav Carus, Dresden, and West German Center for Tumour Diseases, Essen) to establish a dose for cetuximab / FOLFOXIRI (cetuximab, oxaliplatin, fluorouracil and irinotecan) in patients with metastatic colorectal cancer and enrolled patients with metastatic colorectal cancer (WHO PS 0-1) from January 2007 to June 2008.

Treatment. Patients received biweekly i.v. doses of cetuximab (500 mg/m², 2 h), followed irinotecan (95, 125, and 165 mg/m² in the dose levels [DL] 1, 2, and 3), followed by oxaliplatin (85 mg/m², 2h) which was given parallel to folinic acid (400 mg/m², 2 h) and followed by 5-FU (3200 mg/m², 46h) in an outpatient setting for a maximum of twelve cycles. DLT were defined as: neutropenia grade 4 or febrile neutropenia, thrombocytopenia grade 3, diarrhea grade 3 lasting > 24h with adequate treatment (loperamide), diarrhea grade 3 in combination with neutropenia grade ≥ 3, nausea/ vomiting grade 3 despite anti-emetic treatment, acne like rash grade 4 and other non–hematological grade 3 toxicity (except alopecia). Hematopoietic growth factors were allowed to treat neutropenia $<1x10^9$/l.

Toxicity and dose escalation. Twenty-one patients were enrolled into the study between January 2007 and June 2008, six evaluable patients per each cohort. Median age was 59 (33-72) years. 17 patients had a PS ECOG 0 and four patients presented with a PS ECOG 1, 16 patients (76%) were male, and ten had rectal cancer. One dose limiting toxicity occurred each of the first two cohorts (irinotecan 95 mg/m² and 125 mg/m²). At the dose level 1, one patient had neutropenia grade 4, at second dose level one patient experienced diarrhea grade 3. In the third cohort (irinotecan 165 mg/m²) two DLT were observed in first three patients (diarrhea grade 3, neutropenia grade 4 in two patients). Therefore, the recommended dose for the phase II trial is 125 mg/m² irinotecan.
Most common grade ≥ 3 toxicities were neutropenia (42%), diarrhea (26%) and acne (16%). No therapy associated death occurred.

Efficacy. One patient with port dysfunction presenting during the first dose was excluded from analysis for efficacy because he was treated with another treatment regimen. In the intention to treat analysis of all cohorts fifteen patients (75 %) had a partial response (PR) or complete response (CR), 5 patients (24%) stable disease. A response was achieved after a median of 2.9 (95%-CI 1.4 to 6.3) months.
Twenty patients were evaluable for KRAS-mutation status; 14 patients (70%) were wild-type KRAS, 6 patients (30%) had KRAS mutation in their tumours. In patients with k-ras wt tumours, one patient had CR, nine PR (overall response rate 71%) and four patients had stable disease. The progression free survival (post study treatment without progression was allowed) and overall survival are shown in Figure 2.

Based on the results of this study, and in the context with irinotecan dose adjustment (see chapter 4.7), a dose of 125 mg/m² irinotecan will be used for patients without increased risk for toxicity.

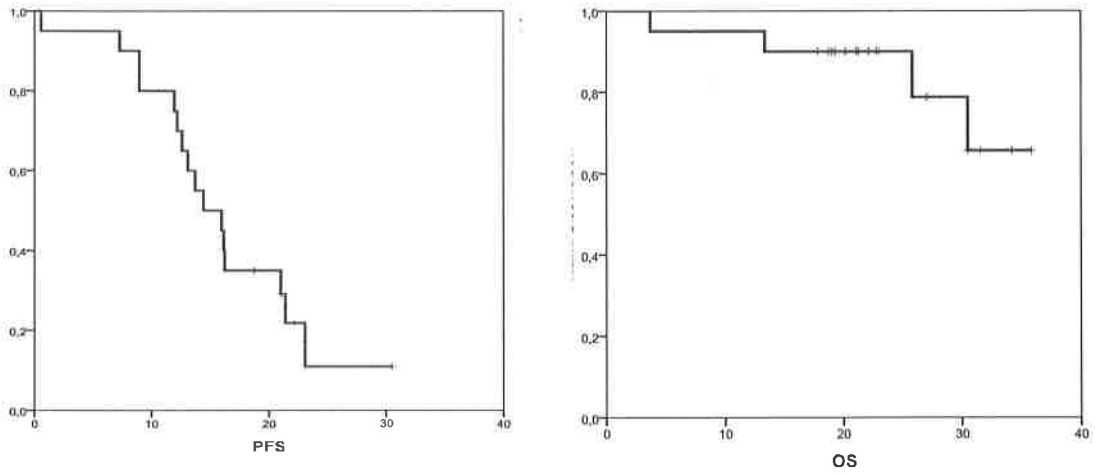


Figure 2: Progression free and overall survival of the COFI study

4.5.2 Phase II POCHER trial[25]

For the POCHER trial, patients with non-resectable or high risk liver metastases received a standard weekly cetuximab regimen plus a chronomodulated, biweekly chemotherapy (irinotecan 130 mg/m², d1; oxaliplatin 20 mg/m²/d d2-5, 150 mg/m² FA and 600 mg/m² 5-FU d2-5). After an interim analysis with 17 patients, the doses were reduced (irinotecan 110 mg/m², 5-FU 550 mg/m², oxaliplatin 15 mg/m² due to high toxicity of the initial schedule (i.e. grade 3/4 diarrhea in 93% of first 17 pts).

43 patients with non-resectable liver metastases were enrolled. Partial or complete tumour response was observed in 34 /43 patients (79%), R0-resection was performed in 26/43 pts (60%). The progression and overall survival is shown in Figure 3.

After the dose reduction, toxicities were observed with the following frequencies: diarrhea grade 3/4 – 36%, abdominal pain 3/4 – 7%, fatigue grade 3/4 – 12%, nausea grade 3/4 – 10%, neutropenia grade 3/4 – 6%, rash grade 3/4 – 15%.

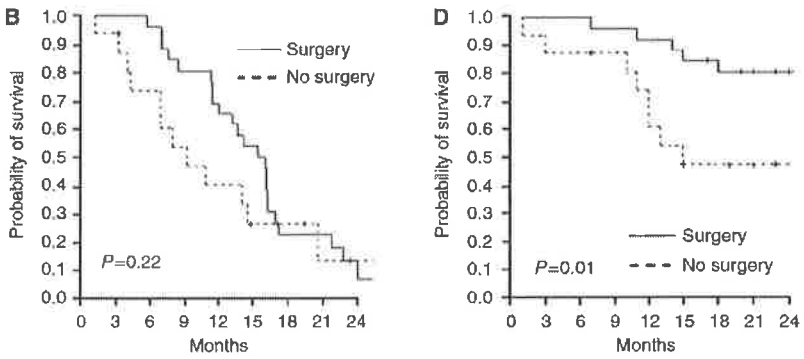


Figure 3: Progression free and overall survival in the POCHER trial[25]

4.5.3 The French trial of FOLFIRINOX and cetuximab [26]

In this trial, cetuximab was used in standard weekly doses plus standard doses of oxaliplatin (85mg/m²), irinotecan (180 mg/m²), folinic acid (L-FA 200 mg/m²) and 5-FU (400 mg/m² bolus, 2400 mg/m² [46h]) in a biweekly schedule as first line therapy in patients with metastatic colorectal cancer and PS 0-1 (not selected for liver metastases). Toxicity was higher than in historical controls with 52% diarrhea gr. 3/4, 38% neutropenia gr. 3/4, 10% vomiting gr. 3/4, 5% febrile neutropenia, 19% neuropathy gr. 3/4.

Partial or complete response was observed in 34/42 (80%) patients, in 13/16 (75%) with k-ras mutations and 20/24 (83%) patients with k-ras wild type. Progression free survival is shown in Figure 4.

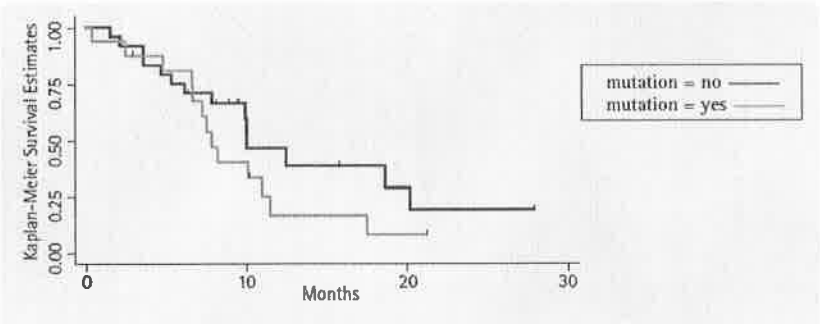


Figure 4: Progression free survival of the French trial

4.6 Studies with FOLFOXIRI and bevacizumab

In patients with *k-ras* mutation, the use of EGFR- antibody in combination with chemotherapy does not increase the efficacy. As outlined above, FOLFOXIRI in the dosage of the Italian GONO group[19] can be regarded as one standard in this situation. It is currently the only regimen with a significantly improved resection rate compared to a chemotherapy doublet (FOLFIRI, Table 3; page 16) for *k-ras* mutant patients.

Adding bevacizumab to FOLFOX had not improved response rates, whilst it had a small, but significant effect on response rate when it was combined with less effective chemotherapy regimen as 5-FU/FA or IFL (Table 2, page 15).

Interestingly, a recent Italian single arm phase II study investigating the combination of FOLFOXIRI and bevacizumab has shown interesting results with a response rate of 77% without differences in k-ras mutant and k-ras wild-type patients. The rate of secondary resection of metastases was 26% in all patients and 40% in the 30 patients with liver limited disease. Main grade ≥3 toxicity in this trial with 57 patients was neutropenia (49%), diarrhea (14%), stomatitis (4%), deep vein thrombosis (7%) and hypertension (11%).[27]

However, due to the character of a single arm trial, the influence of patient selection on study outcome remained unclear. The more strict patient inclusion criteria in trials with anti-angiogenic treatments (especially regarding cardiovascular comorbidity) may contribute to a selection bias. Therefore, a randomized exploration of FOLFOXIRI/bevacizumab with FOLFOXIRI as control arm is warranted.

4.7 Irinotecan dosing and UGT1A1

– deleted for amendment 2 , see chapter 4.9 –

4.8 BRAF mutation and efficacy

– modified for amendment 2 , see chapter 4.9 –

The prognosis of patients with the activating BRAF V600E mutation is limited. [28]

In the retrospective analysis of an international consortium that included trials in pretreated patients, the frequency of BRAF mutations was 36/761 (4.7%) in all patients with pretreatment. "Compared with BRAF wild types, BRAF mutants had a significantly lower response rate (8.3% [2/24] vs 38.0% [124/326] for wild types; OR 0.15, 95% CI 0.02–0.51; p=0.0012) and disease-control rate (37.5% [9/24] vs 77.3% [252/326]; OR 0.176, 0.071–0.41; p<0.0001), and shorter PFS (median 8 vs 26 weeks in wild types; HR 3.74, 95% CI 2.44–5.75; p<0.0001) and overall survival (median 26 vs. 54 weeks in wild types, HR 3.03, 1.98–4.63; p<0.0001). One of the two BRAF mutants that responded had a p.D594G mutation; the other had a p.V600E mutation, present in low copy number in the tumour."[29]

In first line treatment, the frequency of BRAF V600E mutations was 70/800 pts with *k-ras* wildtype treated in the OPUS and CRYSTAL trial. In this analysis, the median overall survival was 9.9 and 14.1 months in *b-raf* mutant patients (without and with cetuximab) compared to 21.1 and 24.8 months in *b-raf/k-ras* wildtype patients. The overall response rates were 13.2% and 21.9% in b-raf mutant patients and confirm the low probability of tumour response with chemotherapy with or without EGFR antibodies.[30]

The reduced prognosis of BRAF V600E mutation was confirmed in most other settings for metastatic colorectal cancer,[31, 32] - except one Italian group, which found a relatively high rate of *b-raf* mutations (10/55 pts, 18%),.[27]

There are no generally accepted data regarding the predictive value of b-raf mutations in first line therapy with anti-EGFR antibodies.

Due to the data of Falcone et al [27]some investigators prefer FOLFOXIRI based regimen whereas other follow the prescription information and do not consider results of b-raf test in decision making regarding treatment.

To reflect the lack established alternative treatment options and the fact that the predictive value of b-raf mutations is currently not regarded as proven, b-raf mutant patients are not further excluded from the trial and the determination of b-raf mutational status as part of pre-treatment diagnostic may be decided by the investigator. All patients with an unknown or wild type b-raf status are randomized according to the ras status. In b-raf mutant / ras wildtype the investigators can choose the wild type or mutant stratum for randomisation patients.

4.9 Amendment 2

4.9.1 Extended ras testing, b-raf testing for scientific purposes, only

Within the PRIME trial comparing FOLFOX +/- panitumumab, a negative effect was demonstrated for adding panitumumab to FOLFOX in patients with k-ras mutations in exon 3 and 4 and in n-ras mutated patients. [33] This effect was similar to the negative effect in k-ras exon 2 mutated patients and led to a change in the approval of panitumumab. Similar data were observed for FOLFIRI+/- cetuximab (CRYSTAL)[34] and FOLFOX +/- cetuximab (OPUS trial),[35] so that the approval status for cetuximab was changed accordingly. In the FIRE 3 trial comparing FOLFIRI/cetuximab with FOLFIRI/bevacizumab, the efficacy of cetuximab was higher in patients with k-ras (exon 2-4)/n-ras wildtype.[36]

The current amendment follows the changed approval status for cetuximab.

Because there are no established other treatment options and because the predictive value of b-raf mutations is currently not regarded as proven, b-raf mutant patients are not further excluded from the trial and determination of b-raf mutational status as part of pre-treatment diagnostic within the decision of the investigator.

All patients with an unknown or wild type b-raf status are randomized according to the ras status. In b-raf mutant / ras wildtype the investigators can choose the wildtype or mutant stratum for randomisation patients.

Independently, patients with *b-raf* mutations should be recommended to participate in trials investigating specific pathway inhibition.

Chapter 4.8(background) is adapted.

4.9.2 Determination of UGT1A1

With higher number of published data of the FOLFOXIRI regimen (all performed without UGT1A1 testing), the pretherapeutic test is not longer regarded as necessary, This use follows the prescription information for irinotecan. Falcone et al reported a second phase III trial comparing FOLFIRI vs. FOLFOXIRI, both arms with bevacizumab without special safety issues. [37] The drugs are meanwhile widely used in patients with pancreatic cancer with slightly higher irinotecan doses.[38] Furthermore, there are parallel trials running with similar combinations (i.e. VOLFI) that have no safety issues in similar doses (NCT01328171).

Chapter 4.7 (background) deleted.

4.9.3 Documentation of grade 1 toxicities

Grade 1 toxicities have – according to the protocol – no influence on dose modifications or delays. Compared to the severity of the disease, they have virtually no influence on the risk-/benefit-ratio of the treatment. Therefore, grade 1 toxicities including changes in laboratory values grade 1 are not recorded in the case report forms. They have to be reported if they have an influence on the further treatment (i.e. cardiac toxicity that is 5-FU related).

4.9.4 Corrections within the laboratory parameters

The schedules of calcium and CEA determination were corrected for consistency within the protocol.

The sampling process for blood and plasma was adapted to the deleted UGT1A1 process and the availability of tubes for shipment at room temperature:

EDTA sampling is part of translational protocol, plasma sampling in Streck tubes and immediate shipment at room temperature.

4.9.5 Timing of the second resection in case of multi-step procedures

It was clarified that the timing of the second resection is determined by the local investigators depending on the surgical conditions and the performance status of the patient after resection. There are two preferred options:

1) resection immediately after the first resection (reduces the total chemotherapy-interruption) or
2) resection after a second series of chemotherapy

4.9.6 Updated subtitle of the protocol

The subtitle of the protocol was updated to reflect the changes in the protocol (i.e. ras instead of k-ras).

5 Objectives of the trial

5.1 General objectives

The aim of this study is to investigate the following schedules for efficacy with regard to response to neoadjuvant treatment of patients with non-resectable liver metastases:

- Cetuximab/FOLFOXIRI and cetuximab/FOLFIRI in patients with *ras* wild type tumours and
- Bevacizumab/FOLFOXIRI and FOLFOXIRI in patients with *ras* mutant tumours.[i]

5.2 End-points

5.2.1 Primary endpoint:

- Rate of patients with partial or complete response according to modified RECIST criteria (definition see chapter 12.2.1, ITT- population)

5.2.2 Secondary endpoint:

- Rate of patients who had a R0 resection of all lesions and are disease free for at least 6 months (definition see chapter 12.2.4, ITT- population)

5.2.3 Other endpoints:

- Resection rate, defined as patients with microscopically complete (R0) resection (ITT- population)
- Rate of liver resection with macroscopically tumour free margins and/or RFA (all patients with R0 or R1 resection and/or complete RFA of all lesion, ITT- population)
- Progression free survival (Kaplan-Meier-estimation, ITT- population)
- Disease free survival after resection (Kaplan-Meier-estimation, resected patients)
- Overall survival (Kaplan-Meier-estimation, ITT- population)
- Toxicity (safety population)
- Pathological response in resected tumour tissue
- Evaluation of molecular predictive markers for response (i.e. other mutations in EGFR signalling pathway, EGFR ligands) and toxicity

[i] For easier readability, „*ras* mutant" tumours is used in the whole protocol instead of „*k-ras* mutant or *n-ras* mutant " tumours.

5.3 Sample size

Study will be performed as "randomized phase II trial". It is planned to randomize138 *ras* wild type patients (69 per arm) and 118 *ras* mutant patients (59 per arm).

Sample size calculation is described in chapter 12.1, page 55.

5.4 Timelines for the trial and analysis

The first patient was recruited in January 2013; the last patient will be recruited in March 2017. The analysis for the primary endpoint (response rate) and for resection rate is planned one year after end of accrual (March 2018). Follow-up for overall survival continues until March 2022.

Besides the analyses for response and resection rates, yearly safety reports, and continuous analysis of recruitment and safety is planned.

