

## Study Title:

**Modulation of the FOLFIRI-based standard 1<sup>st</sup>-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 1<sup>st</sup>-line therapy with or without intermittent cetuximab**

Name of the test products: Cetuximab  
Indication: **Metastatic colorectal Cancer**  
Clinical trial phase II

**Short Title / Acronym: MoLiMoR**  
**Protocol number: Version 3.0, March 9<sup>th</sup>, 2021**  
**EudraCT Number / EUCT number: 2019-003714-14**

*January 7<sup>th</sup>, 2021 – June 11<sup>th</sup>, 2024/December 6<sup>th</sup>, 2024*

## Clinical Study Report

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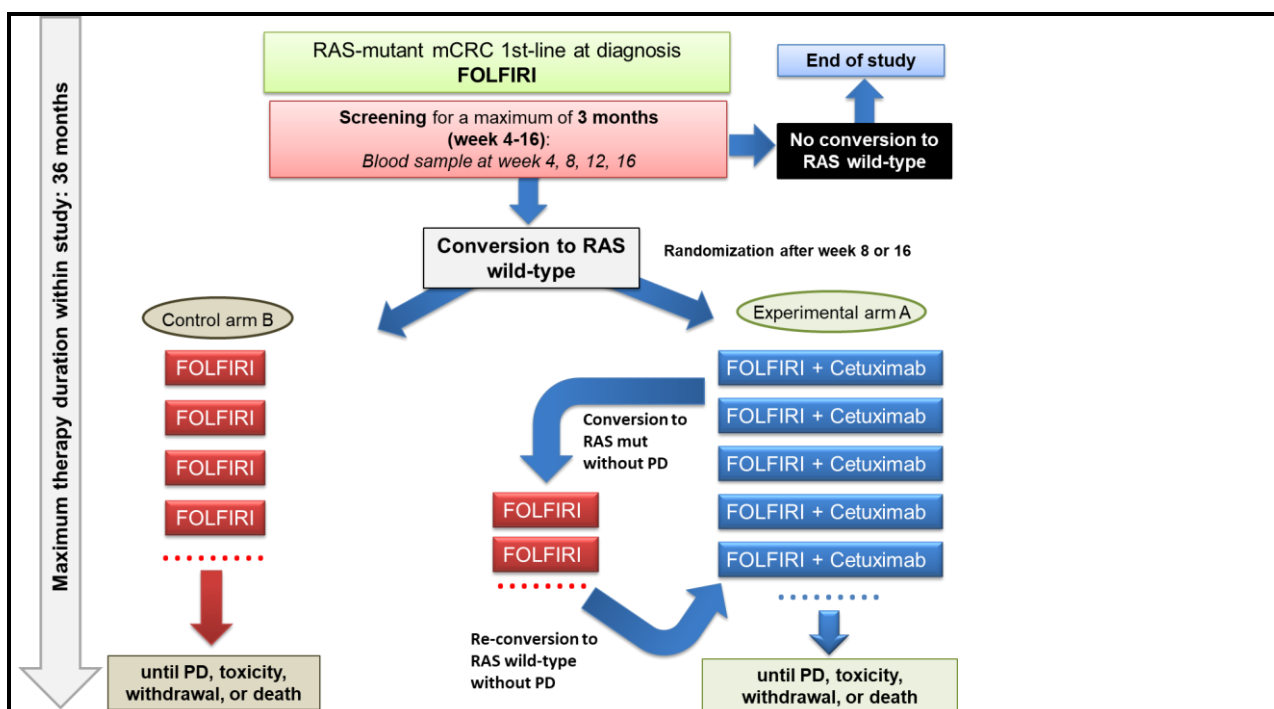
The study was performed in compliance with International Council for Harmonisation (ICH) guideline on Good clinical Practice (GCP), including archiving of essential documents

**Version / Date: v0.2 / March 17<sup>th</sup>, 2025**

This clinical study report is confidential information and may not be disclosed to third parties not associated with the clinical investigation or used for any purpose without the prior to written consent of the sponsor

## SYNOPSIS

<b>Name of Sponsor:</b> <i>TheraOp gGmbH</i>	
<b>Test product:</b> Cetuximab	
<b>Study title:</b>	Modulation of the FOLFIRI-based standard 1 <sup>st</sup> line therapy with cetuximab, controlled by monitoring the <i>RAS</i> mutation load by liquid biopsy in <i>RAS</i> -mutated mCRC patients
<b>Trial registry name:</b>	MoLiMoR
<b>EudraCT-No.:</b>	2019-003714-14
<b>Protocol number:</b>	Version 3.0 dated March 9 <sup>th</sup> , 2021
<b>Principal / Coordinating Investigator:</b> Prof. Dr. med. Alexander Baraniskin	
<b>Study sites:</b> Between September 2020 and July 2021 20 sites in Germany and 1 site in Austria screened patients. Of these, 4 sites randomized patients. <ol style="list-style-type: none"> <li>1) Onkologisches Zentrum Donauwörth, Onkologisches Zentrum, Dachau</li> <li>2) Kliniken Essen-Mitte Evang. Huysens-Stiftung, Klinik für internistische Onkologie/Hämatologie, Essen</li> <li>3) Universitätsklinikum Knappschafts Krankenhaus Bochum, Medizinische Klinik – Innere Medizin, Bochum</li> <li>4) Evangelisches Krankenhaus Hamm, Innere Medizin II, Hamm</li> </ol>	
<b>Publication:</b> not applicable	
<b>Study Period:</b> <b>First patient in:</b> January 7 <sup>th</sup> , 2021 <b>Last patient out:</b> June 11 <sup>th</sup> , 2024 <b>Data base hard lock:</b> December 6 <sup>th</sup> , 2024	<b>Phase of development:</b> II
<b>Result analysis stage:</b> final	
<b>Background and rationale for the study:</b> Colorectal Cancer (CRC) is the third most common cancer worldwide. 20-25% of patients are initially diagnosed with metastatic disease (UICC stage IV). The therapeutic management of CRC is strongly dependent on the disease stage. Next to surgery and chemotherapy, targeted therapies are available. The use of EGFR-Inhibitors such as cetuximab is used in the therapy of <i>RAS</i> wild-type mCRC with left sided primary tumors, since it has been shown that cetuximab is ineffective in CRC with <i>KRAS</i> mutation and location of the primary tumors in the right side is associated with minor response. A major limitation in the treatment of <i>RAS</i> wild-type patients with cetuximab is the development of resistance during anti-EGFR treatment that is predictive for reduced benefit from this therapy. After discontinuation of EGFR inhibition, <i>RAS</i> mutational load rapidly decreases. Therefore, an adaption of the therapy in accordance to regular monitoring of <i>RAS</i> -status should be used to adjust therapy. Patients with mutant <i>RAS</i> received standard 1 <sup>st</sup> line therapy with FOLFIRI until conversion of <i>RAS</i> to wild-type was observed. Patients were randomised to receive adjusted treatment according to <i>RAS</i> status in the experimental arm or FOLFIRI monotherapy in the control arm. The intermittent addition of cetuximab to FOLFIRI until re-conversion to mutant <i>RAS</i> was compared to FOLFIRI alone.	

