Statistical Analysis Plan

MoLiMoR

Modulation of the FOLFIRI-based standard 1st-line therapy with cetuximab, controlled by monitoring the RAS mutation load by liquid biopsy in RAS-mutated MCRC patients

A randomized phase II study with FOLFIRI-based 1st-line therapy with or without intermittent cetuximab

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We, the undersigned, have read the Statistical Analysis Plan and agree that it contains all information required for statistical analysis of the data collected in the above-named non-interventional study.

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1 List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALAT	Alanine aminotransferase (also GPT for glutamate pyruvate transaminase)
ASAT	Aspartate aminotransferase (also GOT for glutamate oxaloacetate transaminase)
BEAM(ing)	Beads, emulsion, amplification, and magnetics (digital PCR)
(β-)HCG	(beta) Human chorionic gonadotropin
BRAF	B-rapidly accelerated fibrosarcoma
CA 19-9	Carbohydrate antigen 19-9
CEA	Carcinoembryonic antigen
CR	Complete response
(m)CRC	(metastatic) Colorectal cancer
(e)CRF	(electronic) Case report form
CRP	C-reactive protein
CT	Computer tomography
CTCAE	Common Terminology Criteria of Adverse Events (version 5.0)
ctDNA	Circulating cell-free tumor DNA
CTFG	Clinical Trail Facilitation Group
ddPCR	Droplet Digital PCR
DNA	Deoxyribonucleic acid
DPD	Dihydropyrimidine dehydrogenase
DpR	Depth of response
DSMB	Data and Safety Monitoring Board
EC	Exclusion criterium
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EOT	End of (study) treatment
(m)FOLFIRI	(modified) Folinic acid, 5-FU, and irinotecan
5-FU	Fluorouracil
GGT	Gamma-glutamyltransferase
IC	Inclusion Criterium
ICD(10)	International Statistical Classification of Diseases and Related Health Problems (10^{th} revision from 2010)
INR	International normalized ratio
(m)ITT	(modified) Intend-to-treat set
iv	intravenous
KRAS	Kirsten Rat Sarcoma Virus
LVEF	Left ventricular ejection fraction
mAB	Monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NRAS	Neuroblastoma RAS viral oncogene homolog
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression free survival
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
PP	Per-protocol
PR	Partial response
PT	Preferred terms

PTCA	Percutaneous transluminal coronary angioplasty
(a)PTT	(activated) Partial thromboplastin time
RAS(wt)	Rat sarcoma (wild-type)
RECIST	Response Evaluation Criteria in Solid Tumors (version 1.1)
SAE	Serious adverse event
SD	Stable disease
SmPC	Summary of medicinal Product Characteristics
SOC	System organ class
SP	Safety population
TLF	Tables, listings, and figures
TFTS	Time to failure of treatment strategy
TNM	Tumor, node, and metastases (classification of malignant tumors)
UICC	Union for International Cancer Control
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
WCRF	World Cancer Research Fund
WOCBP	Woman of childbearing potential

2 Introduction

2.1 Background

Colorectal cancer (CRC) is the third most common cancer worldwide and its therapeutic management strongly depends on the disease stage and the genetic profile of the tumor. Due to improved diagnosis and introduction of new therapies including targeting therapies with anti-epidermal growth factor receptor (EGFR) or anti-vascular endothelial growth factor (VEGF) treatments, the CRC death rates declined over the past three decades.

Differentiating between right-sided and left-sided CRC, multiple randomized studies have consistently shown that primary tumor location in the right side is associated with minor response to anti-EGFR therapy despite Rat sarcoma wild-type (RASwt) status. Hence, the treatment with EGFR antibodies in first-line therapy is recommended for left-sided primary tumors with RASwt only.

Retrospective analyses of patients with RASwt metastatic CRC (mCRC) from the phase III trials CRYSTAL and FIRE-3 show that the administration of standard first-line chemotherapy with fluorouracil, folinic acid, and irinotecan (FOLFIRI) together with the monoclonal antibody (mAB) cetuximab had a markedly better prognosis on progression free survival (PFS), overall survival (OS), and overall response rate (ORR).

2.2 Study design

This study is an open-label, prospective, randomized, and multicenter phase II trial that will evaluate the efficacy and safety of intermittent addition of cetuximab to a (modified) FOLFIRI-based first-line therapy to patients with RAS-mutant mCRC at diagnosis who convert to RASwt using monitoring of RAS mutation status by liquid biopsy. Maximum planned treatment duration amounts to 36 months with a total trial duration of 4.5 years.

3 Analysis data and patient populations

In this section the planned statistical analyses will be outlined in accordance with the study protocol and with respect to the underlying data. The statistical methods will be described in detail and the Mock-ups of the tables, listings, and figures (TLF) to be used in the statistical report will be defined.

3.1 Study objective

The aim of this randomized study is to evaluate whether patients with left-sides RAS-mutant mCRC at diagnosis will derive benefit from the adaption of adding cetuximab to the first-line therapy with FOLFIRI after RAS-mutation status has changed to wild-type and changing back

to FOLFIRI, as required, if RAS-mutation status has changed back to mutant, depending upon, and monitored by longitudinal ctDNA liquid biopsies.

3.2 Analysis populations

Modified Intention to Treat (mITT): All randomized patients who received at least 1 dose, complete or incomplete, of study medication.

Safety population (SP) = mITT population.

Per protocol (PP) population: All randomized patients who received study treatment according to randomization and did not have major disqualifying protocol violations, i.e., did not violate any selection criterion.

3.3 Patient withdrawal(s)

Patients will be encouraged to complete the study but may voluntarily withdraw from the study at any time. The investigator may also, with her/his discretion, withdraw the patient from participating in this study at any time, or the sponsor may discontinue the study. Reasons for early withdrawal from the study are documented in the electronic case report form (eCRF) as:

- Study closed/terminated,
- Patient is lost to follow-up,
- Patient died,
- Investigator's decision,
- Patient withdrew consent,
- Others such as medical advice or patient wish.

Patients withdrawn by withdrawal of informed consent, patient preference, or the investigator's decision, for reasons other than PD, will be defined as premature withdrawals.

3.4 Objectives

Primary objective:

- Evaluate efficacy in terms of PFS from the date of randomization in the study according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria in experimental and control arms.

Secondary objectives:

- OS in experimental and control arms from date of randomization,
- Time to failure of treatment strategy (TFTS) in experimental and control arms after randomization,
- PFS rate one year after date of randomization,
- Depth of response (DpR) in terms of reduction of tumor mass in experimental and control arms after of first-line treatment,
- Metastatic resections in experimental and control arms after first-line treatment,
- ORR defined as proportion of patients with partial response (PR) or complete response (CR) as best response in experimental and control arms after start of first-line treatment,
- Safety profile according to the National Cancer Institute's (NCI) Common Terminology Criteria of Adverse Events (CTCAE) version 5.0 criteria in experimental and control arms recorded from date of signature of informed consent.

Exploratory objectives (optional):

- To identify driver mutations (e.g., BRAF, PI3k/AKT/mTOR etc.) in patients with PD under cetuximab therapy who remain RASwt in liquid biopsy,

- To compare the efficacy in terms of PFS in patients with conversion to RASwt in both BEAMing (standing for beads, emulsion, amplification, and magnetics) digital polymerase chain reaction (PCR) and Digital Droplet PCR (ddPCR) with those patients showing conversion to RASwt in ddPCR but not in BEAMing.

4 Methods of analysis

4.1 Hypotheses

Initially, the hypothesis of this study was to show that the difference in PFS at twelve months between the experimental arm and control arm would amount to 20% meaning an increase from 30% to 50% (Hazard ratio = 0.5757). The estimated number of patients screened was 144 and the estimated number of randomized patients was 116.

4.2 Statistical methods

Due to the actual small number of patients enlisted (seven) the study enrollment was closed. Most analyses will therefore be based on listings. Summary statistics of continuous variables like mean, standard deviation, and quantiles will not be provided. Derived variables like ORR, OS, and PFS will be shown as well and for time-to-event variables Kaplan-Meier plots will be given. A swimmer plot showing the treatment and response timeline for each patient will be added. Each listing will show the patient number, the arm into which the patient was randomized, and all relevant variables.

There will be no differentiation between the analysis populations.

4.3 Statistical analysis

In a first table we give an overview:

- General data such as number of patients, number of participating clinics, and analysis populations (Table 1).

4.3.1 Baseline (anamnesis and one-time-only baseline examinations)

All background data of the patients including demographics, relevant concomitant diseases and medication, and baseline characteristics from pre-screenings which are performed only once will be listed by patient number. Other baseline examinations and laboratory assessments will be summarized together with the same recurring examinations and assessments, respectively. The following listings are planned here:

- Inclusion criteria (Listing 1.1 to Listing 1.3),
- Exclusion criteria (Listing 2.1 to Listing 2.4),
- Eligibility for study participation as well as enrollment for screening phase and randomization (Listing 3),
- Patient characteristics like age, ethnic origin, and gender (Listing 4),
- Initial diagnosis of mCRC (Listing 5.1 to Listing 5.3),
- Relevant diseases according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD10) catalog (Listing 6),
- Relevant premedication (Listing 7.1) and concomitant medication (Listing 7.2),
- Baseline echocardiography with left ventricular ejection fraction (LVEF) (Listing 8),
- Tumor, nodes, and metastases classification of malignant tumors (TNM) staging at baseline (Listing 9),
- Baseline coagulation parameters international normalized ratio (INR) and partial thromboplastin time (PTT) (Listing 10),
- Baseline dihydropyrimidine dehydrogenase (DPD) deficiency (Listing 11)
- Baseline hepatitis serology (Listing 12).

4.3.2 Randomization

All enrolled patients with conversion of mutant RAS as estimated centrally by liquid biopsy of cfDNA within the first 4 months (at week 4, 8, 12, or 16) and without PD as determined by CT scan will be randomized at week 8, for patients converting at week 4 or 8, and at week 16, for patients converting at week 12 or 16, directly after the CT scan in a 1:1 ratio to either experimental Arm A (switch arm) or control Arm B. Patients with PD before the randomization will not be considered for randomization.
The randomization into the respective treatment arm will be displayed together with the patient number in each listing.