6 Patient selection criteria

6.1 Inclusion criteria

Patients can be enrolled, if all of these conditions apply:

1) Non-resectable, histologically confirmed, synchronous or metachronous colorectal liver metastases.
2) Non-resectability will be documented by a local multidisciplinary tumour board with participation of a surgeon experienced in liver surgery. Patients can be enrolled if they
   a) are technically non-resectable (locally determined by a multidisciplinary team discussion based on remaining functional liver tissue after resection, i.e.
      i) involvement of both portal veins, all hepatic veins, portal vein of the liver lobe and hepatic veins draining the segments of the other liver lobe, or
      ii) other reasons for less than 30% remaining functional liver tissue after resection)

   and / or

   b) have ≥ 5 liver metastases

   and / or

   c) are regarded as non-resectable for other reasons (description necessary)
3) Patients with simultaneous liver metastases are eligible,
   a) if the primary tumour was resected at least 1 month prior to chemotherapy

   or

   b) all of the following conditions apply:
      i) the primary tumour is clearly resectable,
      ii) no radiation therapy is planned,
      iii) liver resection is planned before resection of the primary or at the same operation as the resection of the primary,
      iv) no two-stage liver resection is planned, and
      v) all efforts were made to exclude additional distant metastases.
4) WHO PS ≤ 1
5) Written informed consent
6) Adequate bone marrow function, liver function (neutrophils > 1.5 x 10^9/l; platelets > 100 x 10^9/l; haemoglobin > 5.0 mmol/l [8.0 g/dl]; bilirubin ≤ ULN or ≤ 1.5 x ULN and not increasing more than 25 % within the last 4 weeks; SGOT and SGPT < 5 x UNL)
7) Age ≥ 18 years

6.2 Exclusion criteria

1) Any evidence of extrahepatic metastases, distant lymph node metastases and primary tumour recurrence
2) (deleted)
3) Prior systemic antitumour therapy with anti- EGFR-, antiangiogenic drugs or with chemotherapy (except adjuvant chemotherapy for stage II / III with an interval of ≥ 6 months or in combination with radiation as radio sensitizer)

4) Radiotherapy or major abdominal or thoracic surgery (excluding diagnostic interventions or venous port implantation) ≤ 4 weeks before study entry
5) Renal insufficiency with serum creatinine ≥ 1.5 x UNL. If serum creatinine is between 1.0 and 1.5 x UNL, the creatinine clearance according to the Cockroft-Gault formula should be ≥ 60 ml/min
6) Hypertension with an arterial blood pressure > 150/90 mmHg
7) Severe or uncontrolled cardiovascular disease (congestive heart failure NYHA III or IV, unstable angina pectoris, history of myocardial infarction within the last 12 months, significant arrhythmias
8) Known proteinuria > 1 g/day (to be tested if proteinuria more than 1+ in the urinary dipstick analysis)
9) Peripheral neuropathy > CTC grade I
10) Concurrent systemic immune therapy, chemotherapy, hormone therapy, or patients receiving immune suppressive treatment (i.e. for transplantation, severe rheumatologic disease)
11) Participation in clinical trials with investigational agents within 30 days before start of the treatment in study
12) Active treatment of
    a) peptic ulcers or bleeding erosive esophagitis / gastritis within 3 months before study
    b) stroke, transient ischemic attack or symptomatic pulmonary embolism within 6 months before study
    c) deep vein thrombosis within 4 weeks before study
13) Inflammatory bowel disease
14) History of other malignancies, from which the patient is not 5 years disease free, with the exception of colorectal cancer, or adequately treated basal cell or squamous cell carcinoma of skin or in-situ cervical cancer within 5 years before study
15) History of brain metastases
16) History of severe psychiatric illness
17) Active drug- or alcohol abuse
18) Known hepatitis B or C or HIV infection
19) Breast- feeding or pregnant women
20) Lack of effective contraception (for male and female patients, during study until 6 months after end of treatment)
21) Known intolerance to one of the following drugs: cetuximab, bevacizumab, oxaliplatin, irinotecan, 5-FU, folinic acid

7 Trial design

7.1 Type of study

Open, multicentre, randomized phase II trial

7.2 Design and general treatment strategy

7.2.1 General overview

Patients with liver metastases from colorectal and without known extra-hepatic tumour disease will be screened for this study. This includes a *k-ras/n-ras* according to local standard and the prescription information. The test should be performed in a certified laboratory. The test will be performed centrally, if a local certified laboratory is not available. *B-raf* testing may be performed according to local standard. Patients with known *b-raf* mutations can be randomized within the ras mutant stratum according to decision of the investigator.
Patients receive chemotherapy according to the allocation (see chapter 7.2.2) and are re-evaluated for resectability (chapter 9.8) every 8 weeks for a maximum of 6 months. Resectable patients will be resected and receive an adjuvant treatment to complete 12 cycles (details in chapter 9.10). In certain circumstances, a second resection is allowed within the study (details in chapter 9.10.2).

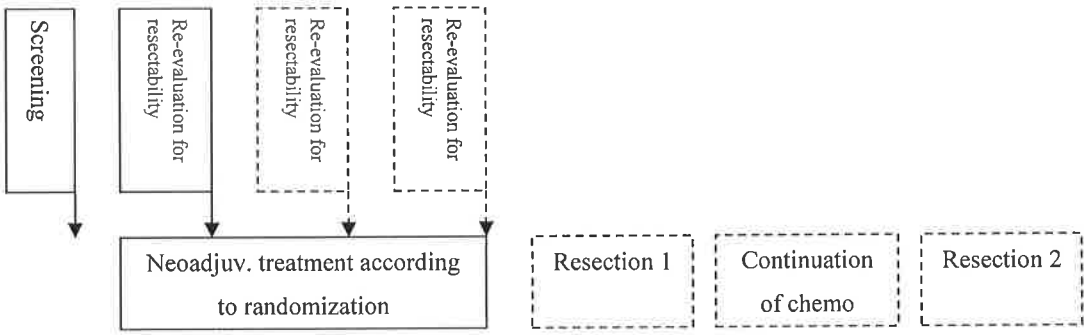


Figure 5: General overview (not all treatment steps may apply to each patient)
The timing of the second resection is determined by the local team. The second resection should be performed immediately (within 6 weeks) after the first resection or following continuation of the chemotherapy depending on the surgical conditions and the performance status of the patients after

7.2.2 Randomization

Patients will be randomized using a web-based computer system that allows randomization if the key basic characteristics are entered.
Patients with ***ras***[i] **wild-type** tumours will be randomized to receive:

- Cetuximab/FOLFIRI or
- Cetuximab/FOLFOXIRI

Patients with ***ras* mutations**[i] will be randomized to receive:

[i] *k-ras exon 2-4 and n-ras exon 2-4*

- FOLFOXIRI or
- FOLFOXIRI/bevacizumab

Stratification will be performed according to:

- Number of metastases (< 5 vs. ≥ 5 metastases)
- Primary tumour *in situ*
- Centre

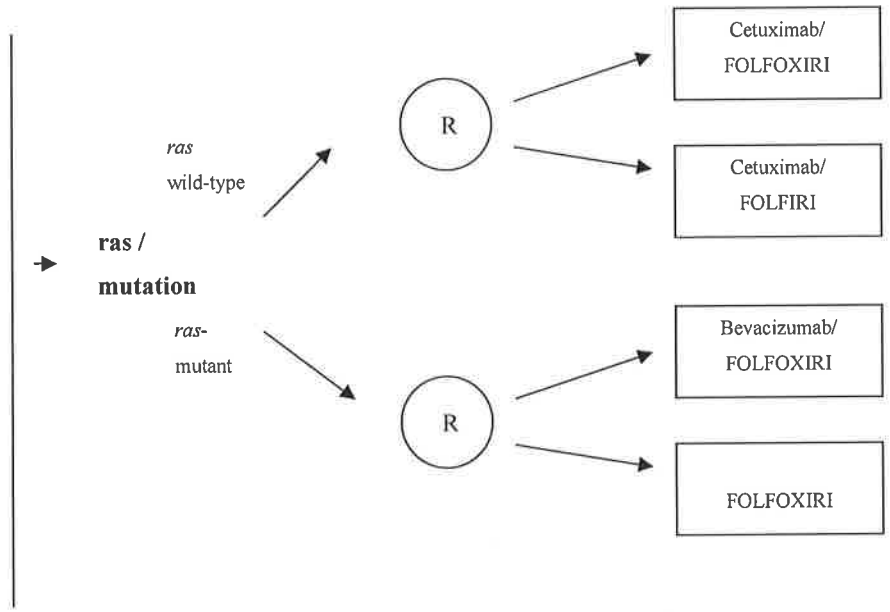
7.2.3 Evaluation for response and resections

Patients are evaluated for response by the same imaging technique as at baseline every 8 weeks. The findings will be discussed for resectability within two weeks after tumour assessment in a local multidisciplinary team. Technically resectable patients should be offered liver resection.

Treatment will be continued with neoadjuvant intent for a total maximum of six months (12 cycles).

Figure 6: Treatment allocation.

Patients with ras wild-type are randomized to Cetuximab/FOLFOXIRI or Cetuximab/FOLFIRI. Patients *with ras* mutations receive FOLFOXIRI ± bevacizumab.



Patients with known b-raf mutations may be randomized within the ras mutant stratum

[1] Patients with known b-raf mutations may be randomized in the ras mutant stratum according to investigators decision

7.2.4 Adjuvant treatment

After liver resection, an adjuvant treatment is recommended with the same schedule as preoperatively, for a maximum pre- and postoperative treatment of 12 cycles. If less than three postoperative cycles remain, no postoperative treatment will be started (see chapter 9.10).

7.2.5 Follow up

After resection, patients will be followed up for 5 years after randomization. This includes

- imaging and clinical investigation every three months for the first 2 years, then every six months (patients without tumour progression / recurrence)
- survival status and surgical (procedure, R-status) /medical treatment (drugs and periods) every three months for the first 2 years and then every six months (all patients)

8 Study drugs

All drugs are used in standard doses (or dose reduced in case of risk of toxicity) and are approved for the first line therapy of metastatic colorectal cancer. All drugs are used within the current approval, will be prescribed and are – except the antibodies – available as generic drugs from several manufacturers.

8.1 Drug names, formulation, packaging

8.1.1 Cetuximab (Erbitux®, Merck KGaA)

Cetuximab is administered before chemotherapy.

Cetuximab is a chimeric antibody to the EGF- receptor.

Approval:	metastatic colorectal cancer (k-ras and n-ras wild type, metastatic, EGFR- expressing) in combination with chemotherapy, and other indications
Preparation:	Cetuximab can be diluted in 0.9% natrium chloride or be used without dilution. It should be used immediately after preparation. If not used immediately, it should be stored at 2…8°C (recommended: max 24 hours, stable 48 h).
Typical toxicity:	Acne- like rash, paronychia and other skin toxicity, infusional allergic reactions, hypomagnesaemia; furthermore: dehydration (due to diarrhea and mucositis), anorexia, headache, aseptic meningitis, conjunctivitis, blepharitis, keratitis, deep vein thrombosis, pulmonary embolism, diarrhea, elevated ASAT, ALAT, AP, superinfection of skin lesions, mucositis with epistaxis, fatigue
Interactions:	No pharmacokinetic interaction with irinotecan. In combination with platinum based chemotherapy increased frequency for severe leukopenia and neutropenia. In combination with fluoropyrimidines increased frequency for cardiovascular ischemic events and hand-foot-syndrome, in combination with platin based chemotherapy increased frequency of leucopenia and neutropenia, in combination with radiation increased frequency of radiation dermatitis and mucositis
Storage:	2-8°C

For detailed information, see introduction and SmPC.

8.1.2 Bevacizumab (Avastin®, Roche)

Bevacizumab is administered before chemotherapy.

Bevacizumab is a humanized antibody to VEGF.

Approval:	metastatic colorectal cancer in combination with fluoropyrimidine-based, and other indications.
Preparation:	Bevacizumab will be diluted with 0.9% natrium chloride to a concentration of 1.4 … 16.5 mg/ml and immediately be used. If stored, the recommended maximum storage time at room temperature is 24 hours at 2…8 °C.
Typical toxicity:	Arterial hypertension, gastrointestinal perforations, fistulas, impaired wound healing, reversible posterior leukencephalopathy syndrome, arterial and venous thrombembolic events, bleeding, congestive heart failure, proteinuria, haemoptysis (esp. patients with

non-small lung cancer), neutropenia/infection, allergic reactions and infusion reactions, eye diseases after intravitreal application; furthermore:
anorexia, headache, eye diseases, hypertension, dyspnoea, epistaxis, rhinitis, constipation, stomatitis, rectal bleeding, dermatitis, dry skin, arthralgia, proteinuria, pyrexia, asthenia, pain, mucositis

Interactions: Microangiopathic haemolytic anaemia in combination with sunitinib. No interactions with irinotecan, oxaliplatin or fluoropyrimidines.

Storage: 2-8°C

For detailed information, see introduction and SmPC.

8.1.3 Irinotecan (i.e. Campto®, Pfizer)

Irinotecan is a semi-synthetic derivative of camptothecin and interacts with the topoisomerase-1.

Approval: first line therapy of metastatic colorectal cancer in combination with 5-FU/FA and other indications.

Preparation: To be diluted in 0.9% natrium chloride or 5% glucose. It should be used immediately after preparation. If not used immediately, it should be stored at 2…8°C (recommended: max 24 hours)

Typical toxicity: Delayed diarrhea, dehydration, acute cholinergic syndrome, nausea, vomiting, neutro-, leukopenia, anaemia, thrombocytopenia, alopecia. Rare side effects are liver toxicity, lung toxicity (interstitial lung disease), allergic reactions, muscle spasms, paresthesia, and larynx oedema), neurotoxicity and cardiotoxicity.

Important interactions:
Suxamethonium, myotonolytic medications. CYP3A inducing drugs (i.e. carbamazepine, phenytoin, St John's wort) may decrease exposure against irinotecan and the metabolites SN38

Storage: controlled room temperature (< 25° C) and protected from light.

For detailed information, see introduction and SmPC.

8.1.4 Oxaliplatin (i.e. Eloxatin®, Sanofi-Synthelabo)

Oxaliplatin is a DACH- platin.

Approval: first line therapy of metastatic colorectal cancer in combination with 5-FU/FA and other indications.

Preparation: To be diluted in 250…500 ml 5% glucose. It should be used immediately after preparation. If not used immediately, it should be stored at 2…8°C (recommended: max 24 hours)

Typical toxicity: Peripheral neuropathy with hypoesthesia and cold- induced neuropathy. Anaemia, neutropenia, febrile neutropenia, thrombocytopenia, nausea/vomiting, mucositis, allergic reactions, furthermore:
liver toxicity (sinusoidal obstruction; elevated liver enzymes, AP, bilirubin, LDH), weight gain and weight loss, elevated creatinine, immunoallergic thrombopenia, haemolytic anaemia, headache, motoric neuritis, meningitis, dysarthria, conjunctivitis, visual

impairment, ototoxicity, dyspnoea, cough, abdominal pain, constipation, gastro-oesophageal reflux, gastrointestinal and rectal bleeding, ileus, intestinal obstruction, colitis, alopecia, skin diseases, arthralgia, anorexia, hypokalaemia, dehydration, infections, rhinitis, epistaxis, haemorrhage, deep vein thrombosis and pulmonary embolism, hypertension, fatigue, depression, insomnia

Important interactions:

no known interactions.

Must not be mixed with natrium chloride, folinic acid, 5-FU

Storage: room temperature

For detailed information, see introduction and SmPC.

8.1.5 5-Fluorouracil (5-FU, i.e. 5-FU medac)

5-Fluorouracil is an antimetabolite.

Approval: advanced colorectal cancer and other indications.

Typical toxicity: Mucositis, stomatitis, diarrhea, neutro-/leukopenia, sepsis, hand-foot-syndrome, cardiotoxicity (ischemic ECG signs, angina pectoris).

Furthermore: nausea/vomiting, thrombopenia, hyperurikemia, allergic reactions, headache, bronchospastic events, furthermore:

allergic reactions, elevated T4 and T3, hyperuricaemia, nystagmus, headache, Parkinson symptoms, pyramidal signs, euphoria, (leuco)encephalopathy with ataxia, speech disorders, aphasia, eye diseases, cardiomyopathy, myocarditis, cardiac arrhythmia, cardiac death, thrombophlebitis, gastrointestinal bleeding, dehydration, liver cell damage, alopecia, impaired wound healing, fatigue

Important interactions:

Brivudine and sorivudine may result in life-threating toxicity

Folinic acid increases 5-FU effects. Cimetidine, metronidazole and interferons increased 5-FU plasma levels

5-FU may increase phenytoin levels

Storage: For storage conditions, the manufacturer advice should be followed.

For detailed information, see introduction and SmPC .

8.1.6 Folinic acid (FA, i.e. Leucovorin®, Wyeth)

Folinic acid is calcium folinate and will be used as the d,l- form in this trial. It enhances the activity of 5-FU by stabilizing the bond between the active metabolite (5-FdUMP) and the enzyme thymidylate synthetase. It is therefore indicated for the treatment of subjects with carcinoma of the colon in combination with 5-FU.

Approval: in combination with 5-FU for cytoxic therapy.

Preparation: dilution not necessary

Typical toxicity: Rare in monotherapy. Increases 5-FU toxicity (diarrhea, nausea, vomiting). Furthermore: allergic reactions, sleeplessness, gastrointestinal disorders, increases probability for seizures,

Important interactions: *may reduce the efficacy of cotrimoxazole, phenobarbital, primidone, phenytoin and succinimide; increases 5-FU effect*
Interactions with other medication that interfere with Folinic acid are possible (Allopurinol, Trimethroprim, Pyrimethamine).
Must not be given with 5-FU in the same line (and not with droperidol, foscarnet or metothrexate)

Storage: 2…8°C, light protected

For detailed information, see introduction and SmPC.

8.2 Labelling

No labelling is planned. Manufacturer and batch numbers will be documented.

8.3 Blinding

Not applicable (open study).

9 Study treatment

9.1 Safety for systemic treatment

Because of possible anaphylactic reactions to some drugs (i.e. to cetuximab, oxaliplatin), patients have to be be observed during i.v. therapy (except outpatient 5-FU infusion). A physician must be present during infusion at least until 1 hour after infusion.

Evaluation before each treatment: see chapter 10.2.1, page 49
Criteria for continuation: see chapter 9.4, page 40
Premedication: see chapter 9.5, page 41

9.2 Treatment regimen and administration for ras wild-type patients

9.2.1 Cetuximab / FOLFIRI [21]

Risk factors for toxicity	**none**	
Cetuximab (1.0 h i.v.)†	**250 mg/m²**	weekly
Irinotecan (1.0 h i.v.)	**180 mg/m²**	d1, 15, ...
D,L Folinic acid (2.0 h i.v.)	**400 mg/m²**	d1, 15, ...
5-FU (Bolus i.v.)	**400 mg/m²**	d1, 15, ...
5-FU (46 h i.v.)	**2400 mg/m²**	d1, 15, ...

† first dose, only: 400 mg/m² (2.0h)

- One cycle is defined as one dose of chemotherapy and all cetuximab doses until the next day of chemotherapy
- Chemotherapy is given after cetuximab
- Irinotecan and folinic acid are given at the same time.

9.2.2 Cetuximab / FOLFOXIRI [24]

Risk factors for toxicity	**none**	
Cetuximab (1.0 h i.v.)†	**250 mg/m²**	weekly
Irinotecan (1.0 h i.v.)	**125 mg/m²**	d1, 15, ...
Oxaliplatin (2.0 h i.v.)	**85 mg/m²**	d1, 15, ...
D,L Folinic acid (2.0 h i.v.)	**400 mg/m²**	d1, 15, ...
5-FU (46 h i.v.)	**3200 mg/m²**	d1, 15, ...

† first dose, only: 400 mg/m² (2.0h)

- One cycle is defined as one dose of chemotherapy and all cetuximab doses until the next day of chemotherapy
- Chemotherapy is given after cetuximab
- Irinotecan is administered before oxaliplatin
- Oxaliplatin and folinic acid are given at the same time via separate lines.

9.3 Treatment regimen and administration for ras mutant patients

9.3.1 FOLFOXIRI [19]

Risk factors for toxicity	**none**	
Irinotecan (1.0 h i.v.)	**165 mg/m²**	d1, 15, ...
Oxaliplatin (2.0 h i.v.)	**85 mg/m²**	d1, 15, ...
D,L Folinic acid (2.0 h i.v.)	**400 mg/m²**	d1, 15, ...
5-FU (46 h i.v.)	**3200 mg/m²**	d1, 15, ...

- One cycle is defined as one dose of chemotherapy
- Irinotecan is administered before oxaliplatin
- Oxaliplatin and folinic acid are given at the same time via separate lines.

9.3.2 FOLFOXIRI / bevacizumab [27]

Risk factors for toxicity	**none**	
Bevacizumab (90 min i.v.)†	**5 mg/kg**	d1, 15, ...
Irinotecan (1.0 h i.v.)	**165 mg/m²**	d1, 15, ...
Oxaliplatin (2.0 h i.v.)	**85 mg/m²**	d1, 15, ...
D,L Folinic acid (2.0 h i.v.)	**400 mg/m²**	d1, 15, ...
5-FU (46 h i.v.)	**3200 mg/m²**	d1, 15, ...