**Objectives:****Primary objective:**

To evaluate efficacy in terms of progression free survival (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:**

- Overall survival (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 1 year after date of randomization
- Depth of response in terms of reduction of tumormass in experimental and control arms after start of 1<sup>st</sup>-line treatment
- Metastasis resections in experimental and control arms after start of 1st line treatment
- Objective response rate (ORR) defined as patients with partial or complete response (CR + PR) in experimental and control arms after start of 1<sup>st</sup>-line treatment
- Safety profile according to CTCAE, Version 5.0 criteria in experimental and control arms recorded from the date of signature of Informed Consent

**Exploratory objectives:**

- To identify driver mutations (e.g. BRAF, PI3K-AKT-mTOR etc.) in patients with progressive disease (PD) under cetuximab therapy who remain *RAS* wild-type in liquid biopsy
- To compare the efficacy in terms of progression free survival (PFS) in patients with conversion to *RAS* wild-type in ddPCR and BEAMing, both sensitive digital Polymerase Chain Reaction methods, with those patients showing conversion to *RAS* wild-type in ddPCR but not in BEAMing

**Methodology:** This was a prospective, open-label, randomized, multicentre phase II trial conducted in Germany and Austria to evaluate the efficacy and safety of intermittent addition of cetuximab to a FOLFIRI-based 1<sup>st</sup>-line therapy in patients with *RAS*-mutant mCRC at diagnosis who converted to *RAS* wild-type.

**Number of patients (planned and analysed):**

It was planned to include a total of 144 patients with left-sided *RAS*-mutated mCRC into pre-randomization phase, the expected number of patients eligible to randomization due to conversion to *RAS* wild-type until week 16 was 116: 58 patients in the experimental arm, 58 patients in the control arm.

129 patients were screened; six patients were randomized (experimental arm: N=4; control arm: N=2).

**Diagnosis and main criteria for inclusion and exclusion:**

Diagnosis: 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)

Inclusion criteria:

1. Age  $\geq$  18 years on day of signing informed consent
2. No previous chemotherapy for metastatic disease (1 - 2 cycles FOLFIRI or mFOLFIRI are permitted before enrolment until *RAS* status is determined)
3. Patients suitable for chemotherapy administration
4. ECOG performance status 0 - 1
5. Consent to liquid biopsy and mutation analysis
6. Estimated life expectancy > 3 months
7. Presence of at least one measurable reference lesion according to the RECIST 1.1 criteria (chest CT and abdominal CT 4 weeks or less before enrolment)
8. Adequate organ system function
9. Time interval of at least 6 months since last administration of any previous neoadjuvant/adjuvant chemotherapy or radiochemotherapy of the primary tumor in curative treatment intention
10. Any relevant toxicities of prior treatments must have resolved to grade  $\leq$  1 according to the CTCAE (version 5), except alopecia
11. Women of childbearing potential (WOCBP) should have a negative urine pregnancy test within 72 hours prior to receiving the first dose of study medication, and agrees to use adequate contraception
12. Signed written informed consent and capacity to understand the informed consent

Exclusion criteria:

1. Right sided mCRC
2. Primarily resectable metastases
3. Previous chemotherapy for the colorectal cancer except for adjuvant treatment, completed at least 6 months before entering the study (1-2 cycles of FOLFIRI or mFOLFIRI are permitted before enrolment)
4. Patients with known brain metastases
5. Symptomatic peritoneal carcinosis
6. Progressive disease before randomization
7. History of acute or subacute intestinal occlusion, inflammatory bowel disease, immune colitis or chronic diarrhea
8. Grade II heart failure (NYHA classification), Myocardial infarction, balloon angioplasty (PTCA) with or without stenting, and cerebral vascular accident/stroke within the past 12 months before enrolment, unstable angina pectoris, serious cardiac arrhythmia according to investigator's judgment requiring medication
9. Medical or psychological impairments associated with restricted ability to give consent or not allowing conduct of the study
10. Active infection with hepatitis B or C
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)

12. Uncontrolled hypertension
13. Marked proteinuria (nephrotic syndrome)
14. Arterial thromboembolism or severe hemorrhage within 6 months prior to randomization (except for tumor bleeding before tumor resection surgery)
15. Hemorrhagic diathesis or tendency towards thrombosis
16. Participation in a clinical study or experimental drug treatment within 30 days prior to study
17. Known hypersensitivity or allergic reaction to any of the study medications
18. Severe, non-healing wounds, ulcers, bone fractures or an infection requiring systemic therapy
19. Known history of alcohol or drug abuse
20. Complete dihydropyrimidine dehydrogenase (DPD) deficiency (phenotype and/or genotype test)
21. Known glucuronidation deficiency (Gilbert's syndrome) (specific screening not required)
22. Absent or restricted legal capacity
23. For female patients only: Pregnancy (absence to be confirmed by  $\beta$ -HCG test) or lactating

**Test product (dosage, method of administration, batch number(s))**
**FOLFIRI + cetuximab**

- Irinotecan 180 mg/m<sup>2</sup> iv, 30-90 min
- Folinic acid (racemic) 400mg/m<sup>2</sup> iv, 120 min
- 5-FU 400 mg/m<sup>2</sup> bolus
- 5-FU 2400 mg/m<sup>2</sup> iv, over 46 h
- Cetuximab: initially 400 mg/m<sup>2</sup> iv, 120 min ( $\leq$  5 mg/min), subsequently 250 mg/m<sup>2</sup> iv, 60 min infusion every week ( $\leq$  10 mg/min)

OR

**mFOLFIRI + cetuximab:**

- Irinotecan 180 mg/m<sup>2</sup> iv, 30 - 90 min
- Folinic acid (racemic) 400 mg/m<sup>2</sup> iv, 120 min
- 5-FU 2400 mg/m<sup>2</sup> iv over 46 h
- Cetuximab initially 400 mg/m<sup>2</sup> as a 120 min infusion ( $\leq$  5 mg/min), subsequently 250 mg/m<sup>2</sup> iv as a 60 min infusion every week ( $\leq$  10 mg/min)

Batch numbers cetuximab:

G00T4B

G00SY1

G00X1K

G010XY

G012F4

G012F5

G013DH

G0157D

GO15RU

GO17AM

G00XGL

**Duration of treatment:**

Patients continued study treatment for a maximum of 36 months or until disease progression, unacceptable toxicity, withdrawal of informed consent, patient preference or death, whichever occurred first

**Reference product (dosage, method of administration, batch number(s))**
**FOLFIRI**

- Irinotecan 180 mg/m<sup>2</sup> iv, 30-90 min
- Folinic acid (racemic) 400mg/m<sup>2</sup> iv, 120 min

- 5-FU 400 mg/m<sup>2</sup> bolus
- 5-FU 2400 mg/m<sup>2</sup> iv, over 46 h

OR

mFOLFIRI

- Irinotecan 180 mg/m<sup>2</sup> iv, 30 - 90 min
- Folinic acid (racemic) 400 mg/m<sup>2</sup> iv, 120 min
- 5-FU 2400 mg/m<sup>2</sup> iv over 46 h