4.3.3 Recurring examinations and lab assessments

Data gathered through examinations or assessments that are possibly not only performed at baseline such as electrocardiogram (ECG) as well as such that are planned in regular intervals including hematological and blood chemistry lab assessments, pregnancy tests, and tumor marker assessments are given here. An exception is the data obtained from RECIST assessments which belongs to the primary objective. The following listings will be included:

- Performed ECG assessments (Listing 13),
- Determined Eastern Cooperative Oncology Group (ECOG) performance statuses (Listing 14),
- Vital signs such as weight and heartrate (Listing 15),
- Hematological parameters hemoglobin, platelets, leukocytes, and neutrophils (Listing 16),
- Biochemical parameters including specific minerals, gamma-glutamyltransferase (GGT), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and C-reactive protein (CRP) (Listing 17.1 and Listing 17.2),
- Tumor marker parameters carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) (Listing 18),
- RAS mutation analyses performed on tumor tissue with possible detection of Kirsten Rat Sarcoma (KRAS) or neuroblastoma RAS viral oncogene homolog (NRAS) mutations (Listing 19),
- Taken blood samplings for liquid biopsy (Listing 20.1 and Listing 20.2),
- Beta human chorionic gonadotropin (β-HCG) pregnancy tests for women of childbearing potential (WOCBP) (Listing 21).

4.3.4 Study treatment

All data concerning treatment cycles and administered chemotherapeutic treatments will be listed by patient number. The following listings are planned:

- General information such as start date, cycle number, and possible resections (Listing 22.1),
- Specific data on administration of irinotecan (Listing 22.2), folinic acid (Listing 22.3), fluorouracil (5-FU) (Listing 22.4 and Listing 22.5), and cetuximab (Listing 22.6).

These listings will be accompanied by:

- A swimmer plot visualizing the treatment (changes) together with points in time of response for each individual study participant (Figure 1).

4.3.5 Primary objective

For the analysis concerning the primary objective the following three listings are given and considered for PFS:

- RECIST assessments (Listing 23.1) and observation of measurable and non-measurable (Listing 23.2) lesions via computer tomography (CT).

In addition,

- a listing containing PFS, OS, and TFTS (Listing 24)

will be created.
Furthermore,

- a Kaplan-Meier plot for PFS (Figure 2)

will be presented.

4.3.6 Secondary objectives (excluding safety)

Due to the small number of patients neither all secondary objectives will be analyzed, nor full Kaplan-Meier methods will be applied to time-to-event analyses. Only OS,TFTS, and ORR will be considered. The first two named will be shown in the listing containing the primary objective PFS above, and in addition two Kaplan-Meier plots will be presented:

- a Kaplan-Meier plot for OS (Figure 3)
- a Kaplan-Meier plot for TFTS (Figure 4)

The remaining derived variable, ORR, will be given in

- a table displaying responses to study treatment together with ORR (Table 2).

4.3.7 Exploratory objectives

Due to the small number of patients no explorative objective will be analyzed.

4.3.8 End of study treatment, follow-up visits, and end of study

Some data related to end of (study) treatment (EOT) or follow-ups such as AEs or lab assessments will already be listed in the corresponding listings. Remaining data will be included in the following listings:

- EOT with possible new tumor therapy (Listing 25),
- Follow-ups with changes to therapy (Listing 26.1) or performed surgeries (Listing 26.2),
- Date and reason for end of study (Listing 27).

4.3.9 Safety

Regarding the secondary objective safety, all adverse events (AEs) will be ordered by patient number and summarized in the following listings:

- Terminology and timeline of AE together with causality to study treatments as well as possible actions taken (Listing 28.1) and serious or special classification (Listing 28.2).

Optionally, if the number of AEs is sufficient, then the AEs will be analyzed in frequency tables including number of treatment-related AEs, number of AEs that cause permanent treatment discontinuation, system organ class (SOC) and preferred terms (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). The following tables will optionally be added:

- An AE overview (Table 4.1), number of AEs with respect to MedDRA grouping and NCI CTCAE grading (Table 4.2), and number of patients with AE by maximal grade with respect to MedDRA coding.

SAEs are classified as special if they involve pregnancy or medication error.

4.4 Methods for handling missing data

Missing data will not be imputed.

4.5 Methods for handling inconsistent data

Not applicable.

4.6 Methods for handling outliers

Outliners will not be excluded from analysis.

4.7 Methods for point and interval estimates

Not applicable.

4.8 Validation of statistical methods

Not applicable.

4.9 Methods for handling multicenter trial data

Patients from all study centers will be pooled and tabulated as a single target group.

4.10 Treatment interactions

There will be no analyses on treatment interactions, but interactions stated in the Summary of medicinal Product Characteristics (SmPC) of each study treatment are beside others:

- Folinic acid may increase the risk of toxicity associated with 5-FU which may be indicated by diarrhea or other gastrointestinal events; both must not be mixed for infusions.
- The combination of cetuximab and fluoropyrimidines such as 5-FU may increase risk of cardiac ischemia or hand-foot syndrome.
- There is no evidence that irinotecan and cetuximab influence each other. Further, the pharmacokinetic of irinotecan is not affected in combination with folinic acid and 5-FU.

4.11 Methods for handling repeated measurements

No formal repeated measures analysis will be performed.

4.12 Calculation of derived variables

First, we will clarify some notions regarding trial periods:

Baseline/pre-screening phase (within four weeks before start of treatment): First period of the trial where baseline examinations and baseline lab assessments are performed to confirm eligibility for study participation.

Screening/pre-randomization phase (begins with enrollment of patients and lasts for a maximum of sixteen weeks from start of standard first-line therapy with (m)FOLFIRI): Second period of the trial where conversion to RASwt is monitored and randomization is taking place if (early) conversions are confirmed.

Randomization/study treatment phase (begins with randomization and has a maximal duration of 36 months from start of first-line therapy): Third period where patients are treated with the respective study treatment according to their randomization into experimental Arm A or control Arm B.

Final assessment: Last assessment about four weeks after last treatment administration.

Follow-up: Time from last administration of study treatment until end of study

Pre-cycle: Notion for a treatment cycle in the pre-randomization phase.

Independent of the trail period, each (pre-)cycle has a duration of 14 days. The date of the eighth day of a cycle may be derived from given data as seventh day after the first day of that cycle.

Pre-medication: All medication before first administration of any study treatment, i.e., before first pre-cycle.

Primary and secondary derived variables are defined and calculated as follows:

PFS: Defined as being the time between date of randomization until date of progression according to RECIST v1.1 criteria or date of death from any cause, whichever occurs first. Any change in RAS mutation status without PD according to the RECIST criteria is not considered a PFS event. In patients without a PFS event, PFS will be censored on the last date they were known to be alive and progression-free (last valid tumor assessment) or at the start of a new anti-tumor therapy. Patients becoming eligible for surgery during study treatment will not be censored for PFS at this resection event.

OS: Defined as time from date of randomization until death from any cause. In patients without an OS event, OS will be censored on the last date they were known to be alive.

ORR: Defined as the proportion of randomized patients with CR or PR as best response since start of first-line therapy.

TFTS: Defined as the time from date of randomization to failure of treatment strategy, i.e., treatment discontinuation for any reason, including disease progression, withdrawal of consent, treatment toxicity, patient preference, loss to follow up, or death from any cause.

An AE will be called treatment-related if its occurrence is definitely, probably, or possibly related to the administration of any study treatment.

Note that a year is equal to 365 days, a month is equal to 30.4 days, and a week is equal to 7 days for duration calculations.

4.13 Use of baseline values

The staging results of RECIST tumor assessments including date of assessment, size(s) of target tumor(s), or number of metastases at baseline are used for PFS analysis.

4.14 Use of covariates

Not applicable.

4.15 Identification of fixed and random factors

Not applicable.

4.16 Subset analyses

No subgroup analyses are planned.

4.17 Interim and follow-up analyses

No interim analyses will be done due to the small number of participants. No follow-up analyses are planned.

4.18 Study stopping rules

The study may be discontinued at the discretion of the sponsor in any of the following events:

- Medical or ethnical reasons affecting the continued performance of the study (e.g., recommendations of the DSMB in the above-mentioned special stopping rules after randomization of the first twenty patients and screening of the first fifty patients, respectively),
- Difficulties in the recruitment of patients,
- Inefficacy of the study treatment,
- Occurrence of AEs previously unknown in respect of their nature, severity, and duration or unexpected incidence of known AEs.

4.19 Statistical significance levels

Not applicable.

4.20 Methods for handling dropouts and protocol violators

Patients withdrawn from the study for reasons stated in section 3.3 will not be replaced.

For patients considered to be significantly noncompliant by the investigator or sponsor with the requirements of the protocol, i.e., protocol violations such as pregnancy, the treatment will be permanently discontinued. Other reasons for permanent treatment discontinuation for a patient include withdrawal criteria and:

- Three years of study treatment,
- Patient experiences PD,
- Patient experiences unacceptable toxicity or an adverse experience that would, in the investigator’s or sponsor’s judgment, make continued administration of the study regimen an unacceptable risk,
- Situations requiring a therapeutic intervention not permitted by the treatment plan,
- Development of an intercurrent illness or situation which would, in the judgement of the investigator, affect assessments of clinical status and study endpoints to a significant degree,
- Specific request of the sponsor.

Patients for whom the treatment is permanently discontinued will remain in the study unless withdrawal. All patients with permanent treatment discontinuation, except for withdrawal of informed consent, lost to follow-up, or death, will be followed up as planned.

4.21 Methods for handling more than two treatment groups

Not applicable.

4.22 Methods for handling concomitant medications

Concomitant medications will be listed in Listing 6.2. There will be no analysis of their impact on study treatment or outcome.

4.23 Changes to the planned analyses

Due to the small number of patients, most analyses are shown in listings. Not all study objectives can be considered.

5 Mock-ups for tables, listings, and figures

The following TLF are planned. The fields marked in checked grey (listings) and the grey text in curly braces (tables) show the programmer where the parameter to be analyzed may be found and will not appear in the report.

Regarding listings, alternative choices such as yes or no, male or female, and positive or negative will not be displayed, but units will be given as shown below. Furthermore, abbreviations listed in chapter 1 will be used for legibility.