† Infusion time can be reduced to 60 min at the second dose and 30 min at the third dose

- One cycle is defined as one dose of chemotherapy
- Bevacizumab is administered before chemotherapy
- Irinotecan is administered before oxaliplatin
- Oxaliplatin and folinic acid are given at the same time via separate lines.

9.4 Criteria for treatment continuation

9.4.1 Criteria for continuation of cetuximab

Cetuximab will continue to be administered in case of acne like rash or paronychia grade ≤ 2, even if chemotherapy is delayed due to other reasons.

9.4.2 Criteria for continuation of bevacizumab

Bevacizumab will be administered with chemotherapy, if

1) Blood pressure is < 150/100 mmHg and
2) dipstick urine analysis for protein is 0 or 1+, or (if > 1+) total protein in urine is < 2g / 24h and
3) no venous thrombosis within the last 2 weeks and

4) there is no reason for permanent discontinuation of bevacizumab (gastrointestinal perforation, oesophago-tracheal fistulae or any fistulae grade 4, hypertensive crisis, nephrotic syndrome, arterial thromboemolic event, grade 3/4 hemorrhage event, signs of posterior leucoencephalopathy).

9.4.3 Criteria for continuation of chemotherapy

Chemotherapy will not be reduced or delayed for anemia, acne like rash, dry skin or paronychia, hypertension. Chemotherapy will not be delayed for neuropathy (but oxaliplatin dose reduced or discontinued, Table 9 page 43).

Chemotherapy will be continued if other toxicities have resolved to:

1) Platelets $\geq$ 75 Gpt/l
2) Neutrophil count $\geq$ 1.0 Gpt/l
3) Diarrhea grade $\leq$ 1
4) Other organ toxicities grade $\leq$ 1

9.5 Supportive and concomitant medication

9.5.1 Premedication

Before Cetuximab:

Dexamethasone should be given before the first dose of cetuximab, and before the following doses in case of previous allergic reaction in a dose of 8 mg.

H1- and H2- blockers should be given before the 1st dose of cetuximab and are recommended before all following doses.

Before Chemotherapy:

Adequate antiemetic medication preferentially with 5HT3- antagonists and dexamethasone (16 mg, if not already administered before cetuximab).

9.5.2 Hematopoetic growth factors

If neutropenia grade 3 or 4 occurs, G-CSF or GMCSF is allowed in the same cycle and all following cycles to maintain the dose density. Other use should follow the current ASCO guidelines. [39]

9.5.3 Concomitant treatment

No additional investigational products, additional cytotoxic or other anti-tumour, or anti-angiogenic drugs are allowed. Radiotherapy is not allowed during the protocol treatment, except in special situations, where a local multidisciplinary team decides that stereotactic, hypofractionated radiotherapy replaces RFA.

Patients requiring other forms of radiotherapy will stop protocol treatment.

Brivudine and sorivudine induces life-threating toxicity when combined with 5-FU and are not allowed.

9.6 Special instructions regarding treatment of toxicity

9.6.1 Acute cholinergic syndrome (irinotecan)

These include 'early' diarrhea, sweating, hypersalivation, visual disturbances, abdominal cramps and lacrimation. If any cholinergic symptoms, including 'early' diarrhea, occur and are considered to be severe, 0.25 mg atropine should be administered subcutaneously unless absolutely contraindicated, e.g. in glaucoma. The administration of atropine sulfate before each dose of irinotecan should be considered in subjects who experienced cholinergic symptoms.

9.6.2 Delayed diarrhea (irinotecan)

The median time until the onset of the first liquid stool is day 5 after administration. Subjects must be informed of the possibility of delayed diarrhea before the start of treatment. The management of diarrhea has to be properly explained at this time (e.g. the necessity of oral rehydration and taking loperamide).
As soon as the first liquid stool or abnormal bowel movement occurs, the subject must inform the investigator and must immediately start loperamide, two capsules (4 mg) orally, then one capsule (2 mg) orally every 2 h for at least 12 h after the last liquid stool. Oral rehydration with large volumes of water and electrolytes is necessary throughout the diarrhea episode.
If diarrhea persists for more than 24 h despite the recommended loperamide treatment, a 7-day course of prophylactic, oral, broad spectrum antibiotics, e.g. a fluoroquinolone, must be started after medical advice. If necessary, the subject should be hospitalized for parenteral support.
In case of severe diarrhea that fails to respond to loperamide, the administration of 100 µg octreotide s.c. 3 times daily in combination with rigorous fluid and electrolyte replacement is recommended until the diarrhea ceases.
An oral fluoroquinolone (or an equivalent broad-spectrum antibiotic therapy) should also be given to subjects with:

- grade 4 diarrhea.
- diarrhea + grade 3–4 leukopenia or fever.

In addition to antibiotic treatment, hospitalization is recommended for management of the diarrhea, in the following cases:

- diarrhea associated with fever
- severe diarrhea (requiring intravenous rehydration)
- diarrhea persisting beyond 48 h following the initiation of high dose loperamide therapy

Loperamide and the fluoroquinolone must be continued when subjects leave hospital. Adequate explanation and written information on their use and the management of diarrhea must be given to the subject and/or carer at this time, including the necessity for oral rehydration if diarrhea persists. Loperamide must not be given prophylactically, even in subjects who experience delayed diarrhea during previous cycles.

9.6.3 Hand-foot syndrome (5-FU)

Symptomatic local treatment is recommended, as efficacy of specific treatment (i.e. vit. B6) is not proven.

9.6.4 Cardiac toxicity (5-FU)

The typical signs of cardiac toxicity under treatment with 5-FU are ischemic pain occurring a few hours after 5-FU administration with characteristic ECG changes. Silent ECG alterations may also occur. Myocardial infarction has been reported.

Treatment must be stopped in subjects who develop such symptoms or have any other cardiac event of unclear origin after treatment with 5-FU. These patients must be withdrawn from the study.

9.6.5 Nausea/vomiting

In addition to the recommended premedication (chapter 9.5.1), patients should be supplied with antiemetics for on-demand treatment (i.e. MCP, additional doses of dexamethasone). Adequate secondary prophylactic treatment (i.e. NK1 antagonists) has to be initiated once nausea or vomiting has occurred.

If the adverse event recurs despite prophylaxis, then dose modifications should also be according to chapter below.

9.6.6 Neuropathy (oxaliplatin)

Prophylactic use of glutathione and magnesium/calcium infusion, and carbamazepine/pentamidine is not recommended.

9.7 Dose modification for adverse events

In case of adverse events, doses should be reduced as listed in Table 9.

Table 9: Dose modification recommendations

Toxicity	Grade	Action to be taken
Diarrhea	Grade 2	Delay chemotherapy until diarrhea grade ≤ 1 *2nd occurrence with dose delay:* Delay chemotherapy until diarrhea grade ≤ 1 and reduce irinotecan, 5-FU and FA to 80%
	Grade ≥ 3	Delay chemotherapy until diarrhea grade ≤ 1 Reduce all further doses of irinotecan, 5-FU and FA to 80%. See also chapter 9.6.2, Delayed diarrhea (irinotecan)
Mucositis	Grade ≥ 2	Delay chemotherapy until resolution to grade ≤ 1 *2nd occurrence requiring dose delays:* Delay chemotherapy until diarrhea grade ≤ 1 and reduce irinotecan, 5-FU and FA to 80%
	Grade ≥ 3	Reduce all further doses of 5-FU and FA to 75%
Neutropenia	Grade 3 or grade 4 for < 5 days	Delay chemotherapy until resolution to grade ≤ 2 Consider use of GCSF *2nd dose delay within study:* Reduce all further doses of oxaliplatin, irinotecan, 5-FU and FA to 80%

	Grade 4 for ≥ 5 days or Febrile neutropenia	Delay chemotherapy until resolution to grade ≤ 2 Reduce all further doses of oxaliplatin, irinotecan, 5-FU and FA to 80% See also chapter 9.5.2, Hematopoetic growth factors
Thrombopenia	Grade 2	Delay chemotherapy until resolution to grade ≤ 1
	Grade ≥ 3	Delay chemotherapy until resolution to grade ≤ 1 and reduce all further doses of oxaliplatin, irinotecan and 5-FU to 80%
	Grade 4	Discontinue treatment. Further treatment at reduced dose (oxaliplatin, irinotecan and 5-FU 80%) depending on the judgement of the investigator
Cardiac events	Any grade	Discontinue treatment if suspected to be related to 5-FU (i.e. typical, reversible ECG signs)
Arterial thrombo-embolic events	Any grade	Discontinue bevacizumab
Venous thrombo-embolic events	Grade ≥ 4	Discontinue bevacizumab
Hand-foot-syndrome	Grade ≥ 2 at time of planned next chemotherapy	Delay chemotherapy until resolution to grade ≤ 1
	Grade ≥ 3 at any time	Delay chemotherapy until resolution to grade ≤ 1 and reduce all further doses of 5-FU and FA to 80%
Neuropathy	Cold related dys-aesthesia	No dose modification
	Paraesthesia / sensory neuropathy grade 1 or grade 2 persisting < 14 days	No dose modification
	Paraesthesia / sensory neuropathy grade 2, persisting ≥ 14 days	Reduce all further doses of oxaliplatin to 80%.
	Paraesthesia / sensory neuropathy grade 3	Delay oxaliplatin until resolution to grade 2. Reintroduction of oxaliplatin with dose reduction for all further doses to 80% resolution during preoperative treatment.
	Paraesthesia / sensory neuropathy grade 4	Discontinue oxaliplatin
Acne like rash, dry skin, paronychia	Grade ≥ 3	*1st occurrence* Delay cetuximab until resolution to grade ≤ 2 *2nd and further occurrence* Delay cetuximab until resolution to grade ≤ 2, and reduce dose

		to 80% (=200 mg/m²) *3rd occurrence* Delay cetuximab until resolution to grade ≤ 2, and reduce dose to 60% (=150 mg/m²) *Cetuximab should be discontinued in case of further occurrences or if delayed more than 4 weeks*
Hypersensitivity infusional reaction	Grade 1	If related to cetuximab: decrease infusion rate of cetuximab to 50% (total infusion time should be < 4 hours) Related to other drugs: decrease the infusion rate of the suspected drug to 50% under close monitoring
	Grade 2	Cetuximab: Stop infusion until resolution to grade ≤ 1, then restart cetuximab with reduced infusion rate (50%). Related to other drugs: discontinuation recommended
	Grade ≥ 3	Discontinue cetuximab.
Hypertension (patients with bevacizumab)	Asymptomatic, transient increase to >150/100, not confirmed by 2nd measurement	Continue bevacizumab. Antihypertensive treatment may be considered blood pressure is repeatedly > 140/90 mmHg
	Repeated measurements of >150/100 mmHg	Delay bevacizumab until BP is < 150/100 mmHg, start antihypertensive treatment
	Hypertensive crisis	Discontinue bevacizumab.
Proteinuria (patients with bevacizumab)	Urine dipstick > 1+	Measure protein / 24h urine Continue bevacizumab if protein in urine is less than 2 g/day
	Protein in urine ≥ 2 g / day	Discontinue bevacizumab.
Other related organ toxicity (nausea vomiting in case of appropriate concomitant medication, only)	Grade 2	Delay chemotherapy until resolution to grade ≤ 1
	Grade ≥ 3	Delay chemotherapy until resolution to grade ≤ 1 Reduce all further doses of oxaliplatin, irinotecan, 5-FU and FA to 80%

9.8 Evaluation for resectability

Patients will be evaluated for resectability every 8 weeks. Images and clinical findings should be discussed in a multidisciplinary team.

In case of resectability, resection of metastases should be offered. A preoperative treatment of at least eight cycles[1] is recommended.

An earlier resection than after eight cycles should be planned in case of the following conditions:

- technically resectable liver metastases and intolerable toxicity
- technically resectable liver metastases and nearly complete response after the tumour evaluation after 4 cycles

In case of technical non-resectability after eight cycles, therapy will be continued until tumour progression, and the patients will be evaluated for resection every 8 weeks.

9.9 Resection

Resection will be performed according to local standards. An interval of at least 4 weeks is recommended between last dose of chemotherapy and resection. Toxicities (except neurotoxicity) should have been decreased to grade ≤1. Between last bevacizumab dose and resection, a minimum time of 6 weeks is recommended.

For that purpose, bevacizumab may be omitted at the last chemotherapy, if resection is planned.

Simultaneous local ablative therapy is allowed during tumour resection.

In special situations, local ablation may replace resection, if a resection cannot be performed. Similarly, hypofractionated, stereotactic radiotherapy may replace radiofrequency ablation.

9.10 Postoperative, adjuvant chemotherapy

After or between resections, the patient should receive the same treatment as for preoperative therapy, if there was no disease progression.

Treatment after resection should start between four and eight week after resection. Dose reductions or drug omissions according to preoperative chemotherapy also apply to postoperative treatment.

9.10.1 Patients with macroscopically complete procedures

This chapter applies to patients with R0/1 resection +/- complete RFA

Adjuvant chemotherapy (with the same regimen as in preoperative therapy) is administered until a total number of 12 pre- and postoperative cycles. Postoperative treatment should not be initiated if ≤ 2 chemotherapy cycles remain.

Table 10: Number of adjuvant cycles depending on neoadjuvant treatment

No of preoperative cycles	4	5	6	7	8	9	≥ 10
No of postoperative cycles	8	7	6	5	4	3	0

[1] One cycle is defined as one administration of chemotherapy (= 14 days if no delay).

9.10.2 Patients with macroscopically incomplete procedures

If the procedure was incomplete because a two stage intervention was planned, treatment can be continued up to eight additional cycles within the protocol. If the second resection was not performed as R0 resection within the next 8 months, the patient will be regarded as not cured.
Similarly, patients will be regarded as R0 resected only, if the resection of the primary was performed within the 12 months after randomization. Up to 8 additional cycles are allowed between resection of liver metastases and the primary. An adjuvant therapy is only recommended if there were less than 10 cycles administered before the last resection.
According to the inclusion criteria, the resection of the liver metastases should be planned as first intervention. If a clinical decision in reaction of unforeseen events requires the resection of the primary before resection of liver metastases, the patient may receive further study treatment as for two stage resections.

In case of R2 resection, incomplete RFA, exploration without planned second curative intervention, the patient will be regarded as not cured and will receive no further treatment within the study.
The patients will be followed up for overall survival and will receive further therapy at the discretion of the investigator.

9.11 Reasons for discontinuation of study treatment

The study treatment will be discontinued after 12 cycles if the patient has not become resectable. The investigator may decide to continue treatment with a dose reduced schedule outside the clinical trial. It should be noted, that it is generally unusual to switch to a new drug in the absence of clinical progression.

Treatment will be discontinued in case of:

1) Progressive disease
2) Intolerable toxicity
3) non-curative procedure (R2 resection, incomplete RFA, explorative laparotomy) if not performed as first resection in the concept of a two stage resection
4) Withdrawal of patients consent
5) Investigators decision in best interest of patient
6) Non-curative intervention, if no second intervention is planned (see chapter 9.10.2)
7) Ineligibility
8) Non-compliance of patient
9) Significant protocol deviation
10) Administrative decision by the investigator, the sponsor or the health authority (see chapter 11.7)

After the last administration of study adjuvant treatment or if a treatment is discontinued early and hepatic resection is not performed, an end-of-study visit should be planned 30 ± 2days after last treatment.

10 Study visits

10.1 Screening visit

Patients with colorectal cancer liver metastases will sign an informed consent before any study procedure is performed.

The following data are collected:

1) Patients demographic data (month/year of birth, gender, ethnic origin)
2) Tumour history, including: date of diagnosis, histology, tumour site (within the colon; rectum) and clinical and TNM stage, previous treatment(s)
3) Previous surgery
4) Concomitant disease(s)
5) Concomitant medication

The following examinations will be performed during screening:

1. WHO Performance status
2. Physical examination, weight, height, vital signs (blood pressure, heart rate, temperature)
3. Evaluation of general operability according to local standards
4. ECG
5. Standard laboratory workup (haematology: haemoglobin, leukocytes, platelets and neutrophils; biochemistry: sodium, potassium, magnesium, albumin, creatinine, alkaline phosphatase, total bilirubin, LDH, SGOT, SGPT); CEA; dipstick urine analysis, 24 hour urine analysis if dipstick >1+).
6. Plasma for translational research (2x8ml), special tubes provided
7. Shipment of tumour block (paraffin embedded tissue of liver metastases (preferred, if available) or primary tumour) for ras-/raf mutational analysis
8. Female patients: gravidity test (not necessary if > 1 year postmenopausal or with conditions that exclude gravidity, i.e. hysterectomy), to be done within 7 days before treatment start
9. Abdomino-pelvic and thoracic, contrast-enhanced spiral- CT scan including three-phasic contrast-enhanced CT scan of the liver (to be performed within 4 weeks before treatment start).
   The abdomino-pelvic CT scan can be substituted by MRI; in this case, all subsequent examinations must be performed by MRI.
   The CT (or MRI) should be sent - DICOM formatted, on CD or DVD – to the coordinating study office
10. Documentation of the reason of non-resectability (technical resectability and number of metastases)
11. 18-FDG PET- examinations are optional will be performed at discretion of the local investigator. Participation in additional studies investigating the impact of PET or other imaging methods in staging or response evaluation is **not** excluded.

All investigations should be performed within 3 weeks before randomization, except CT scan (4 weeks).

10.2 During treatment

10.2.1 Before each treatment and weekly between until two weeks after last dose

1) Blood count, including haemoglobin, and leukocytes, platelets, neutrophils
2) Toxicity evaluation / documentation of adverse events
3) Documentation of concomitant medication for treatment of adverse events
4) Vital signs (blood pressure, heart rate)
5) At day 1: biochemistry: sodium, potassium, magnesium, creatinine, alkaline phosphatase, total bilirubine, LDH, SGOT, SGPT
6) Dipstick urine analysis, 24 hour urine analysis if dipstick >1+ (for bevacizumab arms before dose, only)

10.2.2 Additionally after every four preoperative cycles

1) Abdominal spiral CT scan (or MRI; imaging has to be performed with the same method as at baseline). The CT (or MRI) should be sent - DICOM formatted, on CD or DVD – to the coordinating study office
2) Chest imaging (CT or conventional x- ray)
3) Physical examination, WHO performance status
4) Standard laboratory clinical workup (haematology: haemoglobin, leukocytes, platelets and neutrophils; biochemistry: sodium, potassium, magnesium, albumin, creatinine, alkaline phosphatase, total bilirubine, LDH, SGOT, SGPT); CEA;
   for patients with bevacizumab- treatment: dipstick urine analysis, quantitative protein analysis in 24 hour urine if dipstick >1+)
5) Plasma for translational research (2x8ml)
6) Evaluation for resectability

10.2.3 Perioperative evaluation

1) Type of intervention, classified as segment resections, hemihepatectomy, extended hemihepatectomy, central resections, non-anatomical resections, explorative laparotomy and local ablations, or combinations of these methods
2) Resection status as R0/R1/R2 for resections and – for ablations – as complete/incomplete according to imaging
3) Perioperative morbidity according to Clavien et al. (see appendix 20)
4) Days of mechanical ventilation
5) Bilirubin at days 3, 8, (if not normalized at day 8, on days 15, 22, 28) after surgery
6) Report of surgery and pathology reports (patient name /date of birth and other identifiers replaced by patient numbers).
7) Pathological specimen: tumour block of resected liver metastases and of non-metastatic liver tissue (to determine tumour regression and potential effects of normal liver tissue, i.e. sinusoidal obstruction, steatosis/steatohepatitis, in a central review process)

10.2.4 End of study visit (30 ± 2 days after last study treatment administration)

1) Toxicity evaluation / documentation of adverse events
2) Documentation of concomitant medication for treatment of adverse events

3) Vital signs (blood pressure, heart rate, temperature)
4) Physical examination, WHO performance status
5) Standard laboratory clinical workup (haematology: haemoglobin, leukocytes, platelets and neutrophils; biochemistry: sodium, potassium, magnesium, albumin, creatinine, alkaline phosphatase, total bilirubin, LDH, SGOT, SGPT); CEA
   for patients with bevacizumab- treatment: dipstick urine analysis, quantitative protein analysis in 24 hour urine if dipstick >1+)

10.3 Follow-up visits

These visits will be performed every 3 months in the first two years and thereafter every 6 months until 5 years after randomization or until disease progression, whichever occurs first.