**Batch numbers Irinotecan:**

Pre-randomization phase:	Randomization phase:
M2006116	M2010732
M2010732	M2014001
AC0283S	AC0283S
M2014001	AC0284S
CF41	AC0292AS
CF45	AC0303S
CM94	AC291
	M2015432
	AC0921
	CF41

**Batch number Folinic Acid**

Prerandomization phase	Randomization phase
OH125HO	9N109N9
BK81U	0N138N0
BR90	BK81U
CB21	CB21
BL10U	CH89
CL13	BL10U
	CL13
	0N139C1
	CL10U
	10CL13
	CL24
	16QG1971
	OG124H0

**Batch number 5-FU**

Prerandomization phase	Randomization phase
PY06909	F200304A
E200264A	F200322AA
E200270A	F200306A
F200304A	F200307A
2004009S	F200328A
2004010S	P2001386
L190730AA	F200324A
C200111AA	F200333A
F200323AA	H210313A
G200389AA	P2000331
F200331AA	2004010S

C200152AA  
 AF0074S  
 AF0077  
 D200202AA  
 AF0087F  
 E200259AA  
 AF0087S  
 AF0101S  
 F210313A  
 H210305A  
 H210307A  
 H210309A  
 H210312A  
 K210463A

**Endpoints:** not applicable

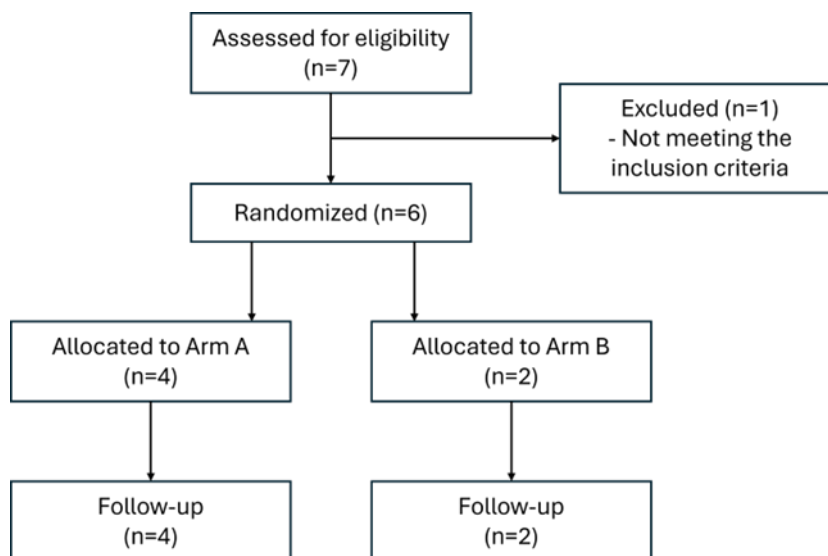
**Statistical methods:**

Due to the small number of patients included in the study, most analyses were presented as listings. Summary statistics of continuous variables like mean, standard deviation, and quantiles were not provided. Event-related data like ORR, OS, and PFS were estimated by the Kaplan-Meier method. A swimmer plot showing the treatment and response timeline for each patient was calculated. Each listing showed the patient number, the arm into which the patient was randomized, and all relevant variables.

There was no differentiation between the analysis populations mITT (modified Intention to treat population), SP (Safety Population) and PP (per protocol population).

**Summary of results and Conclusion:**

Subject Disposition: Between September 2020 and July 2021, 129 patients were screened by 20 sites in Germany and 1 site in Austria. Six patients were enrolled by four sites in Germany. Four patients were randomized into the experimental arm and two patients the control arm. All six patients received at least one dose of study treatment. The following figure gives an overview of the patient distribution.



Demographic and baseline characteristics: Patients enrolled in the study were between 41 and 80 years old. One female and five male patients were included in the study. All patients were Caucasian. Four out of six randomized patients had an ECOG of 0 at Baseline. Two Patients had ECOG 1 at Baseline.

Regarding previous therapies five out of six patients received a resection of the primary tumor before study inclusion, all with a Resection status of R0.

The time from baseline sampling until conversion to *RAS* wild-type ranged between 21 days and 64 days in the experimental arm and between 21 and 29 days in the control arm..

Primary efficacy endpoint: PFS of patients

PFS of patients, defined as time between date of randomization until the date of progression according to RECIST v.1.1 criteria or date of death from any cause, whichever occurred first, ranged from 1.97 to 9.77 months in the experimental treatment group. In the control group PFS ranged from 3.68 to 8.95 months.

Secondary efficacy endpoint: Objective response rate (RECIST v1.1 criteria)

The ORR was defined as patients with partial or complete response (PR + CR).

No patient irrespective of treatment received a CR. Three patients in the experimental arm achieved PR. For the control arm, one patient showed PR

Secondary efficacy endpoint: Overall survival

OS was calculated from the date of randomization until death from any cause. OS in the experimental arm ranged from 10.86 to 35.07 months, in the control arm from 10.23 to 28.36 months.

Secondary efficacy endpoint: Time to failure of treatment strategy

TFTS was defined as time from date of randomization to failure of treatment strategy defined as treatment discontinuation for any reason. In the experimental arm the shortest TFTS was 1.88 months, the maximum TFTS was 7.83. The median was 4.9.

In the control arm one patient had a failure of treatment strategy after 4.05 months, the other patient after 7.83 months. The calculated median was 4.9; however, the small sample size of patients limited the statistical validity of this calculation.

Safety results:

All six patients who received at least one cycle of the study treatment reported a total of 78 adverse events (AE). Thereof, 47 AEs were classified as treatment-related. Three patients had at least one AE with maximal grade of 2, one patient had at three AEs of grade 3. Two patients with AEs died as result of an AE. 50% of the patients experienced a serious AE (SAE).

Most frequently reported AEs were nausea (N=5), diarrhoea (N=4), fatigue and alopecia (N=3 each).

AEs were defined as special if they involved pregnancy or medication error. There were two cases of medication error reported as special AE. Once medication was overdosed, the other time medication dose was changed.

Conclusion(s):

This multi-centre, randomized phase-II clinical study aimed to investigate the efficacy and safety of the adaption of adding cetuximab to 1<sup>st</sup>-line therapy with FOLFIRI after *RAS*-mutation status changed to wild-type and changing back to FOLFIRI, as required if *RAS*-mutation status changed to mutant.

The planned number of patients was not reached. The recruitment phase was terminated early. Only six patients were randomized (experimental arm: N=4, control arm: N=2). All randomized patients were evaluable for analysis of efficacy and safety. Due to the small number of evaluable patients the explanatory power of these results is limited.

The primary efficacy endpoint was PFS. In the experimental arm, PFS ranged from 1.97 to 9.77 months, in the control arm PFS ranged from 3.68 to 8.95 months.

Analysis of the secondary efficacy objectives (ORR, OS, TFTS) Was not able to show differences between experimental and control group due to limited data.



78 AEs in six patients were recorded during the study. NCI grade of the AEs ranged from 1 (N=57) to 5 (N=2). Four SAEs occurred in three patients. Mainly AEs in the SOC 'gastrointestinal disorders' and 'Investigations' were experienced which is in line with the toxicity profile of FOLFIRI and Cetuximab. No new safety issues for FOLFIRI and Cetuximab were identified in the study.