5.1 Tables

Table 1: General data

Populations	[N, %]
Number of patients	xx (100.00)
Number of patients in analysis populations	
mITT=SP	
PP	
Number of patients in treatment arms	
A	
B	
Number of participating clinics	

Table 2: Patients' first conversion to RAS wild-type

	Time from baseline sampling until first detection of RASwt [days]								
	N	Mean	STD	Min	Q1	Median	Q3	Max	NMiss
A									
B									
Total									

Table 3: Responses

Responses according to RECIST v1.1 criteria including Overall response rate (ORR)	Arm A [N, %]	Arm B [N, %]	Total [N, %]
Number of randomized patients			
Most recent response			
Complete response (CR)			
Partial response (PR)			
Stable disease (SD)			
Progressive disease (PD)			
Best response			
Complete response (CR)			
Partial response (PR)			
Stable disease (SD)			
Progressive disease (PD)			
Overall response			
CR or PR (ORR)			

(Optionally) Table 4.1: AEs - overview

Overview	5-FU [N, %]	Folinic acid [N,%]	Irinotecan [N,%]	Cetuximab [N, %]	Total [N, %]
Number of patients in mITT					
Patients with any AE					
Patients with AEs by maximal grade					
Grade 1					
Grade 2					
Grade 3					
Grade 4					

Grade 5					
Number of AEs					
Patients with treatment-related AEs					
Number of treatment-related AEs					
Patients with any SAE					
Patients with SAEs by seriousness criteria					
Death					
Life-threatening					
Hospitalization					
Persistent or significant disability/incapacity					
Congenital anomaly/birth defect					
Important medical event					
Number of SAEs					
Patients with any special AE					
Patients with special AEs by speciality criteria					
Pregnancy					
Medication error					
Number of special AEs					
Patients with AEs leading to discontinuation					
Number of AEs leading to discontinuation					

(Optionally) Table 4.2: AEs - System Organ Class (SOC) and Preferred Term (PT) by NCI CTCAE grade

		NCI CTCAE grade					Total	
SOC	PT	1	2	3	4	5	N	%
Number of AEs								100

SOC1								
	PT11							
	PT12							
	…							
SOC2								
	PT21							
	PT22							
	…							
…								

(Optionally) Table 4.3: AEs - number of patients with respect to System Organ Class (SOC) and Preferred Term (PT) by maximal NCI CTCAE grade

		Maximal NCI CTCAE grade					Total	
SOC	PT	1	2	3	4	5	N	%
Number of patients with any AE								100
SOC1								
	PT11							
	PT12							
	…							
SOC2								
	PT21							
	PT22							
	…							
…								

5.2 Listings

Eligibility criteria:

Listing 1.1: Inclusion criteria - legend

Abbreviation	Full text
IC 01	Histologically confirmed, UICC stage IV adenocarcinoma of the left-sided colon or rectum with metastases, primarily non-resectable, confirmed RAS mutations proven in the primary tumor or metastasis (KRAS and NRAS exon 2, 3, 4)
IC 02	Age ≥ 18 years on day of signing informed consent
IC 03	No previous chemotherapy for metastatic disease (1-2 cycles FOLFIRI or mFOLFIRI are permitted before enrollment until RAS status is determined)
IC 04	Patient is suitable for chemotherapy administration
IC 05	ECOG performance status 0-1
IC 06	Consent to liquid biopsy and mutation analysis
IC 07	Estimated life expectancy > 3 months
IC 08	Presence of at least one measurable reference lesion according to the RECIST v 1.1 criteria (chest CT and abdominal CT four weeks or less before enrollment)
IC 09	Adequate bone marrow function defined as: Leukocytes 3.0 x 10^9/L with neutrophils 1.5 x 10^9/L, thrombocytes 100 x 10^9/L, and hemoglobin 9 g/dL
IC 10	Adequate hepatic function defined as: Serum bilirubin 1.5 x ULN, ALAT, and ASAT 2.5 x ULN (in the presence of hepatic metastases, ALAT and ASAT 5 x ULN)
IC 11	Adequate renal function defined as: Creatinine clearance ≥ 50 mL/min
IC 12	Adequate cardiac function defined as: Normal ECG and echocardiogram with a LVEF of 55%
IC 13	INR < 1.5 and activated PTT (aPTT) < 1.5 x ULN (patients without anticoagulation). Therapeutic anticoagulation is allowed if INR and aPTT have remained stable within the therapeutic range for at least two weeks
IC 14	Time interval of at least six months since last administration of any previous neoadjuvant/adjuvant chemotherapy or radio chemotherapy of the primary tumor in curative treatment intention to start of first-line treatment
IC 15	Any relevant toxicities of prior treatments must have resolved to grade ≤ 1 according to the CTCAE (version 5), except alopecia
IC 16	WOCBP should have a negative urine pregnancy test within 72 hours prior to receiving the first dose of study medication
IC 17	Highly effective contraception for both male and female patients throughout the study and for at least three months after last dose of study medication administration if the risk of conception exists. Highly effective contraception must be in line with the definition of the CTFG recommendation
IC 18	Signed written informed consent and capacity to understand the informed consent
IC 19	Date of signing written informed consent

Listing 1.2: Inclusion criteria 01-09

patient.patient_no	registration.registration_arm_randomized	patient.patient_ic_01	patient.patient_ic_02	patient.patient_ic_03	patient.patient_ic_04	patient.patient_ic_05	patient.patient_ic_06	patient.patient_ic_07	patient.patient_ic_08	patient.patient_ic_09
Patient No.	Arm	IC 01 [yes/no]	IC 02 [yes/no]	IC 03 [yes/no]	IC 04 [yes/no]	IC 05 [yes/no]	IC 06 [yes/no]	IC 07 [yes/no]	IC 08 [yes/no]	IC 09 [yes/no]

Listing 1.3: Inclusion criteria 10-19

patient.patient_no	registration.registration_arm_randomized	patient.patient_ic_10	patient.patient_ic_11	patient.patient_ic_12	patient.patient_ic_13	patient.patient_ic_14	patient.patient_ic_15	patient.patient_ic_16	patient.patient_ic_17	patient.patient_ic_18	patient.patient_ic_ic_date
Patient No.	Arm	IC 10 [yes/no]	IC 11 [yes/no]	IC 12 [yes/no]	IC 13 [yes/no]	IC 14 [yes/no]	IC 15 [yes/no]	IC 16 [yes/no/na]	IC 17 [yes/no/na]	IC 18 [yes/no]	IC 19 [DDMMMYY]

Listing 2.1: Exclusion criteria - legend

Abbreviation	Full text
EC 01	Right-sided mCRC
EC 02	Primarily resectable metastases
EC 03	Previous chemotherapy for the colorectal cancer except for adjuvant treatment, completed at least six months before entering the study (1-2 cycles FOLFIRI or mFOLFIRI are permitted before enrollment)
EC 04	Patients with known brain metastases
EC 05	Symptomatic peritoneal carcinosis
EC 06	Progressive disease before randomization
EC 07	History of acute or subacute intestinal occlusion, inflammatory bowel disease, immune colitis, or chronic diarrhea
EC 08	Grade II heart failure (NYHA classification), Myocardial infarction, balloon angioplasty (PTCA) with or without stenting, and cerebral vascular accident/stroke within the past twelve months before enrollment, unstable angina pectoris, serious cardiac arrhythmia according to investigator's judgment requiring medication
EC 09	Medical or psychological impairments associated with restricted ability to give consent or not allowing conduct of study
EC 10	Active infection with hepatitis B or C
EC 11	Additional cancer; exceptions include adequately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy without evidence of recurrence
EC 12	Uncontrolled hypertension
EC 13	Marked proteinuria (nephrotic syndrome)
EC 14	Arterial thromboembolism or severe hemorrhage within six months prior to randomization (with exception of tumor bleeding before tumor resection surgery)
EC 15	Hemorrhagic diathesis or tendency towards thrombosis
EC 16	Participation in a clinical study or experimental drug treatment within thirty days prior to study
EC 17	Known hypersensitivity or allergic reaction to any of the study medications
EC 18	Severe, non-healing wounds, ulcers, bone fractures, or an infection requiring systematic therapy
EC 19	Known history of alcohol or drug abuse
EC 20	Known complete DPD deficiency (phenotype and/or genotype test) (patients with partial DPD deficiency may be included in this clinical trial at the discretion of the investigator and should receive a reduced starting 5-FU dose); known glucuronidation deficiency (Gilbert's syndrome) (specific screening not required)
EC 21	Absent or restricted legal capacity
EC 22	For female patients only: Pregnancy (absence to be confirmed by ß-HCG test) or lactating

Listing 2.2: Exclusion criteria 01-08

patient.patient_no	registration.registration_arm_randomized	patient.patient_ec_01	patient.patient_ec_02	patient.patient_ec_03	patient.patient_ec_04	patient.patient_ec_05	patient.patient_ec_06	patient.patient_ec_07	patient.patient_ec_08
Patient No.	Arm	EC 01 [yes/no]	EC 02 [yes/no]	EC 03 [yes/no]	EC 04 [yes/no]	EC 05 [yes/no]	EC 06 [yes/no]	EC 07 [yes/no]	EC 08 [yes/no]

Listing 2.3: Exclusion criteria 09-15

patient.patient_no	registration.registration_arm_randomized	patient.patient_ec_09	patient.patient_ec_10	patient.patient_ec_11	patient.patient_ec_12	patient.patient_ec_13	patient.patient_ec_14	patient.patient_ec_15
Patient No.	Arm	EC 09 [yes/no]	EC 10 [yes/no]	EC 11 [yes/no]	EC 12 [yes/no]	EC 13 [yes/no]	EC 14 [yes/no]	EC 15 [yes/no]

Listing 2.4: Exclusion criteria 16-22

patient.patient_no	registration.registration_arm_randomized	patient.patient_ec_16	patient.patient_ec_17	patient.patient_ec_18	patient.patient_ec_19	patient.patient_ec_20	patient.patient_ec_21	patient.patient_ec_22
Patient No.	Arm	EC 16 [yes/no]	EC 17 [yes/no]	EC 18 [yes/no]	EC 19 [yes/no]	EC 20 [yes/no]	EC 21 [yes/no]	EC 22 [yes/no/na]