1) Imaging (if no R0 resection with the same method as at baseline; after complete resection: abdominal ultrasound and chest x-ray as minimum investigation, thoracic and abdominal CT scan recommended)
2) Documentation of progression / survival status
3) Documentation of subsequent procedures or treatment lines

10.4 Follow up for overall survival

Patients will be followed up for overall survival until 5 years after randomization.

11 Evaluation of toxicity

11.1 Documentation of adverse events (AEs)

An adverse event (AE) is generally defined as any unfavourable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding) syndrome or disease which either occurs or worsens during the study. Adverse events are to be recorded regardless of their relationship to the study intervention.
This study will use the NCI CTC, version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/About.html) for toxicity and adverse event reporting if applicable. Perioperative complications are graded according to Clavien et al, chapter 20. [40]
All adverse events (AEs) have to be documented in the patients chart and within 2 weeks in the eCRF.
Adverse events will be reported after application of the first dose of study medication.

Adverse events will be assessed according to relationship to the protocol treatment using the following definitions:
Unrelated - There is no evidence of any causal relationship to the protocol treatment
Likely related - There is (some) evidence to suggest a causal relationship to the protocol treatment and influence of other factors is unlikely or absent.
Related – clear relationship between protocol treatment and adverse event
Not assessable - There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship to the protocol treatment.

The participant will be followed until remission of the symptoms or until to the sponsors decisions that no new information will be obtained. If the adverse event results in a persistent disease, it has to be classified as "serious" and to be documented at the end of the trial.
The following data have to be documented in the CRF:

- term of adverse event (symptoms, diagnoses etc.),
- differentiation between serious or non-serious adverse event (see chapter 11.2),
- start and end day of the event,
- intensity (according to NCI CTC criteria or to Clavien classification)
- assessment of causal relationship to the study medication (investigator's judgement),
- measures taken to recover the participant's health,
- outcome.

All adverse events will be recorded on the case report forms; the investigator will decide if those events are drug related (unrelated, likely related, not assessable) and his decision will be recorded on the forms for all adverse events.
Adverse events not drug related (i.e. reported as unrelated or unlikely related) will not be considered as side effects or toxicity, but reported separately.
The frequencies of the adverse events by group terms will be computed. Adverse events reported as "likely related", "related" or with missing relationship to study medication will be considered as related to study medication.

The sponsor (or its representative) has to document all reported adverse events completely and has to send this information to the health authorities or the DSMB if requested.

11.2 Serious adverse events

Serious Adverse Events (SAE) are defined as an event causing significant hazard to the patient, whether or not considered related to the investigational drug. Adverse events are considered serious if they result in:

- death
- a life-threatening event
- hospitalization or prolongation of hospitalization (A planned hospitalization for medical procedure without an adverse event is not a serious adverse event)
- persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the patient)

All Serious Adverse Events (SAEs), related or not to the protocol treatment, occurring after randomization and within 30 days after the last protocol treatment administration, must be reported within 24 hours to the sponsor representative:

fax : +49 351 7965 621

All SAEs have to be documented as adverse event in the eCRF and at the SAE form. Each SAE has to be reported as completely as possible (in case of death an autopsy report [with blinded patient information] should be performed and the report should be handed out to the sponsor if possible). The monitor will check that documented data in the study centre are complete and that data in the SAE form are in accordance with documentation in the data bank and other data sources.
Cases of overdoses, misuse, or relevant deviations in the administration of the study medication (i.e. unintended change of study arm) have to be documented even when there is no adverse event.
Any late Serious Adverse Drug Reaction (SADR; severe harmful and unintended reaction on the study medication), occurring after this 30-day period also must be reported to the sponsor delegates (coordinating study office).

All SUSAR reports and all reports involving expected SADR that are life threatening or caused death, will additionally be forwarded to all participating investigators.

To enable the study central/sponsor to comply with regulatory reporting requirements completed documentation of any reported serious adverse events or serious adverse drug reactions must be returned within 10 calendar days of the initial report. If the completed form is not received within this deadline, the coordinating study office requests it from the investigator.

Any AE that occurs in the course of a clinical study must be monitored and followed up until the End of Study visit. It is the responsibility of the investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

11.3 Suspected unexpected severe adverse events (SUSARS)

An adverse reaction is any harmful and unintended reaction on the study medication regardless its dosage. Severe adverse events will be considered as "Suspected Unexpected Serious Adverse Reaction" (SUSAR, see guidelines 2001/20/EG), if they have a certain degree of probability that it is an adverse reaction to the administered drug and if the adverse reaction is not described in the summary of product characteristics.
All suspected unexpected severe adverse reactions (SUSARs) will be reported on behalf the sponsor by his delegates (coordinating study office) within 15 days to the health authorities, the Ethics committee and the participating investigators.
In case of a fatal or life threading SUSAR, the coordinating study office will report the events immediately, at latest within 7 days to the Ethics committee, the health authorities and the investigators and will provide the further relevant data within 8 additional days.

The sponsor (or its representative) has to report any reported SUSAR immediately, the latest within 15 days after notification, to the relevant ethical committee, health authorities (i.e. Paul-Ehrlich-Institute for Germany) and to the investigators.
The sponsor (or its representative) has to send any important information that is relevant for assessment immediately, the latest within 7 days after notification, to the relevant ethical committee, the health authorities (Paul-Ehrlich Institute) and to the investigators when the SUSAR was followed by death or is life threatening for the participant. Other relevant information has to be sent no later than within the following 8 days.

11.4 Evaluation of risk-benefit-ratio

For each severe adverse event will be checked whether it might influence on the risk-/benefit ratio for patients treated in the clinical trial. If the safety of the participants is impaired and the sponsor (or its representative) as well as the investigator take action to prevent the participants from any harm.

The sponsor (or his delegates) informs within 15 days the relevant ethics committee(s), the DSMB and the health authorities on each event requiring a new evaluation of the risk-benefit ratio, especially in case of:

- reports of SAEs with unexpected outcome
- increased frequency of clinically relevant severe adverse events
- suspected cases of severe adverse events that occurred after the patient finished the clinical trial
- events in relationship with the study management or the development of the study drug that might impair the safety of the study patients.
- if actions are undergone to prevent immediate harm to the safety of the study patients.

11.5 Yearly reports

The sponsor informs the ethics committee, the health authorities and the DSMB during the study once yearly or on demand on all suspected cases of SAEs and provides a yearly report on the safety of the study patients.

11.6 Data safety monitoring board

For adequate monitoring of patients' safety an independent DSMB consisting of a Medical Oncologist (head), a Surgical Oncologist and a person experience in biostatistics. The DSMB is responsible for the supervision of patients' safety under medical and ethical aspects (e.g. perform a risk/ benefit assessment in order to weigh possible safety disadvantages against a possible gain in efficacy). Furthermore, the DSMB may decide to perform a futility analysis for efficacy after each meeting.

The DSMB will be composed of qualified clinicians with scientific expertise relevant to the indication of liver metastases from colorectal cancer, with practical experience in conducting clinical trials and with expertise in bio statistical and ethical questions. The members of the DSMB are listed in the protocol (chapter 2.6). The members have no financial or non-financial interest in the outcome of the study. They will be informed of the status of the study and its safety data regularly. Closed DSMB meetings will take place after inclusion of 25 and 50 patients per arm, but at least once per year, preferably as telephone conference. The content of the meetings will be documented and treated confidentially to prevent that unblinded study data will be disseminated.

11.7 Study discontinuation

Study discontinuation is at the discretion of the Sponsor in any of the following events:

- Medical or ethical reasons affecting the continued performance of the study.
- Difficulties in the recruitment of patients.

In addition, the study may be discontinued at the discretion of the Sponsor if previously unknown unacceptable adverse drug reactions (with respect to their nature, severity and/or duration) occur, or if an unexpected incidence of known unacceptable adverse drug reactions is observed. Safety data from the ongoing study will be reviewed by the Sponsor and the Data safety monitoring board on a regular basis in order to ensure that the continuation of the study is appropriate.

11.8 Evaluable patients for toxicity

For final analysis, all eligible patients who have received at least one (even incomplete) dose of any study drug will be included in overall toxicity analysis. Patients who have discontinued treatment because of toxicity will always be included in the toxicity analysis.

12 Statistics and Analysis

12.1 Calculation of sample size

12.1.1 Sample size for ras wild type patients:

The response rate for FOLFIRI/cetuximab is estimated at 70% (π_1).[21]
Trials with FOLFOXIRI/cetuximab have achieved response rates of nearly 80% for the entire patient population (not selected for k-ras wild type, see chapter 4.5). Trials with chemotherapy and cetuximab observed higher response rates in patients with liver limited disease than in the ITT population (Table 8), and in k-ras wild type than in k-ras mutant patients. Therefore, a response rate of 85% (π_2) is expected for the experimental arm cetuximab/FOLFOXIRI.
With a beta error of 20 % and alpha error of 10 %, 69 patients are required per arm to reject the H_0 hypothesis: $\pi_2 - \pi_1 \leq 0$.
Thus, 138 *ras/b-raf* wild type patients have to be randomized and will be included in the ITT population.

12.1.2 Sample size for ras mutant patients:

With an estimated response rate for FOLFOXIRI/bevacizumab of 78%[27] (π_2) and a response rate for FOLFOXIRI of 60% (π_1),[19] a power of 80% and an alpha of 10 %, 59 evaluable patients are necessary per arm to reject the H_0 hypothesis: $\pi_2 - \pi_1 \leq 0$.
Thus, 118 *ras* mutant patients have to be randomized and will be included in the ITT analysis.

12.1.3 Sample size for screening

With the distribution of k-ras and b-raf mutations of the CRYSTAL study, [30] up to 310 patients are to be screened.
The sample size was calculated with ADDPLAN, Cologne, Germany, version 5.0.3.

12.2 Efficacy parameters

All efficacy parameters will be analyzed for the intent-to-treat population, defined as all patients randomized.

12.2.1 Response rate

For evaluation of efficacy, confirmed response rates will be reported. Response evaluation will be performed by RECIST- criteria version 1.1. [41]

According to the type of study, the following exception is defined:
Response will be regarded as confirmed, if it was confirmed by a second imaging scan as per RECIST 1.1 ***or if a macroscopically complete resection / ablation was performed after the first scan that documented a partial or complete remission before the confirmatory imaging was scheduled.***

According to RECIST criteria, **target lesions** are defined as measurable tumour lesions (liver metastases with a maximal diameter of at least 10 mm). A maximum of 2 liver metastases (preferably the two largest metastases) will be defined as target lesions.

All other liver metastases are **non-target lesions.**
Target lesions and non-target lesions will be numbered at baseline and followed up by the same method as at baseline (i.e. spiral-CT). Each target lesion will be measured with the maximum diameter, and the sum of the diameters will be calculated.

Tumour response of the target lesion is defined as:

Complete response – disappearance of all lesions

Partial response - At least a 30% decrease in the sum of the longest diameter of target lesions taking as reference the baseline sum LD.

Stable disease – Sum of the longest diameters not decreasing more than 30% from baseline and not increasing more than 20 % from the smallest diameter since treatment start.

Progressive disease – At least a 20 % increase in the sum of the longest diameter of target lesions since treatment start.

Tumour response of the non-target lesion is defined as:

Complete response – disappearance of all lesions and normalization of the tumour marker level

Stable disease – Persistence of one or more non-target lesions and/or maintenance of tumour marker level above the normal level.

Progressive disease – Unequivocal progression of existing non-target lesions.

Overall response is defined as:

Overall response	Target lesion	Non- target lesion	Appearance of new lesions
Complete response (CR)	CR	CR	no
Partial response (PR)	CR	SD	no
Partial response (PR)	PR	SD or CR	no
Stable disease (SD)	SD	SD or CR	no
Progressive disease (PD)	PD	any	yes or no
Progressive disease (PD)	any	PD	yes or no
Progressive disease (PD)	any	any	yes

All responses have to be confirmed by a second scan with the same imaging method with a time interval of at least four weeks, except in case of macroscopically complete resection (see above).

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

For patients with ras wild type CRC the null hypothesis H_0: $\pi_2 - \pi_1 \leq 0\%$ will be tested as described in Section 12.1.1. The test for the H_0 hypothesis in the ras mutant group will independently be performed and not adjusted.(see Section 12.1.2).

In addition to the analysis within each treatment arm, exploratory multiple logistic regression analysis will be performed separately for ras wild-type and ras mutant patients to estimate the odds ratio (and corresponding 95% confidence intervals) for the association between study treatment and response rate. Various demographic and disease characteristics will be considered as explanatory covariates in the logistic regression to estimate the treatment effect adjusted for these covariates and to explore their impact on the response rates. The details will be specified in the statistical analysis plan (SAP).

12.2.2 Resectability

The abdominal CT scans will be discussed in the local multidisciplinary team. The technical resectability will be determined locally. For decision making, the criteria of inclusion criteria for technical resectability should be used (see chapter 6.1)

Patients will be regarded as R0 resected if all liver metastases and the primary tumour were resected with microscopically tumour free margins and no progression occurred between the two resections.

Patients will be regarded as macroscopically tumour free resected if liver metastases were resected with macroscopically tumour free margins and / or complete RFA according to imaging, and the primary tumour was resected with microscopically tumour free margins, and if no progression occurred between the two resections.

In case of R2 resection, incomplete RFA, exploration without planned second curative intervention, the patient will be regarded as not cured and will receive no further treatment within the study.

For a central, retrospective review, the CT- or MRI scans before treatment, and after 4 and 8 cycles will be collected on a pseudonymised, DICOM-formatted CD or DVD (to be shipped to study coordinating office, see 2.5, page 5).

The resection rates will be calculated per arm and the two-sided 95 % confidence limit will be calculated. In addition, the same exploratory statistical methods will be applied to investigate the treatment effect on the R0 resection rate, as specified for response rates (see Section 12.2.1)

12.2.3 Disease free survival

The disease free survival is calculated as the time from resection to either the evidence of recurrence / metastases or to the date to death, whichever occurs first.

Patients still alive without evidence of recurrence / metastases at the time of their last visit are censored at the time of the last examination.

The disease free survival will calculated using Kaplan-Meier plots per arm, including the estimated disease free survival rates at different time points with 95% CI. Additionally, exploratory univariate and multivariate Cox proportional hazard methods will be used separately for ras wild type and mutant patients to estimate the hazard ratio (and corresponding 95% confidence intervals) for the assessment of the relative risk between the two treatment arms. Various demographic and disease characteristics will be considered as explanatory covariates in

the multivariate Cox proportional hazard analysis to estimate the treatment effect adjusted for these covariates and to explore their impact on disease free survival. The details will be specified in the SAP.

12.2.4 Rate of patients R0 resected and disease free

For the secondary endpoint, the number of patients who are known to be R0 resected for all tumour lesions and alive for at least 6 months and have no recurrence or metastases within the first 6 months after resection divided by all patients (ITT population) will be calculated.
The rates will be calculated per arm, with the confidence intervals. In addition, the same exploratory statistical methods will be applied to investigate the treatment effect on the rate of patients R0 resected and disease free, as specified for response rates (see Section 12.2.1)

12.2.5 Progression free survival

The progression free survival is calculated as the time from randomization to either the first progression of the disease or the date of death, whichever occurs first. Patients starting another treatment without progression are censored at that time.
Patients still alive without disease progression at the time of their last visit are censored at the time of the last examination.
The progression free survival will calculated using Kaplan-Meier plots per arm, including median and the confidence intervals. In addition, the same exploratory statistical methods will be applied to investigate the treatment effect on progression free survival, as specified for disease free survival (see section 12.2.3).

12.2.6 Overall survival

The overall survival is calculated as the time from randomization to the date to death from any cause. Patients who were alive at the time of last contact are censored at that date. In addition, the same exploratory statistical methods will be applied to investigate the treatment effect on overall survival, as specified for disease free survival (see section 12.2.3).

12.2.7 Safety Parameters

Safety will be reported in absolute numbers and as a percentage in patients who received at least one dose of treatment by treatment arm. Safety will be reported for all adverse events, and for full reporting additionally as toxicity related to study treatment according to investigator judgement.
Number and percentage of patients dying during study (from first treatment until 30 days after the last study treatment) will be reported according to treatment arms, relationship to treatment (by investigators judgement), and occurrence with respect to the perioperative period.
Adverse events outwith and during the perioperative period will be reported according to NCI CTC criteria version 4.0 or Clavien et al, respectively (see chapter 11.1). The perioperative period is defined as the time from operation to discharge, but at least until 30 days after surgery. If chemotherapy restarts within 30 days after surgery, events related to chemotherapy are not regarded as perioperative events.

13 Randomisation and data management

13.1 Randomization and stratifications

Randomization will be performed after main baseline characteristics are entered in the eCRF system using the eCRF system by a computer generated list. Randomization will be stratified according to chapter 7.2.2.

13.2 Method of assigning patients

All patients will be assigned a five-digit identification number at the pre-screening visit. Patients from different centres will be identified throughout the study by the first two digit number(s) starting with a 10 to avoid leading zeros (e.g. 10001, 12001..25001) that indicates the centre, the third to fifth digits indicate the patient at the screening visit, starting with xx001.
Patient numbers will be unique (i.e. reallocation of patient numbers is not permitted). Withdrawal after start of treatment and before the first treatment dose has to be documented carefully.

13.3 Removal and replacement of patients

Patients have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.
Withdrawal of full consent for a study means that the patient does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation. Any patient may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the patient the most appropriate further treatment. Any patient who withdraws full consent to participate in the study will be removed from further treatment and/or study observation immediately upon the date of request.
Withdrawal of partial consent means that the patient does not wish to undergo therapeutic procedures (including administration of study drugs) any longer but is still willing to collaborate in providing further data by continuing on study (e.g.: participate in all subsequent study visits or procedures). Patients may decline to continue receiving investigational product at any time during the study. These patients, as well as those who have stopped receiving investigational product for other reasons (e.g.: investigators or sponsors decision, see chapter 9.11) should continue the schedule of study observations.
Should a patient (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information should be reported on the applicable case report forms.
Patients who are removed or withdrawn from study after receipt of any study medication will not be replaced.

13.4 Documentation and data base

Data management and electronic CRF are performed and provided by KKS Dresden (address: chapter 2.5.1) by means of study software MACRO 3.0. Data are proven by programmed range checks, validity checks, and consistency checks. In addition, a manual/visual data check for medical plausibility is done according to GCP guidelines. There might be discrepancies that are to be clarified by authorized persons by means of the study software.

After the study is finished and before data are analysed, a blinded meeting will be held between the sponsor and statistician. When the database has been declared to be complete and accurate, it will be locked. This procedure has to be documented.

The data base is under control of the sponsor. Before primary analysis, the data base can be accessed for analyses specified in chapter 1112.1 (toxicity and recruitment). The time points are outlined in chapter 5.4. The Data Safety Board Data base can request additional analyses.

The data documented in the electronic CRF must correspond to the source data filed in the patients file. The patient files are under responsibility of the investigator.