In 2014, 61.000 people were diagnosed with CRC and a total of 25.5000 patients died due to CRC. In 2022, the number of people affected was roughly constant. The numbers are trending upwards, making clear that there is still a great unmet need for further development of CRC treatment, especially for advanced stages.

The development of resistance to targeted therapies is a major limitation in treatment of mCRC, thus the development of new strategies to overcome secondary drug resistance is very important. The approach of liquid biopsy-guided therapy, in which *RAS* mutation status is analysed at regular intervals and the therapy is adjusted, as investigated in this study could be one solution for this problem. Analysis of ctDNA is component of further studies that investigate re-challenge therapy with anti-EGFR after development of resistance in previous therapies.

Future studies should continue to investigate the value of regular re-evaluation of *RAS* mutation status by liquid biopsy and subsequent adjustment of anti-EGFR therapy in patients with mCR. The optimal timing for sample collection should also be an aspect of the research.

To address the problem of low patient recruitment in future studies, the study design should be kept as simple as possible. Consideration should be given to administering cetuximab at a once every-second-week dose of 500 mg/m<sup>2</sup> instead of 250 mg/m<sup>2</sup> on day 1 and day 8. The safety of this administration of cetuximab was assessed in a phase-I dose escalation study.

Another problem in this study was the time required to determine the *RAS* mutation status in patients with high therapy pressure. Faster molecular pathological analysis of samples could make these patients eligible for the study.

**Date and version of this report:** v0.1 January 22<sup>nd</sup>, 2025

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## 4 LIST OF ACRONYMS & ABBREVIATIONS AND DEFINITIONS

(a)PTT	(activated) Partial thromboplastin time
5-FU	5-fluorouracil
AE	Adverse event
ALAT	Alanine-aminotransferase (= SGPT = serum glutamate pyruvate transaminase)
AMG	German Medicinal Products Act
ASAT	aspartate-aminotransferase (= SGOT = serum glutamate oxalacetate transaminase)
BRAF	Human gene that encodes B-Raf
CA-19-9	Carbohydrate-Antigen 19-9
CEA	Carcinoembryonic antigen
CI	Confidence interval
Cq	Cycle quantification value
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CT	Computer tomography
CTC	Circulating tumor cells
CTCAE	Common Terminology Criteria of Adverse Events
ctDNA	Circulating cell-free tumor DANN
CTFG	Clinical Trial Facilitation Group
ddPCR	Droplet Digital Polymerase chain reaction
DNA	Deoxyribonucleic acid
DPD	Dihydropyrimidine dehydrogenase
DpR	Depth of response
DSMB	Data and Safety Monitoring Board
EDC	Electronic data capture
e.g.	For example
ECG	Electrocardiogram
eCheck	Electronic check
ECOG (PS)	Eastern Cooperative Oncology Group (Performance Status)
eCRF	electronic case report form
EGFR	Epidermal growth factor receptor
ESMO	European Society of Medical Oncology
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
h	Hour
HR	Hazard ratio
ICH GCP	International Conference on Harmonisation - Good Clinical Practice
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G
INR	International normalized ratio
IRB	Institutional Review Board
iv	Intravenous
KRAS	Kirsten Rat Sarcoma Virus
LVEF	Left ventricular ejection fraction
m <sup>2</sup>	Square meter
mAB	Monoclonal antibodies
Max.	Maximum
mCheck	Manual check
mCRC	Metastatic colorectal cancer
MeDRA	Medical dictionary for regulatory activities

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mFOLFIRI	Modified FOLFIRI
mg	Milligram
min	Minute
Min	Minimum
mITT	Modified Intention to treat
ml	Millilitre
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ng	Nanogram
NGS	Next generation sequencing
NPY	Neuropeptide Y
<i>NRAS</i>	Nenuroblastoma Rat Sarcoma viral oncogene homolog
NTC	Non-target control
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
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 term
PTCA	Percutaneous transluminal coronary angioplasty
qPCR	Quantitative polymerase chain reaction
<i>RAS</i>	Rat sarcoma
RECIST	Response Evaluation Criteria In Solid Tumors V 1.1
SAE	Serious adverse event
SAP	Statistical analysis plan
SDV	Source Data Verification
SmPC	Summary of medicinal Product Characteristics
SOC	System organ class
SP	Safety population
TFTS	Time to failure of treatment strategy
UICC	Union for International Cancer Control
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
WIF1	Wnt inhibitory factor 1
WOCBP	Women of childbearing potential
Wt	Wild-type

## 5 ETHICS

### 5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The documents on the pharmacological and toxicological testing of trial medication were filed with the Competent Authorities in accordance with national law. The application for approval of a clinical trial with a medicinal product for human use was made by the Contract Research Organization (CRO, Alcedis GmbH) and by the sponsor.

Before the beginning of the trial, an application for approval was submitted to the Ethics Committees of the coordinating investigator and to the ethics committees of the participating investigators. First approval with conditions was given on June 30<sup>th</sup>, 2020, by the ethics committee of the University Medicine Bochum.

Supplements or changes to the protocol could only be made by the sponsor representative and submitted to the Ethics Committees and the national competent authorities as an amendment to the protocol. Amendments made to the protocol are listed in Table 1.

**Table 1:** Overview of protocol versions.

<i>Version</i>	<i>Date</i>	<i>Comments</i>	<i>Changes in Patient information/informed consent</i>
<i>Version 1.0</i>	<i>28.08.2019</i>	<i>Final version for competent authorities and ethics committee</i>	<i>First version: Version 1.0, 28.08.2019</i>
<i>Version 1.1</i>	<i>20.02.2020</i>	<i>Revision according to deficiency letter of competent authority</i>	<i>No</i>
<i>Version 2.0</i>	<i>18.05.2020</i>	<i>Revision according to deficiency letter of ethics committee including changes required for competent authority</i>	<i>Version 2.0, 18.05.2020</i>
<i>Version 2.1</i>	<i>03.07.2020</i>	<i>Inserting information according to appraisal letter of ethics committee</i>	<i>Version 2.1, 03.07.2020</i>
<i>Version 3.0 (including Amendment 1)</i>	<i>09.03.2021</i>	<i>Amendment 1 includes:</i> <ul style="list-style-type: none"> <li><i>- Adaptation of some inclusion / exclusion criteria (i.e., Permission of 1-2 cycles FOLFIRI before enrolment. exclusion of patients with complete DPD deficiency confirmed by genotyping or phenotyping)</i></li> <li><i>- Permission to administer FOLFIRI without 5-FU bolus (mFOLFIRI)</i></li> <li><i>- Update of table ‘Schedule of visits and assessments’</i></li> <li><i>- Update of section 7.1 and 7.2 accordingly</i></li> <li><i>- Correction of a mistake in section 3.1.2 Randomization</i></li> <li><i>- Specification of monitoring of vital signs during study treatment in section 6.0</i></li> <li><i>- Specification of start date for analysis of efficacy parameters</i></li> </ul>	<i>Version 3.0, 09.03.2021</i>



## 5.2 Ethical Conduct of the Study

The regulatory basis of the conduct of this study consisted of the Declaration of Helsinki (in its current version), the AMG [German Medicinal Products Act] / Regulation EU No 536/2014 (Clinical Trials Regulation), Regulation (EU) 2016/679 (General Data Protection Regulation), and the principles of Good Clinical Practice (ICH GCP).