Listing 3: Eligibility, enrollment, and randomization

patient.patient_no	patient.patient_study_eligibility	enrollment.enrollment_enrollment_date	registration.registration_registered_at	registration.registration_arm_randomized
Patient No.	Eligible for participation [yes/no]	Date of enrollment for screening phase	Date of randomization	Randomized into study arm

Patient characteristics and initial diagnosis:

Listing 4: Patient demographics

patient.patient_no	registration.registration_arm_randomized	patient.patient_age	baseline.baseline_bodysize,	baseline.baseline_bodyweight	patient.patient_gender	patient.patient_wocbp	anamnesis.anamnesis_ethnic	patient.patient_protocol_version
Patient No.	Arm	Age [years]	Height [cm]	Weight [kg]	Sex [female/male]	WOCBP [yes/no]	Ethnic origin	Protocol version at informed consent [version]

Listing 5.1: Initial diagnosis of mCRC - TNM staging

patient.patient_no	registration.registration_arm_randomized	anamnesis.anamnesis_diagnosis_date	anamnesis.anamnesis_tnm_performed					anamnesis.anamnesis_tnm_stage
Patient No.	Arm	Date of initial diagnosis	TNM staging performed at initial diagnosis [yes/no]	Classification				Stage
				anamnesis.anamnesis_tnm_t_prefix	anamnesis.anamnesis_tnm_t	anamnesis.anamnesis_tnm_n	anamnesis.anamnesis_tnm_m	
				Prefix	T	N	M	

Listing 5.2: Initial diagnosis of mCRC - resection

patient.patient_no	registration.registration_arm_randomized	anamnesis.anamnesis_resection_done	anamnesis.anamnesis_resection_date(_nd)	anamnesis.anamnesis_resection_status(_nd)
Patient No.	Arm	Primary tumor resected before study inclusion [yes/no]	Date of resection	Resection status

Listing 5.3: Initial diagnosis of mCRC - RAS mutation analysis

patient.patient_no	registration.registration_arm_randomized	anamnesis.anamnesis_ras_mutation_performed	anamnesis.anamnesis_ras_mutation_m(_spec), anamnesis.anamnesis_ras_mutation_m_n(_spec)	anamnesis.anamnesis_ras_mutation_status	anamnesis.anamnesis_kras	anamnesis.anamnesis_kras_mutation_list	anamnesis.anamnesis_nras	anamnesis.anamnesis_nras_mutation_list
Patient No.	Arm	RAS mutation analysis performed on tumor tissue [yes/no]	RAS mutation analysis method	RAS mutation status [wt/mutant]	KRAS detected [yes/no]	Exon(s) and Codon(s) of KRAS mutation(s)	NRAS detected [yes/no]	Exon(s) and Codon(s) of NRAS mutation(s)

Medical history and relevant medications:

Listing 6: Medical history

patient.patient_no	registration.registration_arm_randomized	anamnesis.anamnesis_con_diseases	icd10_en2010_code.description	disease.disease_start	disease.disease_end	disease.disease_end_ongoing
Patient No.	Arm	Relevant concomitant diseases [yes/no]	Disease according to ICD10	Start date	Stop date	Ongoing [yes/no]

Listing 7.1: Relevant medication - premedication

patient.patient_no	registration.registration_arm_randomized	anamnesis.anamnesis_prev_medications	medication.medication_drug	medication.medication_start	medication.medication_indication(_spec)					medication.medication_frequency	medication.medication_route	medication.medication_stop
						Dose						
						medication.medication_dose	medication.medication_dose_unit	medication.medication_dose_na	medication.medication_dose_required			
Patient No.	Arm	Relevant premedication [yes/no]	Premedication treatment	Start date	Indication	Quantity	Unit	Unknown	As required	Frequency	Route	Stop date

Listing 7.2: Relevant medication - concomitant medication

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_no	precycle.precycle_prev_medications, therapycycle.therapycycle_prev_medications	medication.medication_drug	medication.medication_start	medication.medication_indication(_spec)					medication.medication_frequency	medication.medication_route	medication.medication_stop
Patient No.	Arm	Point in time	Concomitant medication changes since last study treatment [yes/no]	Medication treatment	Start date	Indication	Dose				Frequency	Route	Stop date
							medication.medication_dose	medication.medication_dose_unit	medication.medication_dose_na	medication.medication_dose_required			
							Quantity	Unit	Unknown	As required			
		Pre-cycle 1											
		…											
		Cycle 1											
		…											

Baseline only examinations:

Listing 8: Baseline echocardiography

patient.patient_no	registration.registration_arm_randomized	baseline.baseline_echocardio_done	baseline.baseline_echocardio_nd(_spedc)	baseline.baseline_echocardio_date	baseline.baseline_echocardio_lvef	baseline.baseline_echocardio_result
Patient No.	Arm	Echocardiography performed [yes/no]	Reason if no	Date of echocardiography	LVEF [%]	Clinical significance

Listing 9: Baseline TNM staging

patient.patient_no	registration.registration_arm_randomized	baseline.baseline_tnm_done	baseline.baseline_tnm_nd(_spec)	baseline.baseline_tnm_date				
Patient No.	Arm	TNM staging performed [yes/no]	Reason if no	Date of TNM staging	Classification			
					baseline.baseline_tnm_t_prefix	baseline.baseline_tnm_t	baseline.baseline_tnm_n	baseline.baseline_tnm_m
					Prefix	T	N	M

Baseline only laboratory assessments:

Listing 10: Baseline coagulation parameters

patient.patient_no	registration.registration_arm_randomized	lab_val_co.lab_val_co_lab_done	lab_val_co.lab_val_co_reason(_spec)	lab_val_co.lab_val_co_date	lab_val_co.lab_val_co_inr_value	lab_val_co.lab_val_co_ptt_value
Patient No.	Arm	Coagulation done [yes/no]	Reason if no	Date of coagulation sampling	INR	PTT [s]

Listing 11: Baseline DPD deficiency

patient.patient_no	registration.registration_arm_randomized	baselab.baselab_dpd_done	baselab.baselab_dpd_reason(_spec)	baselab.baselab_dpd_date	baselab.baselab_dpd_result
Patient No.	Arm	Test for DPD deficiency performed [yes/no]	Reason if no	Date for DPD deficiency test	Test result

Listing 12: Baseline hepatitis serology

patient.patient_no	registration.registration_arm_randomized	baselab.baselab_serological_done	baselab.baselab_serological_nd(_spedc)	baselab.baselab_serological_date	baselab.baselab_serological_hbv	baselab.baselab_serological_hcv
Patient No.	Arm	Serological tests performed [yes/no]	Reason if no	Date of serological tests	Hepatitis B [positive/negative]	Hepatitis C [positive/negative]

Electrocardiogram assessments:

Listing 13: ECG assessments

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_no	baseline.baseline_ecg_performed, precycle.precycle_ecg_performed, therapycycle.therapycycle_ecg_performed	baseline.baseline_ecg_nd(_spedc), precycle.precycle_ecg_nd(_spedc), therapycycle.therapycycle_ecg_nd(_spedc)	baseline.baseline_ecg_date, precycle.precycle_ecg_date, therapycycle.therapycycle_ecg_date	baseline.baseline_ecg_result, precycle.precycle_ecg_result, therapycycle.therapycycle_ecg_result
Patient No.	Arm	Point in time	ECG performed [yes/no]	Reason if no	Date of ECG	Clinical significance
		Baseline				
		Pre-cycle 1				
		…				
		Cycle 1				
		…				

Eastern Cooperative Oncology Group performance statuses:

Listing 14: ECOG performance statuses

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_cycle_no	baseline.baseline_ecog_date, precycle.precycle_ecog_date(_nd), therapycycle.therapycycle_w1_ecog_date(_nd), therapycycle.therapycycle_w2_ecog_date(_nd), eot.eot_date, followup.followup_date	baseline.baseline_ecog, precycle.precycle_ecog, therapycycle.therapycycle_w1_ecog, therapycycle.therapycycle_w2_ecog, eot.eot_ecog, followup.followup_ecog
Patient No.	Arm	Point of time	Date of ECOG evaluation	ECOG performance status
		Baseline		
		Pre-cycle 1		
		…		
		Cycle 1		
		…		
		EOT		
		Follow-up 1		

Vital signs examinations:

Listing 15: Vital signs

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_no	baseline.baseline_vital, precycle.precycle_vital, therapycycle.therapycycle_w1_vital, therapycycle.therapycycle_w2_vital	baseline.baseline_vital_nd(_spec), precycle.precycle_vital_nd(_spec), therapycycle_exam_performed, therapycycle.therapycycle_w1_vital_nd(_spec), therapycycle.therapycycle_w2_vital_nd(_spec)	baseline.baseline_vital_date, precycle.precycle_vital_date, therapycycle.therapycycle_w1_vital_date, therapycycle.therapycycle_w2_vital_date, therapycycle.therapycycle_w1_cycle_date, therapycycle.therapycycle_w2_cycle_date	baseline.baseline_bodyweight, precycle.precycle_bodyweight, therapycycle.therapycycle_w1_bodyweight, therapycycle.therapycycle_w2_bodyweight	baseline.baseline_body_temp, precycle.precycle_body_temp, therapycycle.therapycycle_w1_body_temp, therapycycle.therapycycle_w2_body_temp	baseline.baseline_bloodpressure_s, precycle.precycle_bloodpressure_s, therapycycle.therapycycle_w1_bloodpressure_s, therapycycle.therapycycle_w2_bloodpressure_s	baseline.baseline_bloodpressure_d, precycle.precycle_bloodpressure_d, therapycycle.therapycycle_w1_bloodpressure_d, therapycycle.therapycycle_w2_bloodpressure_d	baseline.baseline_pulse, precycle.precycle_pulse, therapycycle.therapycycle_w1_pulse, therapycycle.therapycycle_w2_pulse
Patient No.	Arm	Point in time	Vital signs examined [yes/no]	Reason if no	Date of examination	Weight [kg]	Temperature [°C]	Blood pressure (systolic) [mmHg]	Blood pressure (diastolic) [mmHg]	Heartrate [per min]
		Baseline								
		Pre-cycle 1								
		…								
		Cycle 1								
		…								