Beside other responsibilities of the investigator (chapter 16.2), he has to ensure the documentation of all relevant data according to the GCP guidelines, the clinical study protocol, and the legal requirements are documented in the source data and all relevant data are recorded immediately, correctly and completely in the electronic CRF. This also includes data of patients that were excluded during the clinical study. The study has to be documented by authorized persons only. Corrections in the eCRF are to be conducted only by authorized personnel and to be justified. The former database entry must stay retrievable. All dates and corrections are recorded automatically concerning date, time point and person.

It has to be ensured that the person responsible for documentation in the source data and CRF can be identified. Therefore, a list with signatures and abbreviations (site signature log) is kept in the investigator site file (chapter 13.5) and in the trial master file.

The investigator records the participation of a patient at the patient identification log. This list is meant to identify participating persons at a later point of time. It includes the complete name, the date of birth, and the date of inclusion into the clinical study. The patient identification log remains in the study centre during the study all the time and after the study is finished.

In addition, participation in the clinical study has to be recorded in the patient's chart (including study medication, participant number/randomization number, start and end of the clinical study).

13.5 Investigator Site File

The sponsor provides the Investigator Site File (ISF) to the study centre. The ISF includes all documents that are required for the clinical study. During monitoring, the ISF will be checked regularly for completeness. After the clinical trial is finished or stopped, the ISF has to be stored for 10 years.

13.6 Data Storage

13.6.1 Responsibilities of the Sponsor

As required by law, all important study documents have to be stored by the sponsor for at least 10 years after the clinical trial was finished or stopped.

13.6.2 Responsibilities of the Investigator

All documents that are related to the clinical study and to the distribution of the study medication (e.g. CRFs, written informed consent forms, study medication lists and other relevant material) have to be stored for at least 10 years.

Source data like patients' charts, laboratory analyses, and other original data have to be stored for the longest possible time that is usual practice at the investigator's site.

14 Quality assurance

14.1 Monitoring

The investigator agrees that the monitor will visit the study centre in appropriate intervals. During these visits the monitor will check the quality of the data recording and ensure that the study centre adheres to the timeframe as set in the study protocol.
The investigator will cooperate with the monitor, especially ensuring the access of the monitor to all study-relevant data and files (including original study documents and source data), discussing problems detected during monitoring visits and ensuring that data are timely (within three days) entered into the eCRF and that queries are answered without delay.

It is the responsibility of the investigator to keep the participant's chart as complete as possible (e.g. history, concomitant diseases, inclusion in the clinical study, visit dates, results of laboratory tests, distribution of the study medication, and adverse events, see also chapter 13.4). Source data are checked and compared with entries in the data bank. The participant has given consent with this procedure by signing the patient information and written informed consent form.

Source data will be checked for concomitant medication to exclude disallowed co-treatment and for treatment of serious adverse events.
The appointed clinical monitor will arrange regular visits to the study centre(s) on a regular basis to check progress of the study and to review completed CRFs. The frequency of monitoring will depend on the number of recruited patients.
Additional tasks of the monitor are:

- to check, whether the study centre fulfils requirements of the clinical study (e.g. participant population, technical equipment, adequate storage of medication),
- instruction of the investigators and personnel for the clinical trial,
- to check the ISF for completeness and actuality,
- documentation of the status of the participant,
- Matching of original data,
- to check SAE reports according to regulations,
- to check secure storage and expiration date of study medication,
- to check compliance.

The monitor has the responsibility to treat all information confidentially and to safeguard the integrity and personal privacy of the study participants.

14.2 Audit

To guarantee the adherence to GCP guidelines, audits (e.g. by the sponsor) and inspections (e.g. by the authorities) can be performed to review the adherence to the protocol, data validity, quality of the study according to GCP guidelines.

The investigator has to inform the sponsor immediately if an external audit or an inspection by health authorities is announced that might interfere with the study. Audit and inspection reports are filed in the ISF and sent to the sponsor. Study audit certificates are added to the final study report.

15 Correlative investigations

One of the main objectives in cancer research is to identify patients with the highest likelihood to benefit from treatment. This chapter describes the procedures and the planned correlative research. Due to the developing knowledge on the molecular background of disease and drug action, an adaption of the plan for correlative investigation is probably necessary during the study.

All correlative research will be expressed in descriptive statistics.

15.1 Histological and molecular research

15.1.1 Genes related to the EGFR pathway

Currently, patients are not offered treatment with EGFR antibodies (i.e. cetuximab) when activating mutations of the *k-ras* are known. Testing for *k-/n-ras* mutations is clinical standard, and EGFR antibodies approved in *k-/n-ras* wild type patients, only. The predictive value of further mutations in the EGFR downstream effector pathway as *b-raf, PI3K* mutations is under discussion. [42]

For study inclusion criteria and the allocation to treatment arms, *b-raf* and *k-ras/n-ras* mutations are determined in paraffin embedded tumour material after macro-dissection and DNA extraction.

To address the question, further mutational analyses of the EGFR downstream molecules *(i.e PI3K)* are planned on the extracted DNA. This includes the analysis of marker mutations for cf DNA analysis and the comparison of typical tumor mutations before treatment. Additionally, EGFR copy number [43] will be determined after recruitment is completed. Therefore, paraffin embedded blocks will be stored for the correlative research at the central laboratory. Material: paraffin embedded material (primary tumour or metastases; blocks preferred)

15.1.2 Pathological response to treatment

Pathological response is used as an early endpoint for clinical trials in several indications and mostly associated with improved long term outcome. [44] Two further retrospective analyses confirmed an association between pathological complete remission (pCR) and overall survival is shown after resection of liver metastases that were pretreated with neoadjuvant chemotherapy. A 5 year overall survival of 75-76% was reported in patients with pCR in resected colorectal liver metastases compared to 33-56% without pCR. [45, 46] Both reports were not limited to patients with initially non-resectable liver metastases.

In the publication of Adam and co-workers, age (≤ 60 y), size (≤ 3 cm), low CEA (≤ 30 ng/ml) and response according to RECIST criteria were significantly associated with pCR.[45] Blazer et al found CEA (≤ 5), size (≤ 3 cm), and chemotherapy with oxaliplatin / bevacizumab / fluoropyrimidine were independently associated with pathological response. Regarding pathological *complete* response, there was no difference for the frequency of pCR with regard to the chemotherapy regimen (irinotecan vs. oxaliplatin, with/without bevacizumab). [46] In both studies, the frequency of pCR was low (3.8%-9%) [45, 46].

Pathological response on paraffin material will be assessed in a central pathological review using a scale with three categories [46] and reported according to radiological response, treatment arms and progression free survival. Material: paraffin embedded material from resected metastases (2 blocks from each metastasis, up to five metastases)

15.1.3 Hepatic toxicity

Treatment associated changes of hepatic tissue is described due to chemotherapy. Most common alterations are steatohepatitis and sinusoidal obstruction. [47, 48]

Steatohepatitis and sinusoidal obstruction with be determined in non-tumour liver tissue of resected patients.

Material: non-tumour liver tissue of resected patients (one paraffin embedded tissue block)

15.1.4 Tumour infiltrating lymphocytes

Tumour infiltrating lymphocytes were correlated with overall survival in colorectal cancer [49]and other tumours.[50] Recently, an association between tumour infiltrating lymphocytes measured by high resolution automated microscopy and response to systemic treatment was described.

In this study, tumour infiltrating lymphocytes will be measured in patients of whom paraffin embedded tumour material is available before from *metastases* before treatment start. Tumour infiltrating lymphocytes will be measured by the method of Halama et al [51] and correlated with response, progression free and overall survival.

Material: paraffin embedded metastatic tissue before treatment

15.1.5 Storage of remaining material

Blood and tumour blocks will be stored in the laboratories in a quality ensured tissue bank (see chapter 18). The use of this material is restricted to tumour or treatment associated research according to the protocol.

It will be ensured by the laboratory that paraffin embedded material can be sent back to the study site if it is requested for clinical questions, especially if further molecular test are planned as part of post protocol treatment.

In case of a final decision during the first 10 years after complete enrolment that no further translational research is planned, paraffin embedded material of patients who are alive of lost to follow up will be sent back to the study site. All material will be destroyed 15 years after complete enrolment.

15.1.6 Plasma

Plasma is collected to determine the frequency of cell free DNA. The individual driver mutation of colorectal cancer patients (e.g. KRAS/NRAS, P53) will be determined by the analysis of formalin fixed, paraffin embedded tissue (FFPE) derived from the tumor. These "marker mutations" will be monitored during chemotherapy for metastatic disease and correlated with radiological response to treatment. In case of recurrence/progression, a deeper analysis will be performed in order to detect "new" mutations (resistant clones) that were not detected at baseline. Newly detected mutations will be analyzed in a look-back procedure in stored plasma samples to determine the first occurrence.

15.2 Central review of imaging

Retrospective review of imaging can provide additional information on the resectability and inter-observer variability. In the CELIM study, a retrospective review confirmed that resectability could be improved. [21].

It is planned to collect the CT- (or MRI scans if applicable) from baseline and the assessments of the first six months for a retrospective review that includes resectability, intra- and inter-observer variability with the same method as in the CELIM study. These results will not have an influence on the actual treatment of the patients.

Material: CT (or MRI) scans of patients on DICOM format coded with patient number, at the time points baseline and planned tumour assessments.

15.3 Further correlative research

If the scientific background of the correlative research changed during the study, the protocol committee will decide on modifications of the mentioned investigations. Modifications may include especially further pathways associated with tumour growth or drug action or the cooperation with other study groups to share the material for joint projects limited to tumour genesis or resistance as well as drug action.

Additional projects will be submitted to the Ethics committee and, the coordinating investigator will organize a vote of all members of the protocol committee. In case of a written vote, no answer within four weeks will be regarded as abstention.

16 Ethical and regulatory consideration

16.1 Ethics Committee and notification to Authorities

This study is to be conducted in accordance with the ICH Note for Guidance on Good Clinical Practice (ICH, Topic E6, 1995) and the World Medical Association Declaration of Helsinki (Appendix 21).

Prior to initiation of the study, the study protocol will be submitted together with its associated documents to the relevant ethics committees and health authorities. The approval of the relevant ethics committee will be filed in the investigator study file and a copy in the study master file.

The study will only commence following provision of a written approval including the written documentation of the date of the meeting, constitution of the committee and voting members present at the meeting, and the version of the version / consent documents will be a precondition to initiate the study.

Any amendments to the protocol will be submitted to the relevant ethics committees and they will be informed about SAEs in accordance with national requirements.

The study protocol and any applicable documentation (patient information sheet and consent form, etc.) will be notified to authorities in accordance with the regulations of the countries involved in the study.

This study must be carried out in compliance with the protocol and in accordance with the sponsor's standard operating procedures. The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

16.2 Responsibilities of the investigator

The investigator is responsible to perform the clinical study in accordance with the clinical study protocol, the GCP guidelines, and the current law.

Beside obligations listed in the protocol elsewhere, the responsibilities of the investigator include:

- understanding of the properties of the study medication as described in the Summary of Product Characteristics (SmPC),
- to provide sufficient time and capacity to perform the clinical study,
- correct collection and documentation of study related data and reporting,
- provision of data for the sponsor, for the monitor, and for audits/inspections,
- ensuring strict confidentiality and requesting similar confidentiality from her/his staff concerning information about participants and information provided by the sponsor. Study documents provided by the sponsor (protocols, Investigator's Brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by the sponsor to the investigator may not be disclosed to others without direct written authorization from the sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial,
- providing financial disclosure.

The clinical investigator has full responsibility for the conduct of the clinical study in the study centre

The sponsor is responsible and will send the applications to the Ethics Committees and to the federal and local authorities.

16.3 Patient information

All patients participating in the study must have given his/her written informed consent after adequate information by the investigator before informed consent is obtained.
A patient information form in the local language and prepared in accordance with the ICH Note for Guidance on GCP (ICH, Topic E6, 1995) will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to this written information, the investigator will inform the patient verbally. In doing so, the wording used will be chosen so that the information can be fully and readily understood by laypersons. The investigator must explain to each patient the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail.
Each patient must be informed that participation in the study is voluntary and that she/he may withdraw from the study at any time and that withdrawal of consent will not affect her/his subsequent medical treatment or relationship with the treating physician.
The patient should read and consider the statement before signing and dating it. (If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from one or more persons not involved in the study, mentioning why the patient was unable to sign the form. No patient can enter the study before his/her informed consent has been obtained.)

The patient information consent will be revised whenever important new information becomes available that may be relevant to the consent of patients.
The written informed consent of the patients to participate in the clinical study has to be given before any study-related activities are carried out. It must be signed and personally dated by the patient and by the investigator/ person designated by the investigator to conduct the informed consent discussion.
Provision of consent will be confirmed in the CRF by the investigator. The signed and dated declaration of informed consent will remain at the investigator's site and must be safely archived by the investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and consent should be provided to the patient prior to participation.
Any changes to the proposed consent form suggested by the investigator must be agreed to by the sponsor before submission to the ethic committee and a copy of the approved version must be provided to the CRO monitor after approval by the ethic committee.

16.4 Compensation to Patients

No compensation is planned.

16.5 Insurance

Insurance coverage is provided by the Sponsor for all patients enrolled in the study from the time of patient inclusion into the study (i.e. date of written informed consent):
Name Allianz VersicherungsAG
Police number AS-9100623801
Address 10900 Berlin

Phone 00 800 11 22 44 44

The insurance covers health impairments resulting from drugs and/or substances/investigational products administered in the course of the clinical trial for which the participant has given his/her written informed consent to participate. It covers also health impairments through measures carried out on the body of the person in connection with the clinical trial of a drug and/or substance/investigational product carried out in accordance with the study protocol procedures. The maximum coverage per patient is 500.000 €.
In order to ensure the cover, the study participants have to follow strictly the instructions of the study team. They are not allowed to undergo any other medical treatment without consent of the investigators (except emergencies).
In case of an emergency treatment they have to inform the investigator as soon as possible.
A health impairment that could possibly result from the study treatment has to be announced immediately to the investigator and to the insurance company.
Furthermore the participants are forced to take all appropriate measures to clarify cause and extensiveness of the damage occurred.
The conditions of the insurance are to be handed out to the participant together with his copy of the Informed Consent.

16.6 Privacy and confidentiality

Recording, storage, disclosure, and analysis of personal data of the patients within this clinical study are in accordance with legal requirements (i.e. national and country specific laws for data protection). The patient has to agree on the handling of his/her data within the informed consent form. The patient has to be informed i.e. about:

- data are recorded in electronically CRFs, will be handled confidentially, and disclosed to others (sponsor, local and federal authorities, independent ethical committee, European data bank) only pseudonymised.
- persons who are authorized by the sponsor and the authorities to monitor and inspect the clinical study can have insight into participant related data. These persons have to handle the data confidentially. The clinical investigator is dispensed from his/her medical confidentiality towards these persons.
- the written consent for data recording and documentation during this clinical study is irreversible. When a participant withdraws the written consent, all data that are documented so far can be used pseudonymised to analyse the effect of the study medication if needed.

16.7 Amendments

Any change or addition to this protocol requires a written protocol amendment that must be approved and signed by the sponsor and the investigator before implementation. Amendments significantly affecting the safety of patients, the scope of the investigation, or the scientific quality of the study require additional approval by the ethic committees, and by the health authorities (e.g. Paul-Ehrlich-Institute). A copy of the written approval of the ethic committee, which becomes part of the protocol, must be given to the monitor. Examples of amendments requiring such approval are:

- an increase in drug dosage or duration of exposure of patients,

- a significant change in the study design (e.g., addition or deletion of a control group),
- an increase in the number of invasive procedures to which patients are exposed,
- addition or deletion of a test procedure for safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by the sponsor in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented by him/her for safety reasons, the sponsor should be notified and the IEC at the centre should be informed within 10 working days. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IEC approval, but the IEC must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IEC approval include:

- change of persons involved in monitoring (e.g., sponsor staff versus a CRO),
- minor changes in the shipment of study material.

16.8 Publication

No single institution results of this multicenter study may be published, presented or distributed before the first publication of the primary study endpoint. Investigators who have contributed 8% or more of evaluable patients to that study, statistician, data manager and the principle investigator will be listed as authors. Further authorship, author order and number per centre depends on the number of patients enrolled in the trial and other significant contribution to the trial.

The coordinating investigator will prepare a draft manuscript within of 90 days after full analysis of the data base and distribute it to the co- authors who review the manuscript. If no comments are made, the manuscript will be submitted within 30 days to a major clinical journal.

17 References

1. Hoskins JM, Goldberg RM, Qu P, Ibrahim JG, McLeod HL. UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. J Natl Cancer Inst 2007;99(17):1290-1295.

2. Giacchetti S, Itzhaki M, Gruia G et al. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. Ann Oncol 1999;10(6):663-669.

3. Alberts SR, Horvath WL, Sternfeld WC et al. Oxaliplatin, Fluorouracil, and Leucovorin for Patients With Unresectable Liver-Only Metastases From Colorectal Cancer: A North Central Cancer Treatment Group Phase II Study. J Clin Oncol 2005;23(36):9243-9249.

4. Pozzo C, Basso M, Cassano A et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. Ann Oncol 2004;15(6):933-939.

5. Folprecht G, Grothey A, Alberts S, Raab HR, Köhne CH. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. Ann Oncol 2005;16(8):1311-1319.

6. Van Cutsem E, Köhne CH, Hitre E et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360(14):1408-1417.

7. Bokemeyer C, Bondarenko I, Makhson A et al. Fluorouracil, Leucovorin, and Oxaliplatin With and Without Cetuximab in the First-Line Treatment of Metastatic Colorectal Cancer. J Clin Oncol 2009;27(5):663-671.

8. Maughan T, Adams RA, Smith CG et al. Addition of cetuximab to oxaliplatin-based combination chemotherapy (CT) in patients with KRAS wild-type advanced colorectal cancer (ACRC): a randomised superiority trial (MRC COIN). Eur J Cancer Supplements 2009;7(3):4 (abstract 6LBA).

9. Douillard JY, Siena S, Cassidy J et al. Randomized, Phase III Trial of Panitumumab With Infusional Fluorouracil, Leucovorin, and Oxaliplatin (FOLFOX4) Versus FOLFOX4 Alone As First-Line Treatment in Patients With Previously Untreated Metastatic Colorectal Cancer: The PRIME Study. J Clin Oncol 2010;28(31):4697-4705.

10. Karapetis CS, Khambata-Ford S, Jonker DJ et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359(17):1757-1765.

11. Amado RG, Wolf M, Peeters M et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26(10):1626-1634.

12. Cunningham D, Humblet Y, Siena S et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351(4):337-345.

13. Folprecht G, Lutz M, Schöffski P et al. Cetuximab and irinotecan/5-fluorouracil/folinic acid is a safe combination for the first-line treatment of patients with epidermal growth factor receptor expressing metastatic colorectal carcinoma. Ann Oncol 2006;17(2):450-456.

14. Tabernero J, Van CE, az-Rubio E et al. Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2007;25(33):5225-5232.

15. Arnold D, Hohler T, Dittrich C et al. Cetuximab in combination with weekly 5-fluorouracil/folinic acid and oxaliplatin (FUFOX) in untreated patients with advanced colorectal cancer: a phase Ib/II study of the AIO GI Group. Ann Oncol 2008;19(8):1442-1449.

16. Venook A, Niedzwiecki D, Hollis D et al. Phase III study of irinotecan/5FU/LV (FOLFIRI) or oxaliplatin/5FU/LV (FOLFOX) {+/-} cetuximab for patients (pts) with untreated metastatic

adenocarcinoma of the colon or rectum (MCRC): CALGB 80203 preliminary results. J Clin Oncol (Meeting Abstracts) 2006;24(18_suppl):3509.