The sponsor had taken out insurance for all subjects who gave consent to participation in the clinical trial.

## 5.3 Patient Information and Consent

An unconditional prerequisite for a patient participating in the study was his/her written informed consent. Before obtaining the informed consent, adequate information was given to the patient by the investigator or a person designated by the investigator. A patient information sheet in the local language was provided for the purpose of obtaining informed consent. In addition to this written information, the investigator or his designate informed the patient verbally. The patient was given sufficient time and opportunity to decide on their participation and to clarify outstanding questions. The informed consent of the patient to participate in the clinical trial had to be given before any trial-related activities were carried out. It had to be signed and personally dated by the patient and by the investigator/person designated by the investigator.

The written patient Information/Informed consent sheet was submitted to the ethics committee and approved before use. The document was revised whenever important new information became available that could be relevant to the consent of patients. The revised version was submitted to the Ethics Committee for approval.

Provision of consent was confirmed in the eCRF by the investigator. The signed and dated declaration of informed consent remained at the investigator's site and was safely archived by the investigator so that the forms could be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the information and of the signed and dated consent was provided to the patient prior to participation.

A sample Patient Information Sheet/Informed Consent Form is provided as stand-alone document, which is available upon request (see Section 16.5)

## 5.4 Funding

This study entailed no additional financial expenditure either for organizations funding the hospital or for the health insurance companies in association with the clinical trial. Third party funds were provided by Merck for study coordination, documentation, monitoring and analysis.

This study entailed no financial expenditure for supplementary laboratory analyses or additional diagnostic measures associated with the therapy, as the study design was deliberately based on the procedure for the therapy administered in the previous standard.

## 6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study was an investigator-initiated trial planned to be conducted in Germany and Austria.

Initiator and National Coordinating Investigator was Prof. Dr. med. Alexander Baraniskin, Evangelisches Krankenhaus Hamm, Werler Str. 110, 59063 Hamm, Germany.

The Sponsor was the TherapOp gGmbH, represented by Bernhard Remes, Winchesterstraße 3, 35394 Gießen, Germany.

The CRO Alcedis GmbH (Winchesterstraße 3, D-35394 Gießen, Germany) was responsible for site management, development, and hosting of the study database and eCRF. Additionally, the CRO was responsible for data management, statistical analysis and preparation of the statistical and clinical study report.

At each trial site in Germany a principal investigator and at least one representative were designated who were responsible for the conduct of all aspects of the trial at the trial site. In Austria only a principal investigator was designated at each site.

A list of principal investigators of active study sites can be found in the Section 16.1.4.

Analysis of *RAS* mutation status were performed by the Immunological-Molecular Biological Laboratory of the Knappschaftskrankenhaus, Ruhr University Bochum, Universitätsstraße 150, ZKF 2, 44801 Bochum.

A DSMB was established for this study.

## 7 INTRODUCTION

### 7.1 Disease Background

Colorectal cancer (CRC) is the third most common cancer worldwide with 1.9 million new cases in 2022. In Germany, about 63,000 persons, 33,200 men and 29,300 women, were diagnosed with CRC in 2022 and more than 26,500 patients died of CRC (World Cancer Research Fund, 2022). The therapeutic management of CRC is strongly dependent on the disease stage and the genetic profile of the tumor. Surgical resection represents the cornerstone of therapy for early-stage CRC. In UICC stages I-III surgery alone may be curative; patients at high risk for recurrence in UICC stage II and all patients in UICC stage III should receive adjuvant chemotherapy additionally. Overall prognosis for patients with CRC in UICC stages I-II is favourable, with a 5-year survival rate of up to 90% (Ciombor, 2018). However, due to often vague symptoms of CRC, 20-25% of patients are initially diagnosed with metastatic disease (UICC stage IV) (van der Geest, 2015). In addition, 35-45% of patients in UICC stages II-III relapse within 5 years after surgery (Schmoll, 2012). Patients in UICC stage IV have a dramatically reduced 5-year survival rate of about 15% (American Cancer Society, 2018).

Due to improvements in diagnosis and introduction of new therapies including targeted therapies with anti-epidermal growth factor receptor (EGFR) and anti-vascular endothelial growth factor (VEGF) antibodies, colorectal cancer death rates declined by approximately 2% per year during the 1990s and by approximately 3% per year during the past decade (Siegel, 2014). The addition of targeted agents to chemotherapy also raised the median OS of mCRC significantly to approximately 30 months (Heinemann, 2014). In recent years retrospective studies demonstrated worse outcomes for patients with right sided CRC compared to left sided CRC. Right-sided CRC can arise out of the transverse colon, ascending colon or cecum. Primary tumors that originated from the descending colon, sigmoid colon or rectum are classified as the left-sided CRC. Recently, multiple randomized clinical trials have consistently shown that primary tumor location in the right side is associated with minor response to anti-EGFR therapy despite wild-type *RAS* status. In light of this evidence, the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) have revised their recommendations for the use of anti-EGFR therapy for first-line treatment in mCRC. Treatment with anti-EGFR antibodies in first line is now recommended only for wild-type *RAS* and left sided primary tumors. However, stratification by primary tumor location has not been extended to subsequent treatment (Venool, 2016; Aljehani, 2018).

### 7.2 Epidermal growth factor receptor

The epidermal growth factor receptor (EGFR) is a commonly expressed transmembrane glycoprotein of the tyrosine kinase growth factor receptor family. EGFR is normally expressed in many human tissues. Binding of its natural ligands 'epidermal growth factor' and 'transforming growth factor  $\alpha$ ' results in activation with auto-phosphorylation of the receptor tyrosine kinase thereby initiating a cascade of downstream protein phosphorylations which finally lead to cell proliferation and differentiation. The implication of EGFR signalling in tumor pathogenesis has been demonstrated in a variety of human cancers, such as head and neck cancer, colorectal cancer, lung cancer, ovarian cancer, cervical cancer, and gastric cancer. Constitutive activation of EGFR leads to stimulation of tyrosine kinase-dependent signal transduction pathways that can contribute to neoplastic transformation and tumor growth. Consequently, inhibition of EGFR signalling has been tested as treatment for various tumor types.

Among the EGFR inhibitors approved so far for tumor therapy are monoclonal antibodies (mAB) (cetuximab, panitumumab) as well as small molecule kinase inhibitors (erlotinib, gefitinib). While kinase inhibitors bind to the intracellular domain of the EGFR and block kinase activity, antibodies target the extracellular part of the receptor, thereby preventing ligand binding, conformational activation, and/or receptor dimerization.