Hematological and blood chemistry laboratory assessments:

Listing 16: Hematological lab assessments

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_no	lab_val_he.lab_val_he_lab_done	lab_val_he.lab_val_he_reason(_spec)	lab_val_he.lab_val_he_date	lab_val_he.lab_val_he_haemoglobin_value	lab_val_he.lab_val_he_platelet_value	lab_val_he.lab_val_he_leucocyte_value	lab_val_he.lab_val_he_neutrophilt_value
Patient No.	Arm	Point in time	Laboratory hematology done [yes/no]	Reason if no	Date of hematology sampling	Hemoglobin [g/dL]	Platelets [10^9/L]	Leukocytes [10^9/L]	Neutrophils (total) [10^9/L]
		Baseline							
		Pre-cycle 1							
		…							
		Cycle 1							
		…							
		EOT							

Listing 17.1: Blood chemistry lab assessments - first part

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_no	lab_val_cc.lab_val_cc_lab_done	lab_val_cc.lab_val_cc_reason(_spec)	lab_val_cc.lab_val_cc_date	lab_val_cc.lab_val_cc_sodium_value	lab_val_cc.lab_val_cc_potassium_value	lab_val_cc.lab_val_cc_magnesium_value	lab_val_cc.lab_val_cc_calcium_value	lab_val_cc.lab_val_cc_got_value
Patient No.	Arm	Point in time	Laboratory blood chemistry done [yes/no]	Reason if no	Date of chemistry sampling	Sodium [mval/L]	Potassium [mmol/L]	Magnesium [mmol/L]	Calcium [mmol/L]	ASAT [U/L]
		Baseline								
		Pre-cycle 1								
		…								
		Cycle 1								
		…								
		EOT								

Listing 17.2: Blood chemistry lab assessments - second part

patient.patient_no	registration.registration_arm_randomized	lab_val_cc.lab_val_cc_date	lab_val_cc.lab_val_cc_gpt_value	lab_val_cc.lab_val_cc_alkphosphatase_value	lab_val_cc.lab_val_cc_bilirubint_value	lab_val_cc.lab_val_cc_ggt_value	lab_val_cc.lab_val_cc_urea_value	lab_val_cc.lab_val_cc_creatinine_value	lab_val_cc.lab_val_cc_creatinec_value	lab_val_cc.lab_val_cc_crp_value
Patient No.	Arm	Date of chemistry sampling	ALAT [U/L]	Alkaline phosphatase [U/L]	Bilirubin (total)	GGT [U/L]	Urea [mg/dL]	Creatinine [mg/dL]	Creatinine-clearance [mL/s]	CRP [mg/dL]

Tumor tissue analyses:

Listing 18: Tumor markers lab assessments

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_no	lab_val_tm.lab_val_tm_lab_done	lab_val_tm.lab_val_tm_reason(_spec)	lab_val_tm.lab_val_tm_date	lab_val_tm.lab_val_tm_cea_value	lab_val_tm.lab_val_tm_ca199_value
Patient No.	Arm	Point in time	Laboratory tumor markers done [yes/no]	Reason if no	Date of tumor markers sampling	CEA [µg/L]	CA 19-9 [U/L]
		Baseline					
		Pre-cycle 1					
		…					
		Cycle 1					
		…					
		EOT					

Listing 19: RAS mutation analyses on tumor tissue

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no	baselab.baselab_ras_mutation_performed, precycle.precycle_ras_mutation_performed	baselab.baselab_ras_mutation_nd(_spec), precycle.precycle_ras_mutation_nd(_spec)	baselab.baselab_ras_mutation_date, precycle.precycle_ras_mutation_date	baselab.baselab_ras_mutation_m(_spec), baselab.baselab_ras_mutation_m_n(_spec), precycle.precycle_ras_mutation_m(_spec), precycle.precycle_ras_mutation_m_n(_spec)	baselab.baselab_ras_mutation_status, precycle.precycle_ras_mutation_status	baselab.baselab_kras, precycle.precycle_kras	baselab.baselab_kras_mutation_list, precycle.precycle_kras_mutation_list	baselab.baselab_nras, precycle.precycle_nras	baselab.baselab_nras_mutation_list, precycle.precycle_nras_mutation_list
Patient No.	Arm	Point in time	RAS mutation analysis on tumor tissue performed [yes/no]	Reason if no	Date of tissue analysis	Method of tissue analysis	RAS mutation status in tissue [wt/mutant]	KRAS detected [yes/no]	Exon(s) and Codon(s) of KRAS mutation(s)	NRAS detected [yes/no]	Exon(s) and Codon(s) of NRAS mutation(s)
			Baseline								
			Pre-cycle 1								
			…								

Liquid biopsy analyses:

Listing 20.1: Samplings for liquid biopsy

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_no	baselab.baselab_blood_taken, precycle.precycle_blood_taken, therapycycle.therapycycle_blood_taken	baselab.baselab_blood_nd(_spec), precycle.precycle_blood_nd(_spec), therapycycle.therapycycle_blood_nd(_spec)	biopsy.biopsy_sample_date	biopsy.biopsy_shipping_date	biopsy.biopsy_sample_analyzed	biopsy.biopsy_sample_analyzed_date
Patient No.	Arm	Point in time	Sampling for liquid biopsy taken [yes/no]	Reason if no	Date of sampling	Date of shipping	Sample intact and analyzable [yes/no]	Date of initial analysis
		Baseline						
		Pre-cycle 1						
		…						
		Cycle 1						
		…						

Listing 20.2: Samplings for liquid biopsy - RAS mutation status

patient.patient_no	registration.registration_arm_randomized	biopsy.biopsy_sample_date	biopsy.biopsy_ras_mutation_method	biopsy.biopsy_ras_mutation_status	biopsy.biopsy_kras	biopsy.biopsy_kras_mutation_list	biopsy.biopsy_nras	biopsy.biopsy_nras_mutation_list
Patient No.	Arm	Date of sampling	Method of liquor analysis	RAS mutation status in liquor [wt/mutant]	KRAS detected [yes/no]	Exon(s) and Codon(s) of KRAS mutation(s)	NRAS detected [yes/no]	Exon(s) and Codon(s) of NRAS mutation(s)

Listing 20.3: Samplings for liquid biopsy - first conversion to RASwt

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no	precylce.precycle_cycle_date	biopsy.biopsy_sample_date	biopsy.biopsy_sample_date	
Patient No.	Arm	Point in time	First day of cycle	Date of sampling of liquid biopsy in which conversion to RASwt was detected first	Date of baseline sampling	Time from baseline sampling until first detection of RASwt [days]
		Pre-cycle x				
		...				

Pregnancy test results:

Listing 21: β-HCG pregnancy tests

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_no	baselab.baselab_preg_test_performed, precycle.precycle_preg_test_performed, therapycycle.therapycycle_preg_test_performed, eot.eot_preg_test_performed	baselab.baselab_preg_test_nd(_spedc), precycle.precycle_preg_test_nd(_spedc), therapycycle.therapycycle_preg_test_nd(_spedc), eot.eot_preg_test_nd(_spedc)	baselab.baselab_preg_test_date, precycle.precycle_preg_test_date, therapycycle.therapycycle_preg_test_date, eot.eot_date	baselab.baselab_preg_test_result, precycle.precycle_preg_test_result, therapycycle.therapycycle_preg_test_result, eot.eot_preg_test_result
Patient No.	Arm	Point in time	Pregnancy test (urine) performed [yes/no]	Reason if no	Date	Result [positive/negative]
		Baseline				
		Pre-cycle 1				
		…				
		Cycle 1				
		…				
		EOT				

Treatment cycles:

Listing 22.1: Treatment cycles - general

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_no	precycle.precycle_exam_performed, therapycycle.therapycycle_exam_performed	precycle.precycle_exam_reason(_spec), therapycycle.therapycycle_exam_reason(_spec)	precycle.precycle_cycle_date, therapycycle.therapycycle_w1_cycle_date	precycle.precycle_folfiri_admin, therapycycle.therapycycle_w1_folfiri_admin	therapycycle.therapycycle_surgery_taken	therapycycle.therapycycle_surgery_date	therapycycle.therapycycle_surgery_type
Patient No.	Arm	Point in time	Examinations and/or treatment performed [yes/no]	Reason if no	First day of cycle	Study treatment administered [yes/no]	Resection of metastases since last visit [yes/no]	Date of surgery	Resected metastases
		Pre-cycle 1							
		…							
		Cycle 1							
		…							

Listing 22.2: Treatment cycles - irinotecan (iv infusion, 180 mg/m^2 over 30-90 min)

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_no, therapycycle.therapycycle_w1_cycle_no, therapycycle.therapycycle_w2_cycle_no	precycle.precycle_irino_admin, therapycycle.therapycycle_irino_admin	precycle.precycle_irino_nd(_spec), therapycycle.therapycycle_irino_nd(_spec)	precycle.precycle_irino_batch, therapycycle.therapycycle_irino_batch	precycle.precycle_irino_admin_date(_nd), therapycycle.therapycycle_irino_admin_date(_nd)	precycle.precycle_irino_pro, therapycycle.therapycycle_irino_pro	precycle.precycle_irino_pro_nd(_spec), therapycycle.therapycycle_irino_pro_nd(_spec)	precycle.precycle_irino_duration, therapycycle.therapycycle_irino_duration	precycle.precycle_irino_dose, therapycycle.therapycycle_irino_dose
Patient No.	Arm	Point in time	Irinotecan administered in standard dose [yes/no]	Reason if no	Batch	Date	Prolonged infusion duration [yes/no]	Reason if yes	Infusion duration [min]	Dose [mg/m^2]
		Pre-cycle 1								
		…								
		Cycle 1								
		…								

Listing 22.3: Treatment cycles - folinic acid (iv infusion, 400 mg/m² over 120 min)