17. Khambata-Ford S, Garrett CR, Meropol NJ et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 2007;25(22):3230-3237.

18. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350(23):2335-2342.

19. Falcone A, Ricci S, Brunetti I et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol 2007;25(13):1670-1676.

20. Souglakos J, Androulakis N, Syrigos K et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). Br J Cancer 2006;94(6):798-805.

21. Folprecht G, Gruenberger T, Bechstein WO et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol 2010;11(1):38-47.

22. Folprecht G, Gruenberger T, Bechstein WO et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol 2009;doi:10.1016/S1470-2045(09)70330-4.

23. Van Cutsem E, Bokemeyer C, Heeger S, Sartorius U, Rougier P, Köhne CH. Outcome according to metastatic site in patients with *KRAS* wild-type tumors: Analysis from the CRYSTAL and OPUS studies. Proc Gastrointest Canc Symp (ASCO/AGA/ASTRO/SSO) , abstract 472. 2011.
Ref Type: Abstract

24. Folprecht G, Schuette K, Stoehlmacher J, Goekkurt E, Trarbach T. Cetuximab and FOLFOXIRI: Dose-escalation study in previously untreated patients with metastatic colorectal cancer. Proc Gastrointest Canc Symp (ASCO/AGA/ASTRO/SSO) , abstract 480. 2010.
Ref Type: Abstract

25. Garufi C, Torsello A, Tumolo S et al. Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in colorectal liver metastases: POCHER trial. Br J Cancer 2010;103(10):1542-1547.

26. Samalin E, Desseigne F, Thezenas S et al. Final results of a multicenter phase II trial evaluating cetuximab in combination with FOLFIRINOX as 1st line treatment of metastatic colorectal cancer (mCRC) patients. Annals of Oncology 20[Suppl 7], abstract 0011. 2009.
Ref Type: Abstract

27. Masi G, Loupakis F, Salvatore L et al. Bevacizumab with FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinate) as first-line treatment for metastatic colorectal cancer: a phase 2 trial. Lancet Oncol 2010;11(9):845-852.

28. Di Nicolantonio F, Martini M, Molinari F et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol 2008;26(35):5705-5712.

29. De RW, Claes B, Bernasconi D et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol 2010;11(8):753-762.

30. Bokemeyer C, Kohne C, Rougier P, Stroh C, Schlichting M, Van Cutsem E. Cetuximab with chemotherapy (CT) as first-line treatment for metastatic colorectal cancer (mCRC): Analysis of the

CRYSTAL and OPUS studies according to KRAS and BRAF mutation status. J Clin Oncol (Meeting Abstracts) 2010;28(15_suppl):3506.

31. Tol J, Dijkstra JR, Klomp M et al. Markers for EGFR pathway activation as predictor of outcome in metastatic colorectal cancer patients treated with or without cetuximab. Eur J Cancer 2010;46(11):1997-2009.

32. Roth AD, Tejpar S, Delorenzi M et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. J Clin Oncol 2010;28(3):466-474.

33. Douillard JY, Oliner KS, Siena S et al. Panitumumab FOLFOX4 Treatment and RAS Mutations in Colorectal Cancer. N Engl J Med 2013;369(11):1023-1034.

34. Ciardiello F, Lenz HJ, Kohne CH et al. Treatment outcome according to tumor RAS mutation status in CRYSTAL study patients with metastatic colorectal cancer (mCRC) randomized to FOLFIRI with/without cetuximab. J Clin Oncol (Meeting Abstracts) 2014;32(15_suppl):3506.

35. Bokemeyer C, Kohne CH, Ciardiello F et al. Treatment outcome according to tumor RAS mutation status in OPUS study patients with metastatic colorectal cancer (mCRC) randomized to FOLFOX4 with/without cetuximab. J Clin Oncol (Meeting Abstracts) 2014;32(15_suppl):3505.

36. Heinemann V, Fischer von Weikersthal L, Decker T et al. Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wildtype metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3). J Clin Oncol (Meeting Abstracts) 2013;31(15_suppl):LBA3506.

37. Falcone A, Cremolini C, Masi G et al. FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group. J Clin Oncol (Meeting Abstracts) 2013;31(15_suppl):3505.

38. Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19):1817-1825.

39. Smith TJ, Khatcheressian J, Lyman GH et al. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J Clin Oncol 2006;24(19):3187-3205.

40. Dindo D, Demartines N, Clavien PA. Classification of surgical complications. Ann Surg 2004;240(2):205-213.

41. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-247.

42. De Roock W, Claes B, Bernasconi D et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol 2010;11(8):753-762.

43. Moroni M, Veronese S, Benvenuti S et al. Gene copy number for epidermal growth factor receptor (EGFR) and clinical response to antiEGFR treatment in colorectal cancer: a cohort study. Lancet Oncol 2005;6(5):279-286.

44. Rubbia-Brandt L, Giostra E, Brezault C et al. Importance of histological tumor response assessment in predicting the outcome in patients with colorectal liver metastases treated with neo-adjuvant chemotherapy followed by liver surgery. Ann Oncol 2007;18(2):299-304.

45. Adam R, Wicherts DA, de Haas RJ et al. Complete pathologic response after preoperative chemotherapy for colorectal liver metastases: myth or reality? J Clin Oncol 2008;26(10):1635-1641.

46. Blazer DG, III, Kishi Y, Maru DM et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. J Clin Oncol 2008;26(33):5344-5351.

47. Rubbia-Brandt L, Audard V, Sartoretti P et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004;15(3):460-466.

48. Vauthey JN, Pawlik TM, Ribero D et al. Chemotherapy Regimen Predicts Steatohepatitis and an Increase in 90-Day Mortality After Surgery for Hepatic Colorectal Metastases. J Clin Oncol 2006;24(13):2065-2072.

49. Pages F, Berger A, Camus M et al. Effector memory T cells, early metastasis, and survival in colorectal cancer. N Engl J Med 2005;353(25):2654-2666.

50. Mahmoud SM, Paish EC, Powe DG et al. Tumor-Infiltrating CD8+ Lymphocytes Predict Clinical Outcome in Breast Cancer. J Clin Oncol 2011;29(15):1949-1955.

51. Halama N, Zoernig I, Spille A et al. Estimation of immune cell densities in immune cell conglomerates: an approach for high-throughput quantification. PLoS One 2009;4(11):e7847.

18 Appendix: Material shipment (Treatment start)

18.1 Paraffin embedded tissue

At the screening visit, tumour material (paraffin embedded, primary tumour, or – if available preferred - metastatic tissue) will be sent to:

PD Dr. Daniela E. Aust
Universitätsklinikum Carl Gustav Carus
Institut für Pathologie
Fetscherstr. 74
01307 Dresden

Tel.: +49 351 458 3004

daniela.aust@uniklinikum-dresden.de

Material will be shipped using the shipment form generated using the electronic CRF which provides the block number and patient number, but no other patient identifiers.

Upon arrival of the tissue blocks a paraffin section will be stained with H&E to affirm that tumour tissue is enclosed in the material sent. Tumour and (if available) normal tissue will then be macro- or microdissected to enrich for tumour cells.
DNA will be stored at -20°C and will be available for translational research analyses, as well as RNA or material for RNA extraction.
Ten unstained slides will be stored for later immunohistochemistry.

18.2 Material for determination UGT1A1 polymorphism

Deleted, but 8 ml EDTA will be shipped at screening for translational research (see chapter 18.3)

18.3 Material for translational research

At screening 8 ml EDTA will be collected.
At the screening visit and at the evaluation visits (after 4, 8 and 12 cycles), plasma from 2x8 ml plasma (STRECK tubes) will be sampled
All samples are shipped at room temperature within 2 days to:

Prof. Dr. med. Christian Thiede
Universitätsklinikum Carl Gustav Carus
Medizinische Klinik I
Forschungslabor

Fetscherstr. 74
01307 Dresden

Tel.: +49 351 458 4680
christian.thiede@uniklinikum-dresden.de

19 Appendix: Shipment of resection material

Metastatic and non-metastatic liver tissue from resected patients will be collected to determine pathological response to treatment and potential treatment induced liver damage (i.e. steatosis/steatohepatitis, sinusoisidal obstruction).

For that purpose, the following material will be collected:

- from each of the two largest metastases:
  one paraffin embedded block from margin and
  one paraffin embedded block from the center of the metastasis
  (with description of the liver segment)
- non-tumour liver tissue: one paraffin embedded block

Tissue will be shipped for late to

PD Dr. Daniela E. Aust
Universitätsklinikum Carl Gustav Carus
Institut für Pathologie
Fetscherstr. 74
01307 Dresden

20 Appendix: Perioperative complications

according to Dindo, Demartines, Clavien, Ann Surg 2004 [40]

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

* Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks.

CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

21 Appendix: World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

21.1 Introduction

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

21.2 Principles for all medical research

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the

research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

21.3 Additional principles for medical research combined with medical care

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22 Trial insurance

- copy of the trial insurance –

23 Appendix: Patient informed consent

24 Appendix: SmPCs

25 Appendix: RECIST version 1.1

Eisenhauer et al, 2009 [41]

17 Appendix: Patient informed consent

Platzhalter für Briefkopf des jeweiligen Prüfzentrums

Patienteninformation – Version 2

CELIM2 Studie:
Cetuximab/FOLFIRI mit oder ohne Oxaliplatin und FOLFOXIRI mit oder ohne Bevacizumab als neoadjuvante Behandlung von nicht-resektablen kolorektalen Lebermetastasen

Sehr geehrte Patientin, sehr geehrter Patient,

bei Ihnen wurden Lebermetastasen eines Dick- oder Enddarmkrebses festgestellt. Zurzeit ist eine Operation der Lebermetastasen nicht möglich oder nicht sinnvoll und wird Ihnen daher eine Chemotherapie empfohlen.

Mit dieser Chemotherapie soll die Größe der Lebermetastasen soweit wie möglich verringert werden. Wir wissen, dass dann bei einem Teil der Patienten die Metastasen anschließend operiert werden können. Diese Operation verbessert die Aussichten bei Ihrer Erkrankung. Die Tumorerkrankung könnte sogar geheilt werden. Ob die Operation bei Ihnen persönlich anschließend möglich ist, lässt sich vor Behandlung nicht sicher vorhersagen. Und auch mit einer Operation sind Rezidive häufig.

Wir möchten Sie bitten, an einer Studie teilzunehmen, die diese Chemotherapie noch optimieren soll. Untersuchen möchten wir dabei, mit wie vielen Medikamenten der Tumor am besten verkleinert werden kann und die besten Chancen für die Operation bestehen.

Dabei werden Sie entweder eine Kombination aus drei oder vier Medikamenten erhalten. Die Behandlung mit vier Medikamenten könnte häufiger zu einem Schrumpfen der Metastasen und damit zu besseren Voraussetzungen für eine Operation führen, hat aber den Nachteil von erhöhten Nebenwirkungen.

Welche Medikamente sie genau erhalten und in welcher Dosierung wird aus den Untersuchungen von Blut- und Tumorproben bestimmt. Die Tumorproben sollen nicht extra entnommen werden. Hierfür genügen die bereits vorhandenen Proben, in denen der Dickdarmkrebs bei Ihnen festgestellt wurde.

An den Tumorproben werden bestimmte Veränderungen (Mutationen) untersucht. Sollte eine Mutation im k-ras vorhanden sein, ist eine Behandlung mit einem bestimmten Medikament (Cetuximab) nicht sinnvoll und Sie erhalten eine Medikamentenkombinationen *ohne* Cetuximab.
Ihr Prüfarzt kann entscheiden, ob er zusätzlich untersuchen möchte, ob eine b-raf Mutation vorhanden ist. Der Wert dieser Untersuchung ist zur Zeit nicht gesichert, so dass die Untersuchung nicht unbedingt notwendig ist..

Welche Behandlung wird Ihnen vorgeschlagen?

Nach dem Ergebnis der Gewebsuntersuchung erhalten Sie:

- wenn *keine* Veränderung am k-ras und am n-raf Gen vorliegt, entweder
  - Cetuximab und FOLFIRI (drei Krebsmedikamente) *oder*
  - Cetuximab und FOLFOXIRI (vier Krebsmedikamente)

- wenn das k-ras oder n-ras Gen verändert ist („Mutation“) entweder
  - FOLFOXIRI (drei Krebsmedikamente) *oder*
  - FOLFOXIRI und Bevacizumab (vier Krebsmedikamente)

Was heißen diese Begriffe?
- ***Cetuximab*** ist ein Antikörper, der sich gegen den EGF-Rezeptor richtet. Mit dem EGF-Rezeptor nehmen Darmkrebszellen, aber auch gesunde Zellen der Haut und der Darmschleimhaut bestimmte Wachstumsfaktoren auf.
- ***Bevacizumab*** ist ein Antikörper gegen Wachstumsfaktoren, die das Gefäßwachstum fördern. Wenn das Gefäßwachstum mit Bevacizumab behindert ist, wachsen Darmtumoren langsamer.
- ***FOLFIRI*** ist eine Abkürzung für **Fol**insäure und die zwei Chemotherapie-Medikamente 5-**F**U und **Iri**notecan
- ***FOLFOXIRI*** ist eine Abkürzung für **Fol**insäure und die drei Chemotherapie-Medikamente 5-**F**U, **Ox**aliplatin und **Iri**notecan

Wie ist der Ablauf der Behandlung?

Die Chemotherapie wird meist als ambulante Behandlung gegeben. Das bedeutet, dass Sie in die Ambulanz kommen, nach Ihren Nebenwirkungen befragt werden, die Blutwerte kontrolliert werden und Sie dann über mehrere Stunden die Medikamente erhalten. Eine Chemotherapie (5-FU) wird heute fast nur noch über eine Pumpe über Nacht gegeben. Diese Pumpe nehmen Sie mit nach Hause; sie muss zwei Tage später von der Nadel entfernt werden.

Wie oft ist die Behandlung?
Die Chemotherapie ist alle 2 Wochen geplant. Der Antikörper Bevacizumab wird mit der Chemotherapie gegeben.
Falls Sie Cetuximab erhalten: Cetuximab erhalten Sie jede Woche – abwechselnd mit der Chemotherapie und in der Woche zwischen zwei Chemotherapien.

Unabhängig von der Häufigkeit der Chemotherapie werden Sie aber gebeten, zur Kontrolle der Nebenwirkungen und der Blutwerte zwischen den Chemotherapien jeweils einmal in die Ambulanz zu kommen.

Der Erfolg der Chemotherapie wird – wie immer bei einer Chemotherapie – alle 8 Wochen mit CT-Untersuchungen kontrolliert. An diesen CT- Bilder werden anschließend in einer gemeinsamen Konferenz von Röntgenärzten, Internisten und Chirurgen beurteilt, ob Ihnen eine Operation der Lebermetastasen vorgeschlagen werden kann. Wenn die Operation nicht möglich ist, wird die Chemotherapie fortgesetzt.

Wie lange ist die Behandlung geplant?

Diese Art der intensiven Behandlung ist für insgesamt 12 Chemotherapie-Zyklen, also ca. ½ Jahr geplant. Sollte die Operation eher durchgeführt werden, wird Ihnen empfohlen werden, die verbleibenden Chemotherapien anschließend durchzuführen. Wenn nur noch ein oder zwei Chemotherapiezyklen gefehlt haben, wird auf diese verzichtet.

Wenn sich die Metastasen nach ½ Jahr weiterhin nicht operieren lassen, wird die intensive Chemotherapie in dieser Studie nicht fortgesetzt. Ihr Prüfarzt wird mit Ihnen dann verschiedene Möglichkeiten besprechen, zu denen z.B. andere Formen der Behandlung der Lebermetastasen, eine reduzierte Chemotherapie oder eine Chemotherapiepause gehören können.
Diese Behandlungen gehören dann nicht mehr zur Studie. Wir möchten aber für unsere Studie erfassen, welche weiteren Behandlungen Sie anschließend erhalten.

Was bedeutet die Anwendung der Chemotherapie für Sie?
Mit welchen Nebenwirkungen der Chemotherapie haben Sie zu rechnen?

Gemeinsame Nebenwirkungen der Chemotherapie FOLFIRI
(Diese Medikamente erhalten Sie auf jeden Fall)

Alle Medikamente führen zu einem Abfall der weißen Blutkörperchen, der roten Blutkörperchen und der Blutplättchen (Häufigkeit ca. 15 %).
Der Abfall der weißen Blutkörperchen äußert sich in einer stärkeren Neigung zu Infektionen und kann selten zu einer Infektion mit Fieber bei stark eingeschränkter Körperabwehr führen. Da diese lebensbedrohliche Komplikation sofort mit Antibiotika behandelt werden muss, sollten Sie bei Fieber in der Zeit der Chemotherapie immer sofort zum Prüfarzt gehen.
Die Verminderung der Blutplättchen kann zu einer erhöhten Blutungsneigung führen. Dadurch und durch die Verminderung der roten Blutkörperchen kann eine Blutübertragung notwendig werden.

Schwäche und Abgeschlagenheit.
Die meisten Patienten fühlen sich in den ersten Tagen nach der Chemotherapie müde und abgeschlagen, und schlafen in den ersten Tagen nach der Chemotherapie mehr. Dieses Gefühl nimmt häufig nach jeder Chemotherapie etwas mehr zu.

Übelkeit und Erbrechen
Nach jeder Chemotherapie kann Übelkeit, Erbrechen und Appetitlosigkeit auftreten. Durch neuere Medikamente kann ein Erbrechen oft verhindert werden. Viele Patienten haben nach der Chemotherapie für einige Tage einen verminderten Appetit.

Durchfall (Häufigkeit leicht > 50%, schwer 15-30 %)
Alle Medikamente können zu einem heftigen Durchfall führen. Da dieser Durchfall ausgesprochen heftig und selten auch lebensbedrohlich verlaufen kann, sollten Sie spätestens bei Durchfall über 6 x pro Tag unbedingt sofort einen Prüfarzt aufsuchen.

Schleimhautschädigung (ca. 10 %)
Es kann zu einer Schädigung der Schleimhäute kommen, die sich besonders in einem Brennen im Mund bei schärferen Speisen äußern kann. Bei einigen Patienten kann durch das Essen und Trinken behindert sein. Sollte dies bei Ihnen auftreten, sollten Sie sich bei Ihrem behandelnden Prüfarzt vorstellen.
Die Schleimhautschädigung kann sich auch durch eine trockene Nase und Nasenbluten, sowie an den Genitalien zeigen.

Haarausfall
Alle Medikamente können prinzipiell zu einem Haarausfall führen. Bei der hier verwendeten Chemotherapie ist ein vollständiger Haarausfall bis zu 10 % möglich. Nach einem Ende der Chemotherapie wachsen die Haare nahezu immer nach.

Hand-Fuß- Syndrom (durch 5-FU, ca. 2 %)
Es kann eine schmerzhafte Rötung der Hand- und Fußflächen auftreten, die selten mit einem „Schälen“ der Haut verbunden ist.

Nebenwirkungen auf das Herz (durch 5-FU, unter 1 %)
Es können (durch 5-FU) Verkrampfungen der Herzkranzgefäße auftreten. Dies führt zu Symptomen wie bei einem Herzinfarkt (heftige Schmerzen im Brustkorb und im linken Arm, selten auch Schmerzen im Unterkiefer oder im Oberbauch, auftretende Luftnot). In diesem Fall sollen Sie umgehend einen Arzt rufen.

"Akutes cholinerges Syndrom" (Häufigkeit ca. 1 %)
Bei einigen Patienten treten während oder direkt nach der Gabe von Irinotecan Augentränen, Speichelfluss und Durchfall auf. Diese Nebenwirkungen lassen sich durch ein Gegenmittel (Atropin) relativ gut behandeln.