### 7.3 Cetuximab

Cetuximab is a chimeric human/mouse monoclonal antibody of the immunoglobulin G (IgG1) subclass that targets specifically the extracellular domain human tyrosine kinase EGFR. Cetuximab binds to EGFR on both normal and tumor cells with a 5- to 10-fold higher affinity than endogenous ligands thereby competitively blocking the binding of endogenous EGFR ligands. This results in inhibition of the ligand-induced, tyrosine kinase-dependent phosphorylation and downstream signalling of the receptor. The use of cetuximab was initially restricted to Kirsten Rat Sarcoma Virus (*KRAS*) wild-type in CRC since it had been shown that cetuximab is ineffective in colorectal cancers with *KRAS* mutation, which causes constant oncogenic activation of *RAS/MEK/ERK* signal transduction at the EGFR downstream independent of EGFR-mediated signalling (Van Cutsem, 2009); resulting in unregulated downstream signalling that leads to tumor growth and survival. Consequently, inhibition of EGFR signalling by cetuximab does not have an inhibitory effect on signalling events that are downstream of constitutively activated mutant *KRAS*. Further retrospective and post-hoc analyses of clinical trials revealed that not only *KRAS* mutation negatively influences response to cetuximab but also other *RAS* mutations. Thus, approval has been restricted to *RAS* wild-type mCRC.

### 7.4 Liquid Biopsy

In contrast to invasive conventional biopsy, which is performed on solid tumors, liquid biopsy uses biological fluids (mainly blood) of cancer patients for molecular DNA analysis. This non-invasive method has emerged in the last few years and is based on the detection of circulating tumor cells (CTCs) and circulating cell-free tumor DNA (ctDNA) in blood.

The analysis of ctDNA has become the established technology for detection of mutations. Furthermore, ctDNA analysis outperforms CTCs for *RAS* mutations in both diagnostic sensitivity and specificity, enabling real-time sampling of multifocal clonal evolution (BloodPAC). The development of highly sensitive analysis methods enables the quantification of small amounts of biological entities (Stroun, 1989; Bettegowda, 2014). It is suspected, that ctDNA in the blood mainly originates from apoptotic or necrotic tumor cells (Thierry, 2016). Also, a correlation of ctDNA release with the ratio of cells in G1 phase was shown. The enhanced release of circulating free DNA from differentiated cells might be due to the active release of circulating free DNA packaged inside exosomes or in other forms that are protected from degradation in the blood (Wang, 2017). However, ctDNA harbors the same mutations as the original tumor cell (Schwarzenbach, 2011).

Detection of ctDNA depends on tumor type and stage; however, in nearly 100% of CRC patients, ctDNA can be found (Bettegowda, 2014).

High concordance of *RAS* mutation analysis between ctDNA samples and FFPE tumor tissue of about 90-95% of CRC patients has been shown by several research groups (Schmiegel, 2017; Grasselli, 2017). Therefore, especially for this cancer entity the analysis of ctDNA provides opportunities for clinical monitoring of results of anti-cancer treatment.

Due to the overall small amount of ctDNA in blood, analysis was only possible after development of high gain amplification techniques which use digitization of signals. Among these techniques are the BEAMing (stands for 'beads, emulsion, amplification, magnetics') digital polymerase chain reaction (PCR) and the Droplet Digital PCR (ddPCR). Both BEAMing and ddPCR are available and established in the study lab. Within this clinical trial ddPCR was preferentially used for the monitoring of *RAS* status during treatment. An optional comparison of results of ddPCR and BEAMing PCR was planned.

## 7.5 Mutation Analysis using ddPCR

As with 'conventional' quantitative PCR (qPCR), ddPCR technology utilizes the primer-probe amplification in a standard PCR reaction to amplify a target DNA fragment from a complex sample using pre-validated primer or primer/probe assays. However, there are two distinct differences:

- 1) For ddPCR, the partitioning of the PCR reaction into thousands of individual reaction vessels based on water-oil emulsion droplet technology to ensure that each partition contains a discrete number of nucleic acid sequences (e.g. 1 or 2) prior to amplification and
- 2) the acquisition of data at the end of reaction.

These factors offer the advantage of direct and independent quantification of DNA without standard curves giving more precise and reproducible data versus qPCR especially in the presence of sample contaminants that can partially inhibit Taq polymerase and/or primer annealing. In addition, end-point measurement enables nucleic acid quantification independently of the reaction efficiency, resulting in a positive-negative call for every droplet and greater amenability to multiplexed detection of target molecules (Taylor, 2017).

Only the difference between a positive (contains respective target nucleic acid sequence) and negative partition (does not contain the target nucleic acid sequence) is measured. The ratio of positive to negative partitions can then be related to the number of molecules in the sample, using Poisson statistics. Due to the concentration effect, the limit of detection is improved because a small reaction volume increases the effective concentration of the target molecules. Additionally, the enrichment effect improves the analysis of complex mixtures by purifying the target of interest from interfering compounds (Basu, 2017).

Thereby, ddPCR technology can be used for extremely low-target quantification from variably contaminated samples where the sample dilution requirements to assure consistent and acceptable reaction efficiency, primer annealing and cycle quantification value (Cq) values for qPCR would likely lead to undetectable target levels (Taylor, 2017).

Since 2011 ddPCR is commercially available for in vitro use. Within this clinical trial the validated ddPCR technology developed by BIORad was used according to the manufacturer's instructions in the Immunological-Molecular Biological Laboratory of the Knappschaftskrankenhaus, Ruhr University Bochum. The laboratory participates in yearly proficiency testing of isolation of DNA from plasma, for *RAS* (and *BRAF* V600E) mutation analysis, by assessing 3 unknown samples with BEAMing as well as with ddPCR technology.

In general, the procedure of ddPCR was performed as described below:

First, cell-free DNA was isolated from blood plasma. Target regions were fractionated into several thousands of water-oil droplets, so that statistically only 1 target sequence together with primers, PCR enzyme and specific fluorescence-labelled probes was included in a single droplet.

The following *KRAS* and *NRAS* mutations on exon 2, 3, 4 will be tested:

<b>KRAS</b>		<b>NRAS</b>	
<b>Exon</b>	<b>Mutation</b>	<b>Exon</b>	<b>Mutation</b>
2	G12S	2	G12S
	G12R		G12R
	G12C		G12C
	G12D		G12D
	G12A		G12A
	G12V		G12V
	G13D		G13R
			G13D
			G13V