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_no, therapycycle.therapycycle_w1_cycle_no, therapycycle.therapycycle_w2_cycle_no	precycle.precycle_fa_admin, therapycycle.therapycycle_fa_admin	precycle.precycle_fa_admin_nd(_spec), therapycycle.therapycycle_fa_admin_nd(_spec)	precycle.precycle_fa_batch, therapycycle.therapycycle_fa_batch	precycle.precycle_fa_admin_date(_nd), therapycycle.therapycycle_fa_admin_date(_nd)	precycle.precycle_fa_prolong, therapycycle.therapycycle_fa_prolong	precycle.precycle_fa_prolong_nd(_spec), therapycycle.therapycycle_fa_prolong_nd(_spec)	precycle.precycle_fa_duration, therapycycle.therapycycle_fa_duration	precycle.precycle_fa_dose, therapycycle.therapycycle_fa_dose
Patient No.	Arm	Point in time	Folinic acid administered in standard dose [yes/no]	Reason if no	Batch	Date	Prolonged infusion duration [yes/no]	Reason if yes	Infusion duration [min]	Dose [mg/m²]
		Pre-cycle 1								
		…								
		Cycle 1								
		…								

Listing 22.4: Treatment cycles - 5-FU (bolus, 400 mg/m²)

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_no, therapycycle.therapycycle_w1_cycle_no, therapycycle.therapycycle_w2_cycle_no	precycle.precycle_ffu1_admin, therapycycle.therapycycle_ffu1_admin	precycle.precycle_ffu1_admin_nd(_spec), therapycycle.therapycycle_ffu1_admin_nd(_spec)	precycle.precycle_ffu1_batch, therapycycle.therapycycle_ffu1_batch	precycle.precycle_ffu1_admin_date(_nd), therapycycle.therapycycle_ffu1_admin_date(_nd)	precycle.precycle_ffu1_dose, therapycycle.therapycycle_ffu1_dose
Patient No.	Arm	Point in time	5-FU bolus administered in standard dose [yes/no]	Reason if no	Batch	Date	Dose [mg/m²]
		Pre-cycle 1					
		…					
		Cycle 1					
		…					

Listing 22.5: Treatment cycles - 5-FU (iv infusion, 2400 mg/m^2 over 46 h)

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_no, therapycycle.therapycycle_w1_cycle_no, therapycycle.therapycycle_w2_cycle_no	precycle.precycle_ffu2_admin, therapycycle.therapycycle_ffu2_admin	precycle.precycle_ffu2_admin_nd(_spec), therapycycle.therapycycle_ffu2_admin_nd(_spec)	precycle.precycle_ffu2_batch, therapycycle.therapycycle_ffu2_batch	precycle.precycle_ffu2_admin_date(_nd), therapycycle.therapycycle_ffu2_admin_date(_nd)	precycle.precycle_ffu2_prolong, therapycycle.therapycycle_ffu2_prolong	precycle.precycle_ffu2_prolong_nd(_spe), therapycycle.therapycycle_ffu2_prolong_nd(_spe)	precycle.precycle_ffu2_duration, therapycycle.therapycycle_ffu2_duration	precycle.precycle_ffu2_dose, therapycycle.therapycycle_ffu2_dose
Patient No.	Arm	Point in time	5-FU infusion administered in standard dose [yes/no]	Reason if no	Batch	Date	Prolonged infusion duration [yes/no]	Reason if yes	Infusion duration [min]	Dose [mg/m^2]
		Pre-cycle 1								
		…								
		Cycle 1								
		…								

Listing 22.6: Treatment cycles - cetuximab (iv infusion, initially 400mg/m^2 over 120 min, subsequently 250 mg/m^2 over 60 min)

patient.patient_no	registration.registration_arm_randomized	therapycycle.therapycycle_no	therapycycle.therapycycle_w1_ce_admin, therapycycle.therapycycle_w2_ce_infu_admin	therapycycle.therapycycle_w1_ce_nd(_spec), therapycycle.therapycycle_w2_ce_infu_nd(_spec)	therapycycle.therapycycle_w1_ce_batch, therapycycle.therapycycle_w2_ce_batch	therapycycle.therapycycle_w1_ce_admin_date(_nd), therapycycle.therapycycle_w2_ce_admin_date(_nd)	therapycycle.therapycycle_w1_ce_pro, therapycycle.therapycycle_w2_ce_pro	therapycycle.therapycycle_w1_ce_pro_nd(_spec), therapycycle.therapycycle_w2_ce_pro_nd(_spec)	therapycycle.therapycycle_w1_ce_od_duration, therapycycle.therapycycle_w2_ce_od_duration	therapycycle.therapycycle_w1_ce(_od)_dose, therapycycle.therapycycle_w2_ce_od_dose
Patient No.	Arm	Point in time	Cetuximab administered in standard dose [yes/no]	Reason if no	Batch	Date	Prolonged infusion duration [yes/no]	Reason if yes	Infusion duration [min]	Dose [mg/m^2]
		Cycle 1 week 1								
		Cycle 1 week 2								
		…								

Primary and secondary objectives:

Listing 23.1: RECIST assessments

patient.patient_no	registration.registration_arm_randomized	precycle.precycle_no, therapycycle.therapycycle_no	baseline.baseline_recist_tm_performed, precycle.precycle_recist_tm_performed, therapycycle.therapycycle_recist_tm_performed	baseline.baseline_recist_tm_nd(_spedc), precycle.precycle_recist_tm_reason, precycle.precycle_recist_tm_nd(_spedc), therapycycle.therapycycle_recist_tm_reason, therapycycle.therapycycle_recist_tm_nd(_spedc)	tm_st.tm_st_st_nr	tm_st.tm_st_date	tm.tm_loc_metastasis_count	tm_st.tm_st_meas_amount	tm_st.tm_st_total	tm_st.tm_st_consultations	Tm_st.tm_st_comment
Patient No.	Arm	Point in time	RECIST assessment performed [yes/no]	Reason	Staging No.	Date of RECIST assessment	Number of metastases at beginning of the study	Sum of sizes [mm]	Overall assessment	Consultation with Administration Office has occurred [yes/no]	Comment
		Baseline									
		Pre-cycle 1									
		…									
		Cycle 1									
		…									

Listing 23.2: RECIST assessments - lesions

patient.patient_no	registration.registration_arm_randomized	tm_st.tm_st_st_nr	tm_st.tm_st_date		tm_le.tm_le_loc	tm_le.tm_le_loc_ext	tm_le.tm_le_method	tm_le.tm_le_size	tm_le.tm_le_tumor_type	tm_st.tm_st_meas_assessment	tm_st.tm_st_immeas_assessment
Patient No.	Arm	Staging No.	Date		Localization	Detailed information about localization	Method	Size of lesion if measurable [mm]	Tumor type if non-measurable	Assessment measurable lesions	Assessment non-measurable lesions

Listing 24: PFS, OS, and TFTS

patient.patient_no	registration.registration_arm_randomized	registration.registration_registered_at	endofstudy.endofstudy_last_contact_date		ae.ae_irino_inter_date, ae.ae_fa_inter_date, ae.ae_ffu_inter_date, ae.ae_ce_inter_date		tm_st.tm_st_date		endofstudy.endofstudy_death_date			
Patient No.	Arm	Date of randomization	Date of last contact	Treatment discontinuation for any reason [yes/no]	Date of (first) discontinuation	Progression [yes/no]	Date of progression	Death [yes/no]	Date of death	PFS [months]	OS [months]	TFTS [months]

End of treatment:

Listing 25.1: EOT - resection and new therapy

patient.patient_no	registration.registration_arm_randomized	eot.eot_date	eot.eot_end_reason(_other_spec)	eot.eot_resection_date	eot.eot_resection_status	eot.eot_tumor_th	tumor.tumor_therapy	tumor.tumor_start	tumor.tumor_end(_nd)
Patient No.	Arm	EOT evaluation date	Reason for EOT	Resection date if resection performed	Resection status if resection performed	New tumor therapy since last study treatment [yes/no]	New therapy	Start date of new therapy	End date of new therapy

Listing 25.2: EOT - RAS mutation status

patient.patient_no	registration.registration_arm_randomized	eot.eot_ras_mutation_status_done	eot.eot_ras_mutation_status	eot.eot_kras	eot.eot_kras_mutation_list	eot.eot_nras	eot.eot_nras_mutation_list
Patient No.	Arm	Results of RAS mutation status available [yes/no]	Mutation status [wt/mutant]	KRAS detected [yes/no]	Exon(s) and Codon(s) of KRAS mutation(s)	NRAS detected [yes/no]	Exon(s) and Codon(s) of NRAS mutation(s)

Follow-up visits:

Listing 26.1: Follow-up visit - first part

patient.patient_no	registration.registration_arm_randomized	followup.followup_no	followup.followup_date	followup.followup_contact	followup.followup_tumor_th	tumor.tumor_therapy	tumor.tumor_start	tumor.tumor_end(_nd)
Patient No.	Arm	Follow-up No.	Follow-up visit date	Contact with patient	Changes in new therapy since last visit [yes/no]	New therapy	Start date of new therapy	End date of new therapy

Listing 26.2: Follow-up visit - second part

patient.patient_no	registration.registration_arm_randomized	followup_followup_no	followup_followup_surgery_taken	followup_followup_surgery_date	followup_followup_surgery_type
Patient No.	Arm	Follow-up No.	Resection of metastases since last visit [yes/no]	Date of resection	Which metastasis were resected

End of study:

Listing 27: End of study

patient.patient_no	registration.registration_arm_randomized	endofstudy.endofstudy_last_contact_date	endofstudy.endofstudy_reason(_spec)	endofstudy.endofstudy_death_date	endofstudy.endofstudy_death_reason(_spec)				icd10_en2010_code.description	endofstudy.endofstudy_withdrawal_date	endofstudy.endofstudy_withdrawal_reason
Patient No.	Arm	Date of last contact	Reason for end of study	Date of death if applicable	Reason of death if applicable	Death related AE if applicable			Death related disease if applicable	Date of withdrawal if applicable	Reason of withdrawal if applicable
						ae.ae_nci	nci_v5_ae.ae	ae.ae_nci_text			
						Grade	Term	Other			

Adverse events:

Listing 28.1: AEs/toxicity - terminology, timeline, and causality

patient.patient_no	registration.registration_arm_randomized				ae.ae_start(_na)	ae.ae_end(_na)	ae.ae_outcome	ae.ae_treatment_started		ae.ae_irino_causal, ae.ae_fa_causal, ae.ae_ffu_causal, ae.ae_ce_causal	ae.ae_irino_action, ae.ae_fa_action, ae.ae_ffu_action, ae.ae_ce_action	ae.ae_medication_treated
Patient No.	Arm	Terminology according to CTCAE version 5			Start date	End date	Outcome	Study treatment started [yes/no]	Study treatment component	Causal relationship suspected [yes/no]	Action taken	Event treated with medication [yes/no]
		ae.ae_nci	nci_v5_ae.ae	ae.ae_nci_text								
		Grade	Term	Other								

Listing 28.2: AEs/toxicity - SAEs and special AEs

patient.patient_no	registration.registration_arm_randomized				ae.ae_start(_na)	ae.ae_sae	ae.ae_criteria_fatal, ae.ae_criteria_life_threatening, ae.ae_criteria_hospital, ae.ae_criteria_disability, ae.ae_criteria_congenital, ae.ae_criteria_important_event (_spec)	ae.ae_special	ae.ae_criteria_pregnancy, ae.ae_criteria_error
Patient No.	Arm	Terminology according to CTCAE version 5			Start date	Serious AE [yes/no]	Reason for classification as serious	Special event [yes/no]	Reason for classification as special
		ae.ae_nci	nci_v5_ae.ae	ae.ae_nci_text					
		Grade	Term	Other					

5.3 Figures

Figure 1: Swimmer plot

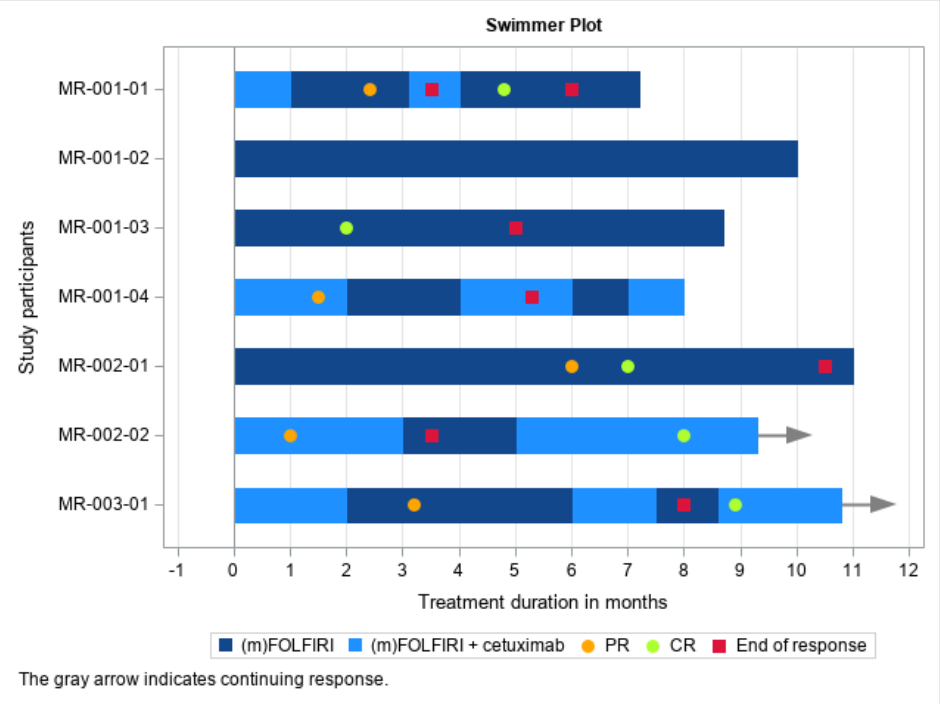
Figure	Figure 1	Example (no study data)
Title 1	Treatment and response timeline	
Title 2	for each randomized patient	
Type of graph	Swimmer plot	
y-axis	Patient numbers.	
y-axis (label)	Study participants	
x-axis	0 to maximum rounded up number to nearest month	
x-axis (label)	Treatment duration in months	
Legend	Study treatment: (m)FOLFIRI, (m)FOLFIRI + cetuximab, Treatment response: CR, PR, SD, PD, and death	
Footnote	The gray arrow indicates continuing response.	
Additional information	-	

Figure 2: Progression-free survival (PFS) [months]

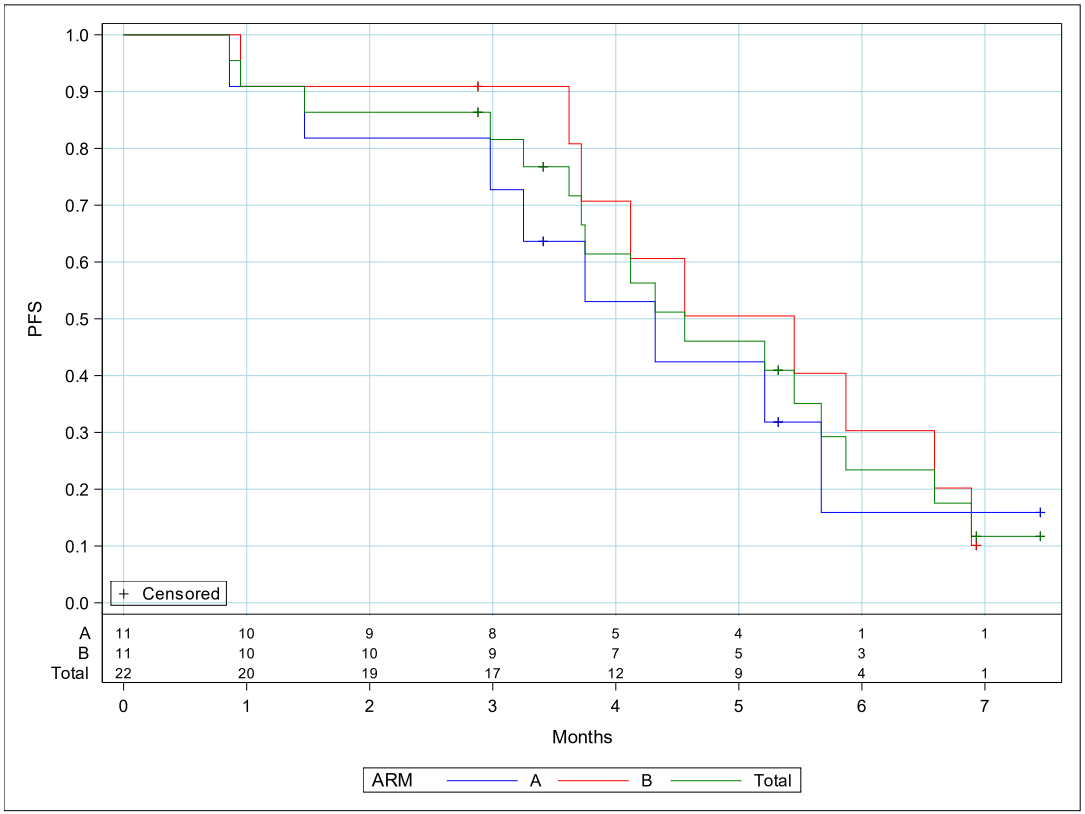
Figure	Figure 2	Example (no study data)
Title 1	Progression-free survival (PFS) [months]	
Title 2		
Type of graph	Kaplan-Meier plot	
y-axis	0 to 1	
y-axis (label)	PFS	
x-axis	0 to maximum event time	
x-axis (label)	Months	
Legend	Study arms A and B and Total	
Footnote		
Additional information	Patients at risk will be displayed for specified timepoints on x-axis. One PFS curve for each study arm and the total population will be displayed. Due to the small number of patients, no p-value will be displayed.	

Figure 3: Overall survival (OS) [months]