Nervensystem
Sehr selten kann die Koordination gestört sein („zerebelläre Ataxie") oder kann durch die Medikamente die Krampfneigung zunehmen.

Sie dürfen während der Zeit einer Behandlung mit 5-FU auf keinen Fall die Herpes-Medikamente Brivudine oder Sorivudine einnehmen.

Nebenwirkungen der Medikamente, die nur ein Teil der Patienten erhält

Oxaliplatin
(Sie erhalten Oxaliplatin zusätzlich, wenn Sie **FOLFOXIRI** bekommen.)

Kälteempfindlichkeit (besonders: Hände/Gesicht/Rachen, Häufigkeit ca. 30 %)
Eine typische Nebenwirkung von Oxaliplatin ist eine Kälteempfindlichkeit, die bei fast allen Patienten auftritt. Meist hält diese Kälteempfindlichkeit mit jeder Gabe des Medikaments etwas länger an. Dabei wird das Berühren von kalten Gegenständen oder der Kontakt mit kalter Luft als unangenehm oder auch als schmerzhaft empfunden. Kalte Getränke können zu dem Gefühl von Luftnot führen. Wenn Sie sich in den Tagen nach der Chemotherapie zum Beispiel durch Handschuhe vor Kälte schützen, können Sie diese Nebenwirkung deutlich vermindern.

Nervenschädigung: Gefühlsstörung (Häufigkeit ca. 30 %)
Oxaliplatin führt zu einem Taubheitsgefühl, das besonders an den Fingern und Zehen auftritt, das im Laufe der Behandlung zunimmt. Es bildet sich nach Ende der Behandlung langsam wieder zurück.

Besonders Blutbildveränderungen, Übelkeit und Erbrechen sowie die Abgeschlagenheit nach der Chemotherapie können mit Oxaliplatin noch stärker auftreten.

Antikörper Cetuximab
(Sie erhalten den Antikörper nur, wenn Ihr Tumor keine Veränderung am k-ras oder n-ras Gen hat.)

Hautveränderungen:
Es treten oft akneähnliche Hautveränderungen (Grad 3 13%, mildere Formen 84%) auf, die sich meist im Laufe der Behandlung bessern und nach einem Absetzen des Medikamentes zurückbilden. Insbesondere am Anfang der Behandlung kann die Akne sehr stark ausgeprägt sein. Sie tritt insbesondere im Gesicht und am Oberkörper auf.
Die Akne bildet sich meistens im weiteren Verlauf zurück. Es tritt dann öfters eine trockene, schuppige Haut auf.
Im Laufe der Behandlung treten öfter Entzündungen des Nagelbetts auf (keine schweren Formen, mildere Formen 35%). Diese kann man durch äußerlich anzuwendende Medikamente (Cremes und Salben) oft gut behandeln. Selten ist eine Antibiotikagabe oder chirurgische Mitbehandlung notwendig. Patienten mit mehr Hautnebenwirkungen haben meist einen günstigeren Krankheitsverlauf.
Von diesen Veränderungen kann auch die Haut an den Augen betroffen werden

Überempfindlichkeits-/ allergische Reaktionen (1-3%)
Sie können in Form von Ausschlägen, Medikamentenfieber, Nesselsucht (Urticaria) oder in seltenen Fällen in Form einer schweren allergischen Reaktion mit lebensbedrohlichem Schockzustand auftreten, die das sofortige Eingreifen eines Arztes erfordert. Um eine allergische Reaktion zu vermeiden, wird der Prüfarzt Ihnen vor der ersten Cetuximab-Infusion ein Allergie-Medikament verabreichen.

In der Kombination mit Chemotherapie kann es zu häufigerem Auftreten von Durchfall und Entzündungen der Schleimhäute (Stomatitis) kommen. Außerdem kann oft ein Magnesiummangel gemessen werden.

Antikörper Bevacizumab
(Sie erhalten den Antikörper unter Umständen, wenn Ihr Tumor eine Veränderung am k-ras oder n-ras Gen hat.)

Der Antikörper wirkt gegen die Neubildung von Blutgefäßen und am Kreislaufsystem. Die meisten Patienten spüren wenige Nebenwirkungen.
Auftreten können aber: Wundheilungsstörungen, Bluthochdruck, Herzinfarkt / Schlaganfall (selten), Herzinsuffizienz, Nierenschädigung (Ausscheidung von Eiweiß über die Niere), Magen-/ Darmdurchbruch (selten), Blutungen am Tumor oder andere Blutungen (z.B. Nasenbluten), arterielle Thromboembolien, Thrombosen, Müdigkeit und Abgeschlagenheit, selten Infusionsreaktionen.

Wodurch unterscheidet sich die Behandlung innerhalb der Studie mit der sonst üblichen Standard-Chemotherapie

1) Die Entscheidung, ob Sie drei oder vier Krebsmedikamente erhalten, wird per Zufall durch einen Computer in Dresden entschieden und nicht durch Sie oder Ihre(n) behandelnde(n) Ärztin/Arzt. Dies ist ein wissenschaftlich anerkanntes Prinzip und nennt sich Randomisation. Wenn Sie also einwilligen, im Rahmen dieser Studie behandelt zu werden, haben Sie eine 50%ige Chance, die eine oder andere Therapie (drei oder vier Medikamente) zu bekommen.
2) Die Verlaufsuntersuchungen werden nach einem festen Plan („Studienprotokoll“) durchgeführt. Um die Studie besser auswerten zu können, sind die Verlaufsuntersuchungen, wie Computertomografie (CT) oder Blutabnahmen genauer geplant. Die CT- Untersuchungen gehen nicht über das übliche Maß (alle 8 Wochen) hinaus. Sie werden auch zu Ihrer Sicherheit gebeten, zu den Verlaufsuntersuchungen zu kommen.
3) Falls Sie nicht nach Abschluss der Studie ohnehin weiter in unserer Behandlung sind, werden Sie oder Ihr Hausarzt in ¼- jährlichen Abständen angerufen oder angeschrieben, um Ihren Gesundheitszustand zu erfragen. Dabei möchten wir auch spätere Behandlungen wissen und in unserer Studie erfassen.
4) Wir erfassen Daten zu Ihrer Tumorerkrankung, der Behandlung und den Ergebnissen/ Nebenwirkungen und Daten zu Ihrer Person. Diese Daten werden pseudonymisiert, das bedeutet verschlüsselt in einem Computersystem gespeichert und computergestützt ausgewertet. Die entsprechenden Hinweise entnehmen Sie bitte dem gesonderten Blatt über den Datenschutz. Wenn Sie der Datenschutz- Vereinbarung nicht zustimmen, können Sie an der Studie nicht teilnehmen.
5) Ihre CT- Bilder werden eingeschickt.
6) Zusätzlich zu der Bestimmung des k-ras und b-raf- Mutation erfolgen zu wissenschaftlichen Zwecken weitere Untersuchungen des Metastasengewebes und des anhängenden Lebergewebes. Das Ziel ist, bei zukünftigen Patienten die Wirksamkeit und die Nebenwirkungen der Chemo- und Antikörpertherapie besser vorhersagen zu können. Dazu werden auch genetische Untersuchungen durchgeführt. Hierzu erhalten Sie aber eine gesonderte Einwilligungserklärung.
7) Ferner wird parallel zu jeder CT-Untersuchung eine Blutabnahme zu wissenschaftlichen Zwecken durchgeführt. Auch hierzu können Sie gesondert einwilligen.

Welchen persönlichen Nutzen haben Sie von der Teilnahme an der Studie?

Wenn Sie eine Medikamentenkombination mit vier Medikamenten erhalten, vergrößert sich möglicherweise Ihre Chance, dass die Lebermetastasen im Anschluss an die Chemotherapie vollständig entfernt werden können.
Dem können größere Nebenwirkungen der Chemotherapie entgegenstehen.
Die Ergebnisse dieser Studie können aber möglicherweise dazu beitragen, die Behandlung von Darmkrebspatienten zukünftig zu verbessern und die Heilungschancen zu erhöhen.

Welche anderen Behandlungsmöglichkeiten gibt es?

Eine Operation der Lebermetastasen ist bei Ihnen derzeit nicht möglich. In Ihrer Situation sind andere Verfahren, bei denen die Lebermetastasen komplett zerstört werden (z. Bsp. mit Radiowellen [„Radiofrequenzablation, RFA"] oder eine gezielte Bestrahlung) sind in der Regel dann technisch ebenfalls nicht möglich. Ob bei Ihnen eine Ausnahme vorliegt, können Sie mit Ihrem Prüfarzt besprechen. Gelegentlich werden Chemotherapie oder radioaktive Medikamente (SIRT, selektive interne Radiotherapie) über die Leberarterie gegeben. Diese Verfahren sind in Ihrer Situation nicht generell empfohlen. Etwas häufiger werden diese Verfahren eingesetzt, wenn die normale Chemotherapie nicht mehr wirksam ist. Vor Beginn der Behandlung wurden Ihre Befunde in einem Tumorboard besprochen. Bei dieser Diskussion werden die genannten Alternativen mit berücksichtigt. Ihr Prüfarzt kann Ihnen gegebenenfalls erläutern, ob eines dieser Verfahren für Sie in Frage kommt.
Das Ziel der Chemotherapie ist es jedoch, eine Schrumpfung der Metastasen zu erreichen, um eventuell anschließend eine Operation zu ermöglich. Dieses Ziel kann mit keinem der anderen genannten Verfahren erreicht werden.

Wer führt die Studie durch?
Die Studie wird an ca. 15-20 Kliniken in Deutschland und Österreich durchgeführt. Insgesamt werden ca 250 Patienten an der Studie teilnehmen. Der Auftraggeber nach Deutschem Arzneimittelgesetz ist die Technische Universität Dresden, Studienleiter ist PD Dr. Gunnar Folprecht.

Wie wird die Studie finanziert?
Die üblichen Kosten für die Behandlung (Chemotherapie und begleitende Medikamente, Untersuchungen, ärztliche Betreuung etc.) werden - wie auch außerhalb der Studie - von Ihrer Krankenversicherung übernommen. Alle Medikamente sind auch zur Behandlung von Darmkrebs zugelassen.
Zusätzliche Kosten für sonst nicht anfallende Untersuchungen, die zusätzliche Laboruntersuchungen, die Dokumentation im Studiensekretariat, Kontrollen der Sicherheit etc. werden den Kliniken von der TU Dresden erstattet. Hierfür steht der Technische Universität eine Forschungsförderung der Firma Merck zur Verfügung. Die behandelnden Prüfärzte erhalten durch die Durchführung der Studie keinen persönlichen finanziellen Vorteil.
Ihnen als Patient entsteht durch die Behandlung innerhalb der Studie kein finanzieller Nachteil.

Wichtige Hinweise

1. **Verhalten bei Durchfall:**
   Bei Durchfall nehmen Sie sofort 2 Tabletten Loperamid, dann alle 2 Stunden 1 Tablette, bis 8 Stunden kein Durchfall mehr aufgetreten ist. Trinken Sie reichlich und melden Sie sich möglichst am gleichen, spätestens am nächsten Tag bei ihrem behandelnden Arzt.

2. **Verhalten bei Fieber**
   Stellen Sie sich bitte möglichst am gleichen Tag bei Ihrem behandelnden Arzt vor.

3. **Verhalten bei Herzschmerzen**
   Rufen Sie den Notarzt, weisen Sie ihn auf die Chemotherapie mit 5-FU hin und unterbrechen Sie die 5-FU- Pumpe.

4. **Empfängnisverhütung**
   Frauen dürfen während der Teilnahme an dieser Studie nicht schwanger sein und nicht stillen, da die Medikamente einem ungeborenen Kind oder einem Säugling Schaden zufügen können. Bei Männern kann es zu einer Störung der Spermienbildung kommen.
   Aus diesem Grund müssen alle Patienten (Männer und Frauen) während der gesamten Behandlung, sowie für 12 Monate danach, eine wirksame Methode zur Empfängnisverhütung anwenden. Eine orale Empfängnisverhütung (sog. „Antibabypille“ ist als alleinige Verhütungsmaßnahme NICHT ausreichend, da eine zuverlässige Aufnahme im Magen-Darm-Trakt aufgrund der Therapienebenwirkungen (z.B. Durchfall) nicht immer gewährleistet ist. Ebenso ist die Anwendung eines Kondoms als alleinige Verhütungsmaßnahme NICHT ausreichend. Zu empfehlen ist eine Kombination mehrerer Verhütungsmethoden, z.B. orale Empfängnisverhütung und Kondom oder Spirale und Kondom.
   Dies trifft nicht für Frauen zu, die die Wechseljahre überschritten haben oder einen chirurgischen Eingriff hinter sich haben, der zur Sterilität führt. (z.B. Entfernung der Gebärmutter), sowie für Männer, deren die eine Partnerin jenseits der Wechseljahre bzw. mit den genannten chirurgischen Eingriffen haben.
   Die Empfängnisverhütung wäre allerdings auch bei einer Chemotherapie außerhalb der Studie notwendig.

   Beginn der Studie wird bei Frauen zusätzlich ein Schwangerschaftstest durchgeführt
   Sollten Sie Fragen haben, was eine sichere Empfängnisverhütung ist, fragen Sie bitte Ihren Prüfarzt.
   Sollte während der Behandlung eine Schwangerschaft auftreten, ist Ihr Prüfarzt umgehend zu informieren.

   Sollten Sie hierzu Fragen haben, wenden Sie sich bitte an Ihren behandelnden Arzt.

5. **Freiwilligkeit**
   Ihre Teilnahme an der Studie ist freiwillig. Sie können die Teilnahme an der Studie zu jedem Zeitpunkt abbrechen, ohne dass Ihnen davon Nachteile entstehen.
   Sie sollten diesen Entschluss aber Ihrem Prüfarzt mitteilen und ihn über mögliche Probleme, die während der Studienteilnahme bei Ihnen auftraten, informieren. Er wird Sie dann bitten, zu einer Abschlussuntersuchung zu kommen. Diese Untersuchung ist nicht zwingend vorgeschrieben, wird aber empfohlen, um gegebenenfalls studienbedingte Gesundheitsschäden aufzudecken und den Versicherungsschutz nicht zu gefährden. Ihr Prüfarzt wird andere Behandlungsmöglichkeiten Ihrer Erkrankung mit Ihnen besprechen.

   Daten, die bis zu diesem Zeitpunkt erfasst wurden, können auf Grund von gesetzlichen Bestimmungen nicht gelöscht werden.

6. **Vorzeitige Beendigung**

   Sie können aber auch aus der klinischen Prüfung ausgeschlossen werden, wenn es medizinische oder organisatorische Gründe notwendig machen.
   Sollte Ihr Prüfarzt zu der Überzeugung gelangen, dass eine Beendigung der klinischen Studie in Ihrem Interesse sei, wird er dies mit Ihnen besprechen und Ihre Teilnahme beenden. Weiterhin ist ein vorzeitiger Studienabbruch möglich, falls die Prozeduren, die in diesem

Informationsblatt beschrieben worden sind, nicht korrekt befolgt wurden und dadurch Ihre Sicherheit gefährdet sein könnte.
Weiterhin kann der Auftraggeber der Studie oder die Bundesoberbehörde die gesamte klinische Prüfung (für alle Teilnehmer) beenden.
Wird lediglich die Einnahme des neuen Medikaments/ der Prüfmedikation abgebrochen, werden Sie gebeten, auch weiterhin an den Nachfolgeuntersuchungen teilzunehmen.
In allen genannten Fällen einer vorzeitigen Beendigung der Studie werden Sie zu Ihrer Sicherheit abschließend medizinisch untersucht.

Wie sind Sie während Ihrer Teilnahme an dieser klinischen Prüfung versichert?

Für die Teilnehmer an dieser klinischen Prüfung wurde eine gesetzlich vorgeschriebene Versicherung abgeschlossen bei der

Allianz VersicherungsAG,
10900 Berlin
(Versicherungsschein AS-9100623801)
Tel 00 800 11 22 44 44).

Diese Versicherung deckt alle Schäden, die Ihnen durch Maßnahmen der Studie entstehen. Von dieser Versicherung ausgeschlossen sind allerdings Gesundheitsschäden und Verschlimmerungen bereits bestehender Erkrankungen, die auch dann eingetreten wären oder fortbestünden, wenn Sie nicht an der Untersuchung teilgenommen hätten.

Eine Kopie der allgemeinen Versicherungsbedingungen wird Ihnen Ihr Prüfarzt übergeben.

Um den Versicherungsschutz nicht zu gefährden. beachten Sie bitte insbesondere folgende Punkte:
Die Versicherung tritt nur für Schadensfälle ein, solange Sie sich als Studienteilnehmer genau an die Anweisungen Ihres Prüfarztes halten. Zu Ihren Pflichten gehören das strikte Einhalten der ärztlichen Anweisungen und die sofortige Meldung jeder Nebenwirkung und jeder Gesundheitsschädigung, die als Folge der klinischen Prüfung eingetreten sein könnte. Um den Versicherungsschutz nicht zu gefährden, dürfen Sie sich einer medizinischen Behandlung nur nach Rücksprache mit Ihrem behandelnden Prüfarzt unterziehen (Notfälle ausgenommen) und müssen jede Änderung, insbesondere aber eine Verschlechterung Ihres Gesundheitszustandes, die als Folge der klinischen Prüfung aufgetreten sein könnte, unverzüglich dem Versicherer schriftlich mitteilen. Gleichzeitig sollten Sie sich an Ihren behandelnden Prüfarzt wenden. Ihr Prüfarzt wird daraufhin sofort mit der Versicherungsgesellschaft Kontakt aufnehmen, so dass Fragen unverzüglich geklärt werden können. Im Schadensfall werden auch Ihre personenbezogenen versicherungsrelevanten Daten an den Versicherer gemeldet.

Fragen

Sollten Sie weitere Fragen bezüglich der klinischen Prüfung haben, wenden Sie sich bitte an den Ihren Prüfarzt:

Prüfarzt:

Adresse:
Telefon:

Bei Fragen zu klinischen Prüfungen können Sie sich auch an die zuständige Bundesoberbehörde wenden:

Paul Ehrlich Institut (PEI), Referat Klinische Prüfungen, Paul-Ehrlich-Str. 51-59, 63225 Langen, Telefon +49 6103 77 1810, Fax +49 6103 77 1277.

Bei Fragen zur vorliegenden Studie geben Sie bitte die sogenannte EudraCT-Nummer 2011-003288-31 an, unter der die Studie bei den Behörden registriert ist.

Platzhalter für Briefkopf der entsprechenden Klinik

CELIM2 Studie:
Cetuximab/FOLFIRI mit oder ohne Oxaliplatin und FOLFOXIRI mit oder ohne Bevacizumab als neoadjuvante Behandlung von nicht-resektablen kolorektalen Lebermetastasen

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Einwilligungserklärung in die Teilnahme an der klinischen Prüfung

Patient: _____
Name (durch Patienten selbst einzutragen) Vorname geb.

Ich wurde durch

(Name u. Vorname des aufklärenden Arztes sowie Anschrift der durchführenden Institution)

umfassend über die klinische Prüfung mit dem o. g. Titel aufgeklärt.

Ich hatte die Gelegenheit und ausreichend Zeit, Fragen zu stellen. Diese wurden zufriedenstellend, verständlich und vollständig beantwortet. Ich hatte ausreichend Bedenkzeit, eine Entscheidung über meine Teilnahme zu treffen.