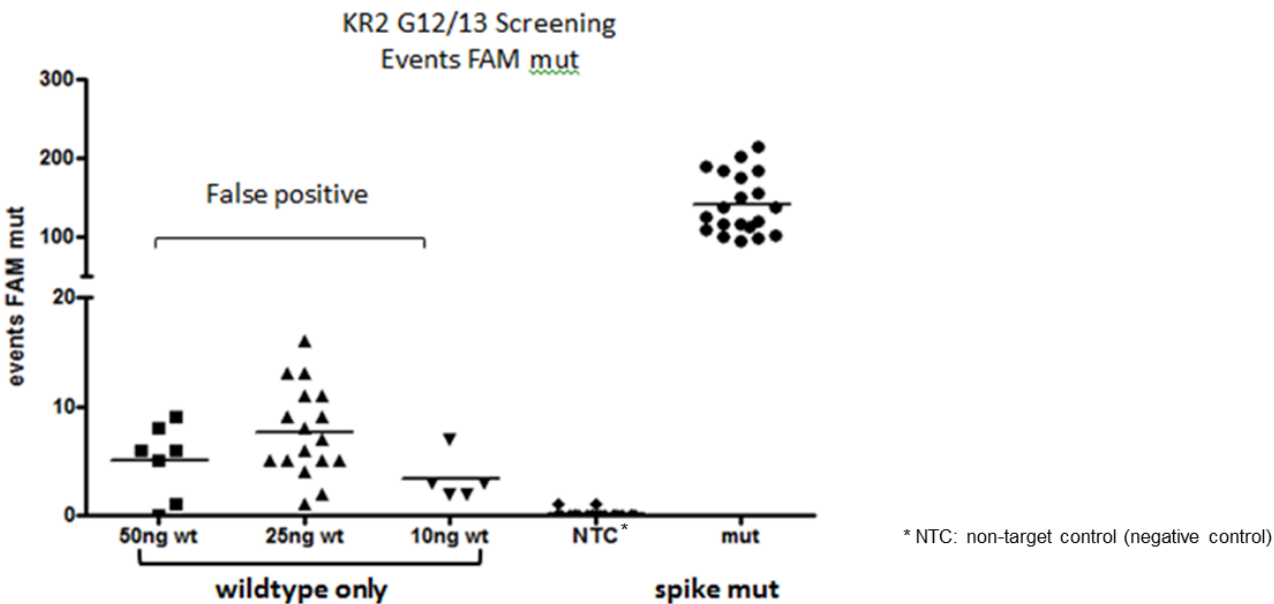
KRAS		NRAS	
Exon	Mutation	Exon	Mutation
3	A59T	3	A59T
	Q61L		Q61K
	Q16H*		Q61R
	Q16H*		Q61L
4	K117N*		Q61H*
	K117N*		Q61H*
	A146T	4	K117N*
	A146V		A146T

\*Two separate mutations detected for each of these codons

As quality control, standardized samples were used additionally in each analysis.

The cutoff value was determined with ‘wild-type only’ samples (fragmented genomic DNA of a human cell line) and titrations of defined mutated samples and samples assessed as positive or negative by BEAMing technique.

Conversely, the cutoff for detection of a mutation was determined with regard to the false positive signals detected in several ‘wild-type only’ analyses. As shown below, the proportion of false positive signals depended on the amount of wild-type DNA.



The percentage of false positive signals of 30 ‘wild-type only’ samples analysed amounted to a mean of 0.09 ± 0.06%. To ensure detection of mutation the cutoff was set to 0.27% (mean including standard deviation).

The mean number of false positive events in these 30 analysed samples was 6.3 ± 4. Thus, a definite detection of the mutation is possible in case of >12 events.

With these determined cutoff values a mutation can be safely distinguished from false positive wild-type signals within low amount of DNA.

27 samples determined as wild-type or mutated by BEAMing technique which is approved for RAS mutation analysis, were analyzed with ddPCR using the before established cutoffs additionally. It could be shown that no sample detected as wild-type (=negative) with BEAMing was identified as mutated (=positive) with ddPCR:

Cutoff 0.27%	BEAMing pos	BEAMing neg	Total
ddPCR pos	11	0	11
ddPCR neg	3	13	16
Total	14	13	27

Thus, the ddPCR analysis determined with a sensitivity of 79% and specificity of 100% a mutation in KR2-12/13 with 89% certainty [False discovery rate ((false negative +false positive) / all) = 11%].

## 7.6 Conversion of *RAS* Status

A major limitation of treatment of *RAS* wild-type patients with cetuximab is the development of resistance. It has been acknowledged that newly detected *RAS* mutations evolve during anti-EGFR mAb treatment and are predictive for reduced benefit from this therapy. More than half of patients with acquired resistance to first-line anti-EGFR containing therapy revealed conversion from *RAS* wild-type to *RAS* mutated status (Klein-Scory, 2018; Morelli, 2015; Yamada, 2016; Siravegna, 2015; Toledo, 2017; Khan, 2018; Cremolini, 2018). By examination of circulating, cell-free DNA, Diaz et al. discovered that acquired resistance to treatment was the result of selection of clonal existing subpopulations (Diaz, 2012). There is predominant suppression of *RAS* wild-type clones during anti-EGFR mAb therapy and, in this manner, indirect selection of *RAS*-mutated clones. However, after the discontinuation of EGFR inhibition, *RAS* mutational load rapidly decreases within a few weeks, probably due to the lack of selective pressure from the anti-EGFR mAb therapy (Klein-Scory, 2018). In addition, new *RAS* mutations can arise without a direct selection pressure by an anti-EGFR mAb. In this case, modifications of therapy agents may lead to renewed disappearance of *RAS*-mutated clones (Klein-Scory, 2018).

Recently, longitudinal analyses of cell-free tumor DNA of mCRC patients with *RAS* mutation at diagnosis demonstrated that they convert to wild-type *RAS* during systemic 1st line chemotherapy in most cases. Remarkably, the conversion was observed even after just one cycle of chemotherapy. The conversion to *RAS* wild-type occurred independent of type and intensity of chemo- and anti-VEGF therapy and amounted to about 70% of patients with initially *RAS* mutated mCRC who showed conversion to *RAS* wild-type (Sunakawa, 2018; Klein Scory, 2020). Additional examination of tumor-specific epigenetic biomarkers (hypermethylation of promoter regions of Wnt inhibitory factor 1 (WIF1) and neuropeptide Y (NPY)) revealed that these were detected in samples with disappearance of *RAS* mutation, thus being a hint, that in these samples tumor-DNA was still present (Klein-Scory, 2020). Aberrant methylation of the promotor regions of NPY and WIF1 has been demonstrated to be involved in decreased expression which promotes development of cancer. Thus, methylation analysis of these promotor regions in liquid biopsy samples can serve as a surrogate marker for cancer cells (Garrigou, 2015; Roperch, 2013).

## 7.7 Study Rationale

As mentioned before, it has been shown, that *RAS*-mutated status of mCRC present at diagnosis mostly converts to wild-type status as assessed by liquid biopsy during the first line chemotherapy. Since treatment options for patients with mCRC are limited, especially for patients with *RAS* mutations, who are not considered eligible for therapy with EGFR antibodies, this study used regular monitoring of *RAS* status by liquid biopsy to treat patients according to their actual *RAS* status. Thus, mCRC patients with mutant *RAS* received standard first line chemotherapy (FOLFIRI) according to guidelines recommending a double or triple chemotherapy in case of *RAS*-mutated mCRC until the conversion of *RAS* to wild-type was observed (S3-Leitlinie Kolorektales Karzinom, 2019). Wild-type patients were then randomized to continue the existing treatment regimen (Control Arm) or to switch to the EGFR antibody cetuximab in combination with FOLFIRI (Experimental Arm) until re-conversion to mutant *RAS*. In both arms the treatment strategy was followed until PD, unacceptable toxicity, withdrawal of informed consent or death, whichever occurred first.