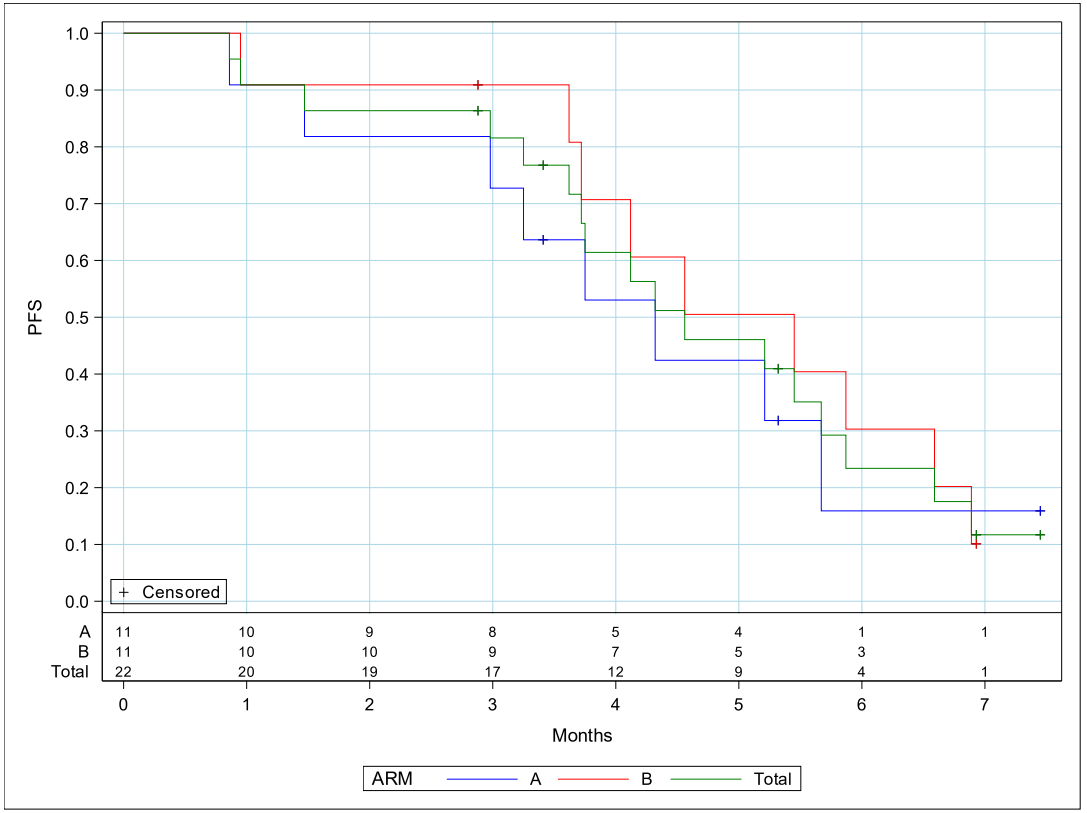
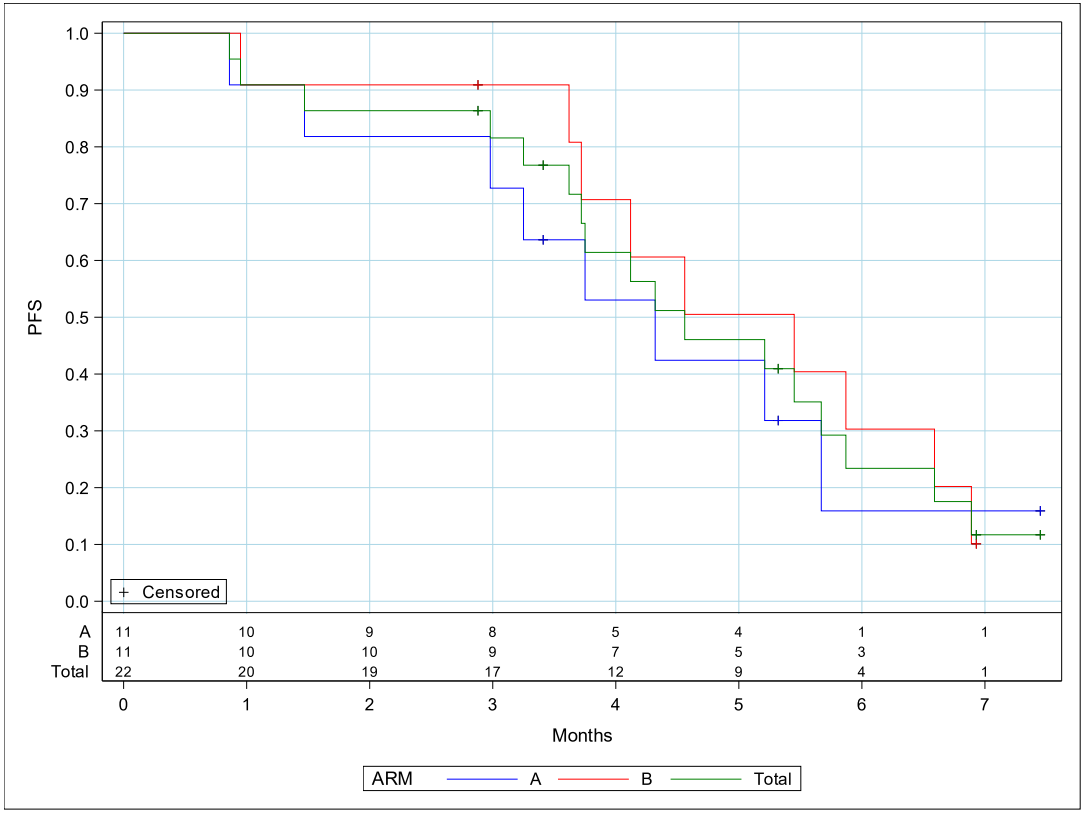
Figure	Figure 3	Example (no study data, no matching y-axis label)
Title 1	Overall survival (OS) [months]	
Title 2		
Type of graph	Kaplan-Meier plot	
y-axis	0 to 1	
y-axis (label)	OS	
x-axis	0 to maximum event time	
x-axis (label)	Months	
Legend	Study arms A and B and Total	
Footnote		
Additional information	Patients at risk will be displayed for specified timepoints on x-axis. One OS curve for each study arm and the total population will be displayed. Due to the small number of patients, no p-value will be displayed.	

Figure 4: Time to failure of treatment strategy (TFTS) [months]

Figure	Figure 4	Example (no study data, no matching y-axis label)
Title 1	Time to failure of treatment strategy (TFTS) [months]	
Title 2		
Type of graph	Kaplan-Meier plot	
y-axis	0 to 1	
y-axis (label)	TFTS	
x-axis	0 to maximum event time	
x-axis (label)	Months	
Legend	Study arms A and B and Total	
Footnote		
Additional information	Patients at risk will be displayed for specified timepoints on x-axis. One TFTS curve for each study arm and the total population will be displayed. Due to the small number of patients, no p-value will be displayed.	

6 Statistical software

All descriptive statistical analyses will be performed by using the statistical software SAS version 9.4.

7 Medical dictionaries

As medical dictionary for analysis we use the latest available version of MedDRA and ICD10.

8 Coding conventions

There are no special coding conventions.

9 Output format

If a statistical report will be written, the respective tables and figures will be presented in the text. The text will be written in Arial 11 pt with 1.0 line spacing with exceptions to title and signature pages. The TLF will be written in Arial 10 pt and dates contained in TLF will be given in DDMMMYY format.

10 List of the tables, listings, and figures planned for the Final Statistical Report

Tables:

- Table 1: General data
- Table 2: Patients' first conversion to RAS wild-type
- Table 3: Patient responses
- (Optionally) Table 4.1: AEs - overview
- (Optionally) Table 4.2: AEs - System Organ Class (SOC) and Preferred Term (PT) by NCI CTCAE grade
- (Optionally) Table 4.3: AEs - number of patients with respect to System Organ Class (SOC) and Preferred Term (PT) by maximal NCI CTCAE grade

Listings:

- Listing 1.1: Inclusion criteria
- Listing 1.2: Inclusion criteria 01-09
- Listing 1.3: Inclusion criteria 10-19
- Listing 2.1: Exclusion criteria
- Listing 2.2: Exclusion criteria 01-08
- Listing 2.3: Exclusion criteria 09-15
- Listing 2.4: Exclusion criteria 16-22
- Listing 3: Eligibility, enrollment, and randomization
- Listing 4: Patient demographics
- Listing 5.1: Initial diagnosis of mCRC - TNM staging
- Listing 5.2: Initial diagnosis of mCRC - resection
- Listing 5.3: Initial diagnosis of mCRC - RAS mutation analysis
- Listing 6: Medical history
- Listing 7.1: Relevant medication - premedication
- Listing 7.2: Relevant medication - concomitant medication
- Listing 8: Baseline echocardiography
- Listing 9: Baseline TNM staging
- Listing 10: Baseline coagulation parameters
- Listing 11: Baseline DPD deficiency
- Listing 12: Baseline hepatitis serology
- Listing 13: ECG assessments
- Listing 14: ECOG performance statuses

- Listing 15: Vital signs
- Listing 16: Hematological lab assessments
- Listing 17.1: Blood chemistry lab assessments - first part
- Listing 17.2: Blood chemistry lab assessments - second part
- Listing 18: Tumor markers lab assessments
- Listing 19: RAS mutation analyses on tumor tissue
- Listing 20.1: Samplings for liquid biopsy
- Listing 20.2: Samplings for liquid biopsy - RAS mutation status
- Listing 20.3: Samplings for liquid biopsy - first conversion to RASwt
- Listing 21: β-HCG pregnancy tests
- Listing 22.1: Treatment cycles - general
- Listing 22.2: Treatment cycles - irinotecan (iv infusion, 180mg/m^2 over 90 min)
- Listing 22.3: Treatment cycles - folinic acid (iv infusion, 400mg/m^2 over 120 min)
- Listing 22.4: Treatment cycles - 5-FU (bolus, 400mg/m^2)
- Listing 22.5: Treatment cycles - 5-FU (iv infusion, 2400mg/m^2 over 46h)
- Listing 22.6: Treatment cycles - cetuximab (iv infusion, initially 400 mg/m^2 over 120 min, subsequently 250 mg/m2 over 60 min)
- Listing 23.1: RECIST assessments
- Listing 23.2: RECIST assessments - lesions
- Listing 24: PFS, OS, and TFTS
- Listing 25.1: EOT - resection and new therapy
- Listing 25.2: EOT - RAS mutation status
- Listing 26.1: Follow-up visit - first part
- Listing 26.2: Follow-up visit - second part
- Listing 27: End of study
- Listing 28.1: AEs/toxicity - terminology, timeline, and causality
- Listing 28.2: AEs/toxicity - SAEs and special AEs

Figures:

- Figure 1: Swimmer plot
- Figure 2: Progression-free survival (PFS) [months]
- Figure 3: Overall survival (OS) [months]
- Figure 4: Time to failure of treatment strategy (TFTS) [months]

11 History table

Version	Version of Mock-ups	Date [DDMMMYY]	Author	Sections changed	Brief description of change
Draft v0.1	First version	18FEB22	Dr. Maximilian Parr	None	First version, hence no changes
Draft v0.2	Second version	11MAR22	Dr. Maximilian Parr	Title pages	Actualized
				Section 4.12	Added some conventions
				Chapter 5	Mostly minor adjustments to tables and listings
Draft v0.3	Third version	18MAR22	Dr. Maximilian Parr	Chapter 5	A few more minor changes in listings
Draft v0.4	Fourth version	31MAR22	Dr. Maximilian Parr	Section 4.12	Added time conventions
				Chapter 5	Added third table and Listing 20.3
		14APR22	Dr. Maximilian Parr	Section 4.3.9, Section 5.1, Section 10	Added optionally tables for AEs and their references
		23NOV22	Dr. Maximilian Parr	Section 4.12	Spelling mistake
		06MAR23	Dr. Maximilian Parr	overall	Typos and preparation of Version 1.0
Version 0.9	Pre-final version	16MAR23	Dr. Maximilian Parr	overall	Typos and overseen changes
Version 1.0	Final version	06JUN23	Dr. Maximilian Parr	overall	Incorporating pre-final review feedback
		22JUN23	Dr. Maximilian Parr	Section 4.12, Section 4.17	Wording and typo
Version 2.0	Final Version	12SEP24	Dr. Maximilian Parr	Section 4.2, 4.3.5, and 4.3.6	Added parts for graphical Kaplan-Meier for PFS, OS, and TFTS
				Section 5.3 and 10	Added three figures