Zusätzlich zu der schriftlichen Information wurden folgende Punkte besprochen:

_____

_____

_____

Ich wurde darauf hingewiesen, dass meine Teilnahme an der klinischen Prüfung freiwillig ist und dass ich das Recht habe, diese jederzeit ohne Angabe von Gründen zu beenden, ohne dass mir dadurch Nachteile entstehen.

Ich wurde ausführlich – mündlich und schriftlich – über das Ziel und den Verlauf klinischen Prüfung, Chancen und Risiken der Behandlung, meine Rechte und Pflichten sowie über die Freiwilligkeit der Teilnahme aufgeklärt und mir wurde zugesichert, dass diese Aufklärung vollständig war.

Ich habe die schriftliche Patienteninformation zur o. g. klinischen Prüfung erhalten, und ich werde nach meiner Unterschrift eine Kopie meiner unterschriebenen Einwilligungserklärung zur Teilnahme erhalten. Mit meiner Unterschrift bestätige ich dann auch, dass ich beide Dokumente gelesen und verstanden habe.

Ich weiß, dass ich gegen Schäden, die im Rahmen der klinischen Prüfung aufgetreten sind, versichert bin und ich habe eine Kopie der Allgemeinen Versicherungsbedingungen erhalten.

Ein Ansprechpartner für eventuelle zukünftige Fragen wurde mir genannt.

Datenschutzerklärung

Mir ist bekannt, dass bei dieser klinischen Prüfung personenbezogene Daten, insbesondere medizinische Befunde, über mich erhoben, gespeichert und ausgewertet werden sollen. Die Verwendung der Angaben über meine Gesundheit erfolgt nach gesetzlichen Bestimmungen und setzt vor der Teilnahme an der klinischen Prüfung folgende freiwillig abgegebene Einwilligungserklärung voraus, d.h. ohne die nachfolgende Einwilligung kann ich nicht an der klinischen Prüfung teilnehmen.

1. Ich erkläre mich damit einverstanden, dass im Rahmen dieser klinischen Prüfung erhobene Daten, insbesondere Angaben über meine Gesundheit, in Papierform und auf elektronischen Datenträgern bei meinem Prüfarzt und in der Technischen Universität Dresden aufgezeichnet werden. Soweit erforderlich, dürfen die erhobenen Daten pseudonymisiert (verschlüsselt) weitergegeben werden:
    a. an den Sponsor (Technische Universität Dresden) oder eine von diesem beauftragte Stelle zum Zwecke der wissenschaftlichen Auswertung.
    b. im Falle unerwünschter Ereignisse: an den Sponsor (Technische Universität Dresden), an die jeweils zuständige Ethik-Kommission und die zuständige Bundesoberbehörde (Paul-Ehrlich-Institut) sowie von dieser an die Europäische Datenbank
2. Außerdem erkläre ich mich damit einverstanden, dass autorisierte und zur Verschwiegenheit verpflichtete Beauftragte des Sponsors (Technische Universität Dresden) sowie die zuständigen inländischen und ausländischen Überwachungsbehörden in meine beim Prüfarzt vorhandenen personenbezogenen Daten, insbesondere meine Gesundheitsdaten, Einsicht nehmen, soweit dies für die Überprüfung der ordnungsgemäßen Durchführung der Studie notwendig ist. Für diese Maßnahme entbinde ich den Prüfarzt von der ärztlichen Schweigepflicht.
3. Die Einwilligung zur Erhebung und Verarbeitung meiner personenbezogenen Daten, insbesondere der Angaben über meine Gesundheit, ist unwiderruflich. Ich bin bereits darüber aufgeklärt worden, dass ich jederzeit die Teilnahme an der klinischen Prüfung beenden kann. Im Fall eines solchen Widerrufs meiner Einwilligung, an der Studie teilzunehmen, erkläre ich mich damit einverstanden, dass die bis zu diesem Zeitpunkt gespeicherten Daten ohne Namensnennung weiterhin verwendet werden dürfen, soweit dies erforderlich ist, um
    a. Wirkungen des zu prüfenden Arzneimittels festzustellen,
    b. sicherzustellen, dass meine schutzwürdigen Interessen nicht beeinträchtigt werden,
    c. der Pflicht zur Vorlage vollständiger Zulassungsunterlagen zu genügen.
4. Ich erkläre mich damit einverstanden, dass meine Daten nach Beendigung oder Abbruch der Prüfung mindestens fünfzehn Jahre aufbewahrt werden, wie es die Vorschriften über die klinische Prüfung von Arzneimitteln bestimmen. Danach werden meine personenbezogenen Daten gelöscht, soweit nicht gesetzliche, satzungsmäßige Aufbewahrungsfristen entgegenstehen.
5. Ich bin über folgende gesetzliche Regelung informiert: Falls ich meine Einwilligung, an der Studie teilzunehmen, widerrufe, müssen alle Stellen, die meine personenbezogenen Daten, insbesondere Gesundheitsdaten gespeichert haben, unverzüglich prüfen, inwieweit die gespeicherten Daten für die in Nr. 3 a) bis c) genannten Zwecke noch erforderlich sind. Nicht mehr benötigte Daten sind unverzüglich zu löschen.

	ja	nein
Ich willige in die Behandlung im Rahmen der o. g. Studie ein.	☐	☐
Ich habe eine Kopie der Versicherungspolice erhalten.	☐	☐
Ich bin damit einverstanden, dass mein Hausarzt über die Behandlung im Rahmen der klinischen Studie informiert wird. Name des Hausarztes:_____	☐	☐
Ich habe die Datenschutzerklärung zur Kenntnis genommen und willige in diese ein.	☐	☐

Patient:

_____
Ort, Datum

_____
Unterschrift

Aufklärender Prüfarzt:

_____
Ort, Datum

_____
Unterschrift

_____

Anschließend auszufüllen:

Patientennummer:_____

Platzhalter für Briefkopf des jeweiligen Prüfzentrums

CELIM2 Studie:
Cetuximab/FOLFIRI mit oder ohne Oxaliplatin und FOLFOXIRI mit oder ohne Bevacizumab als neoadjuvante Behandlung von nicht-resektablen kolorektalen Lebermetastasen

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Aufklärung zur wissenschaftlichen Untersuchung der Tumor- und Blutproben

Sehr geehrte Patientin, sehr geehrter Patient,

durch die Patienteninformation über die allgemeine Teilnahme an dieser Studie wurden Sie bereits über die Erkrankung des kolorektalen Karzinoms und die Behandlungsmöglichkeit im Rahmen dieser Studie informiert.
Zusätzlich möchten wir Sie bitten, am wissenschaftlichen Begleitprogramm teilzunehmen. Es dient dazu, wissenschaftliche Erkenntnisse über die Behandlung des kolorektalen Karzinoms zu erlangen, um in Zukunft die Therapie besser auf die einzelnen Patienten auszurichten.

Hierzu möchten wir Sie um folgendes bitten:

1. Wir möchten das Material des Tumorblocks, an dem Ihr Darmkrebs festgestellt wurde, für weitere Untersuchungen nutzen können.
2. Wir möchten zu höchstens 4 Zeitpunkten, an denen Ihnen ohnehin Blut abgenommen wird, 2 zusätzliche Blutröhrchen abnehmen und untersuchen.
3. Wir möchten – falls Sie an der Leber operiert werden sollten – dieses Material zusätzlich untersuchen können.

Diese zusätzlichen Untersuchungen dienen nur wissenschaftlichen Zwecken und haben keinen Einfluss auf Ihre Behandlung.

Sie können die Teilnahme an dem wissenschaftlichen Begleitprogramm ablehnen, *ohne dass Ihnen daraus ein Nachteil entsteht.* Die Teilnahme an diesem Programm ist auch nicht zur Teilnahme an der Hauptstudie erforderlich.

Was möchten wir untersuchen?

1. Wir wissen bereits, dass Veränderungen im k-ras Gen und im n-raf Gen bestimmen, wie häufig ein Dickdarmtumor auf eine Behandlung bestimmten Medikamenten anspricht. Die Bestimmung dieser Veränderungen ist daher sogar vorgeschrieben, bevor das Medikament Cetuximab gegeben wird.
   Jetzt möchten wir untersuchen, ob es noch weitere Veränderungen im Erbgut gibt, durch die die Ergebnisse einer Behandlung besser vorhergesagt werden können. Dafür sind Untersuchungen am eigentlichen Erbgut (DNA) und an den „Arbeitskopien" des Erbguts, der RNA geplant. Diese Untersuchungen sind zum Teil vorgeplant und betreffen die Gene für weitere, mit dem k-ras/n-ras dem EGFR zusammenhängende Eiweiße.
   Außerdem möchten wir die Anzahl der Entzündungszellen in Ihrem Tumor untersuchen, um die Wechselwirkungen zwischen dem Immunsystem und dem Tumor weiter zu untersuchen.
2. An den Blutproben wollen wir mit sehr empfindlichen Methoden DNA des Tumors untersuchen, die von dem Tumor freigesetzt wird. Dabei wollen wir insbesondere herausfinden, wieviel von für den Tumor typischer DNA (zum Beispiel mit k-ras Veränderungen) messbar ist, und ob neue Veränderungen auftauchen.
3. An den Operationspräparaten der Leber möchten wir untersuchen, zu welchem Anteil der Tumor unter der Behandlung zurückgegangen ist. Zusätzlich möchten wir die Auswirkungen der Behandlung auf die gesunde Leber untersuchen.

Die wissenschaftlichen Erkenntnisse entwickeln sich schnell weiter, eine vollständige Analyse der Proben ist erst nach Abschluss der Studie sinnvoll – also mehrere Jahre, nachdem die Studie geplant wurde. Wir rechnen daher damit, dass der Forschungsplan für die Untersuchung der Blut- und Tumorproben im Laufe der Zeit angepasst werden muss, um dann noch aktuell zu sein und möchten Sie darum bitten, auch Untersuchungen im Rahmen eines geänderten Planes unter folgenden Voraussetzungen zuzustimmen:

- der Plan wurde mehrheitlich von einer festen Gruppe von Wissenschaftlern (das Protokollkomitee im Studienprotokoll) verabschiedet und
- der Plan wurde von der Ethikkommission befürwortet und
- alle Untersuchungen, die auch weitere Genuntersuchungen einschließen können, beziehen sich auf Eigenschaften des Darmtumors (einschließlich der Metastasen) oder haben einen unmittelbaren Zusammenhang mit der Reaktion des Körpers auf den Tumor oder einen unmittelbaren Zusammenhang mit der Medikamentenwirkung.

Wieviel Blut wird abgenommen?

Die zusätzlichen Blutproben umfassen insgesamt vier mal zwei Blutröhrchen a 8 ml, also insgesamt 64 ml. Dies sind weniger als 1.5% des im Körper vorhandenen Blutes. Diese Proben sollen mit abgenommen werden, wenn bei Ihnen ohnehin Blut abgenommen wird, damit Sie nicht extra gestochen werden.
Sollte wirklich eine extra Blutentnahme durchgeführt werden, kann es zu einem Bluterguss, Schwindel oder äußerst selten zu einer Nervenverletzung kommen.

Wird zusätzliches Gewebe entnommen?

Nein, es sollen nur die schon vorhandenen Gewebeblöcke untersucht werden, oder bei einer Leberoperation nur das ohnehin entnommene Gewebe eingeschickt werden.

Wo werden die Blut- und Tumorproben aufgehoben?

Die Tumorproben werden im Pathologischen Institut des Universtitätsklinikums Carl Gustav Carus in Dresden aufbewahrt. Falls Ihr Arzt die Proben noch einmal dringend benötigen sollte, um Sie weiterzubehandeln, werden die Tumorproben zurückgeschickt.
Die Blutproben werden im Hämatologischen Forschungslabor des Universitätsklinikums Carl Gustav Carus Dresden (Prof. Dr. Christian Thiede) aufbewahrt. Die Blutproben werden 15 Jahre nach Studienende vernichtet.

Erfahre ich von den Ergebnissen?

Die meisten Untersuchungen werden erst durchgeführt, wenn die Behandlung in der Studie für alle Patienten abgeschlossen ist und werden sich auf Eigenschaften des Tumors beziehen, bei denen wir erst herausfinden möchten, ob sie einen Einfluss auf die Behandlung haben *könnten*.
Eine Mitteilung der Einzelergebnisse ist daher nicht geplant.

Was passiert dann mit den Ergebnissen?

Wir möchten die Ergebnisse wie allgemein üblich als Sammelstatistiken in Fachzeitschriften veröffentlichen. Aus diesen Ergebnissen können keine Rückschlüsse auf einzelne Personen gezogen werden.

Wie sind meine Daten geschützt?
Bei allen Untersuchungen ist sichergestellt, dass deren Ergebnisse nur pseudonymisiert ausgewertet werden, also kein Rückschluss auf Ihre Person gezogen werden kann.

Habe ich einen Nachteil, wenn ich den zusätzlichen Blut- und Tumoruntersuchungen nicht zustimme?
Die Probeentnahmen dienen wissenschaftlichen Zwecken und sind mit keiner Therapieentscheidung verbunden. Sie können die Zusatzuntersuchungen ablehnen und dennoch ohne Nachteil an der Studie teilnehmen.

CELIM2 Studie:
Cetuximab/FOLFIRI mit oder ohne Oxaliplatin und FOLFOXIRI mit oder ohne Bevacizumab als neoadjuvante Behandlung von nicht-resektablen kolorektalen Lebermetastasen

EUDRACT 2011-003288-31

Einwilligungserklärung in das wissenschaftliche Begleitprogramm

Patient: _____
Name Vorname geb.
(durch Patienten selbst einzutragen)

Ich wurde durch

(Name u. Vorname des aufklärenden Arztes sowie Anschrift der durchführenden Institution)

umfassend über das wissenschaftliche Begleitprogramm mit dem o. g. Titel aufgeklärt.

Ich hatte die Gelegenheit und ausreichend Zeit, Fragen zu stellen. Diese wurden zufriedenstellend, verständlich und vollständig beantwortet. Ich hatte ausreichend Bedenkzeit, eine Entscheidung über meine Teilnahme zu treffen.

Zusätzlich zu der schriftlichen Information wurden folgende Punkte besprochen:

_____

_____

_____

Ich wurde darauf hingewiesen, dass meine Teilnahme an dem wissenschaftlichen Begleitprogramm freiwillig ist und dass ich das Recht habe, diese jederzeit ohne Angabe von Gründen zu beenden, ohne dass mir dadurch Nachteile entstehen.

Ich wurde ausführlich – mündlich und schriftlich – über das Ziel und den Verlauf des wissenschaftlichen Begleitprogramms, meine Rechte und Pflichten sowie über die Freiwilligkeit der Teilnahme aufgeklärt und mir wurde zugesichert, dass diese Aufklärung vollständig war.

Ich habe die schriftliche Patienteninformation zum o. g. wissenschaftlichen Begleitprogramm erhalten, und ich werde nach meiner Unterschrift eine Kopie meiner unterschriebenen Einwilligungserklärung zur Teilnahme erhalten. Mit meiner Unterschrift bestätige ich dann auch, dass ich beide Dokumente gelesen und verstanden habe.

Ich weiß, dass ich gegen Schäden, die im Rahmen des wissenschaftlichen Begleitprogrammes aufgetreten sind, versichert bin und ich habe eine Kopie der Allgemeinen Versicherungsbedingungen erhalten.

Ein Ansprechpartner für eventuelle zukünftige Fragen wurde mir genannt.

Datenschutzerklärung

Mir ist bekannt, dass bei dieser klinischen Prüfung personenbezogene Daten, insbesondere medizinische Befunde, über mich erhoben, gespeichert und ausgewertet werden sollen. Die Verwendung der Angaben über meine Gesundheit erfolgt nach gesetzlichen Bestimmungen und setzt vor der Teilnahme an der klinischen Prüfung folgende freiwillig abgegebene Einwilligungserklärung voraus, d.h. ohne die nachfolgende Einwilligung kann ich nicht an der klinischen Prüfung teilnehmen.

1. Ich erkläre mich damit einverstanden, dass im Rahmen dieser klinischen Prüfung erhobene Daten, insbesondere Angaben über meine Gesundheit, in Papierform und auf elektronischen Datenträgern bei meinem Prüfarzt und in der Technischen Universität Dresden aufgezeichnet werden. Soweit erforderlich, dürfen die erhobenen Daten pseudonymisiert (verschlüsselt) weitergegeben werden:
    a. an den Sponsor (Technische Universität Dresden) oder eine von diesem beauftragte Stelle zum Zwecke der wissenschaftlichen Auswertung.
    b. im Falle unerwünschter Ereignisse: an den Sponsor (Technische Universität Dresden), an die jeweils zuständige Ethik-Kommission und die zuständige Bundesoberbehörde (Paul-Ehrlich-Institut) sowie von dieser an die Europäische Datenbank
2. Außerdem erkläre ich mich damit einverstanden, dass autorisierte und zur Verschwiegenheit verpflichtete Beauftragte des Sponsors (Technische Universität Dresden) sowie die zuständigen inländischen und ausländischen Überwachungsbehörden in meine beim Prüfarzt vorhandenen personenbezogenen Daten, insbesondere meine Gesundheitsdaten, Einsicht nehmen, soweit dies für die Überprüfung der ordnungsgemäßen Durchführung der Studie notwendig ist. Für diese Maßnahme entbinde ich den Prüfarzt von der ärztlichen Schweigepflicht.
3. Die Einwilligung zur Erhebung und Verarbeitung meiner personenbezogenen Daten, insbesondere der Angaben über meine Gesundheit, ist unwiderruflich. Ich bin bereits darüber aufgeklärt worden, dass ich jederzeit die Teilnahme an der klinischen Prüfung beenden kann. Im Fall eines solchen Widerrufs meiner Einwilligung, an der Studie teilzunehmen, erkläre ich mich damit einverstanden, dass die bis zu diesem Zeitpunkt gespeicherten Daten ohne Namensnennung weiterhin verwendet werden dürfen, soweit dies erforderlich ist, um
    a. Wirkungen des zu prüfenden Arzneimittels festzustellen,
    b. sicherzustellen, dass meine schutzwürdigen Interessen nicht beeinträchtigt werden,
    c. der Pflicht zur Vorlage vollständiger Zulassungsunterlagen zu genügen.
4. Ich erkläre mich damit einverstanden, dass meine Daten nach Beendigung oder Abbruch der Prüfung mindestens fünfzehn Jahre aufbewahrt werden, wie es die Vorschriften über die klinische Prüfung von Arzneimitteln bestimmen. Danach werden meine personenbezogenen Daten gelöscht, soweit nicht gesetzliche, satzungsmäßige Aufbewahrungsfristen entgegenstehen.
5. Ich bin über folgende gesetzliche Regelung informiert: Falls ich meine Einwilligung, an der Studie teilzunehmen, widerrufe, müssen alle Stellen, die meine personenbezogenen Daten, insbesondere Gesundheitsdaten gespeichert haben, unverzüglich prüfen, inwieweit die gespeicherten Daten für die in Nr. 3 a) bis c) genannten Zwecke noch erforderlich sind. Nicht mehr benötigte Daten sind unverzüglich zu löschen.

	ja	nein
Ich willige in die wissenschaftlichen Untersuchungen der Blutproben ein.	☐	☐
Ich bin damit einverstanden, dass mein Hausarzt über die Behandlung im Rahmen der klinischen Studie informiert wird. Name des Hausarztes:_____	☐	☐
Ich willige in die rein wissenschaftlichen Untersuchungen der Tumorproben (auch nach der Operation) ein.	☐	☐
Ich habe die Datenschutzerklärung zur Kenntnis genommen und willige in diese ein.	☐	☐

Patient:

_____
Ort, Datum

_____
Unterschrift

Aufklärender Prüfarzt:

_____
Ort, Datum

_____
Unterschrift

_____

Anschließend auszufüllen:

Patientennummer:_____