This study design of therapy adaptations as performed in the experimental arm had 2 advantages:

- 1) Patients with initially mutant *RAS* could benefit from anti-EGFR treatment due to conversion of *RAS* status during standard first line therapy and to the data that the treatment with an EGFR antibody is the most effective treatment option for patients with left-sided *RAS* wild-type mCRC
- 2) Emerging resistance to treatment with cetuximab which may limit the clinical benefit was bypassed by early switching to chemotherapy (FOLFIRI) without cetuximab before PD. This ensured that patients with *RAS* mutations in liquid biopsy did not receive EGFR antibodies outside of the approval.
- 3) Steps 1 and 2 could be repeated as long as the patient did not experience disease progression.

Therefore, it was expected that patients in the experimental switch arm will have a longer PFS compared to control arm.

The randomized study design allowed direct comparison of standard therapy and switch treatment without bias by investigator or patient characteristics.



## 8 STUDY OBJECTIVES AND ENDPOINTS

### 8.1 Objectives

#### 8.1.1 Primary objectives

- To evaluate efficacy in terms of progression free survival (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

#### 8.1.2 Secondary objectives

- Overall survival (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 1 year after date of randomization
- Depth of response in terms of reduction of tumor mass in experimental and control arms after start of 1<sup>st</sup> line treatment,
- Metastasis resections in experimental and control arms after start of 1<sup>st</sup>-line treatment
- Objective response rate (ORR) defined as patients with partial or complete response (CR + PR) in experimental and control arms after start of 1<sup>st</sup>-line treatment
- Safety profile according to CTCAE, Version 5.0 criteria in experimental and control arms recorded from the date of signature of Informed Consent

#### 8.1.3 Exploratory objectives:

- To identify driver mutations (e.g. BRAF, PI3K-AKT-mTOR etc.) in patients with progressive disease (PD) under cetuximab therapy who remain *RAS* wild-type in liquid biopsy
- To compare the efficacy in terms of progression free survival (PFS) in patients with conversion to *RAS* wild-type in ddPCR and BEAMing, both sensitive digital Polymerase Chain Reaction methods, with those patients showing conversion to *RAS* wild-type in ddPCR but not in BEAMing

### 8.2 Endpoints

Not applicable.

## 9 INVESTIGATIONAL PLAN

### 9.1 Overall Study Plan / Study Design

This was an open-label, prospective, randomized, multicentre phase II study to evaluate the efficacy and safety of intermittent addition of cetuximab to a FOLFIRI-based 1<sup>st</sup>-line therapy in patients with *RAS*-mutant mCRC at diagnosis who convert to *RAS* wild-type by monitoring the *RAS* mutation status by liquid biopsy.

Patients with left-sided *RAS*-mutated metastatic colorectal cancer (mCRC) eligible for study participation and receiving standard FOLFIRI as 1<sup>st</sup>-line treatment were screened for a maximum of 3 months (week 4 to 16) for conversion to *RAS* wild-type. As soon as *RAS* wild-type was detected, no further blood samples for screening were taken. Conversion to *RAS* wild-type at week 4 or 8 and at week 12 or 16 led to randomization at weeks 8 or 16 (directly after follow-up CT scan), respectively. Patients without conversion to *RAS* wild-type by week 16 ended the study. Figure 1 gives an overview of the study design.

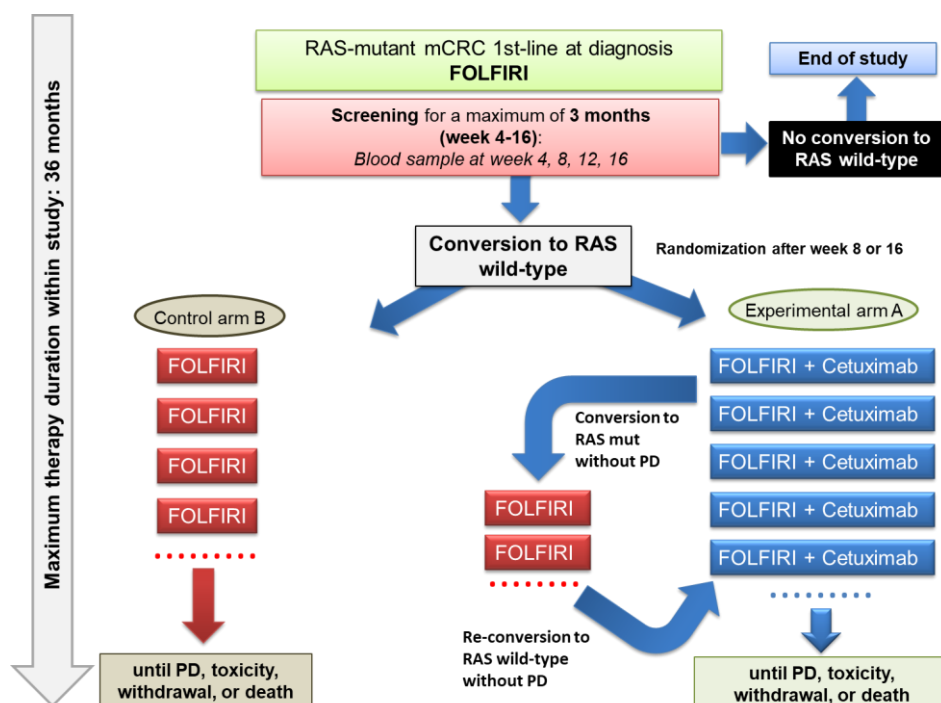


Figure 1: Overview of study design

The estimated number of patients enrolled into pre-randomization phase was 144. A maximum of 116 patients with left-sided mCRC with conversion of mutant *RAS* within the first 4 months were planned to be randomized (58 patients into the control arm, 58 patients in the experimental arm) Until study termination 6 patients were enrolled.

### 9.2 Discussion of Study Design, Including the Choice of Control Groups

All mCRC patients enrolled into this randomized trial received therapy according to the current *RAS* status and approval status of the drugs employed. Thus, it was not expected that study participants were under-treated or were exposed to additional risks from the treatment. Tumor staging was also performed in line with the guidelines for stage IV patients in both randomization arms.

Blood sampling for liquid biopsy was collected during routine blood sampling before chemotherapeutic treatment. No additional invasive methods were used.

Due to limited clinical data supporting this innovative study design, two stopping rules were included to increase patient safety but were not applicable due to number of patients enrolled:

- 1) After randomization of 20 patients, further enrolment into the study should have been paused. Liquid biopsy samples from the first 20 screened patients should have been analysed in parallel by 2 laboratories. In case of concordant results, the study should have continued. In case of discordant results, a Data and Safety Monitoring Board (DSMB) should have made recommendations for further progress of the study. Additionally, tumor-specific genes should have been analysed to define ctDNA in the samples. This should have been primarily performed by measurement of “house-keeping genes” that had been identified by Next Generation Sequencing (NGS) of baseline tumor tissue or if not applicable by methylation analysis of promotor region of the genes WIF1 and NPY which serve as surrogate markers for tumor cells.

The time for this interim analysis was not reached due to the small number of patients enrolled. Nevertheless 7 samples of three different patients were analysed in a second laboratory in Mannheim. 2 of the samples showed discrepancies. No further analysis was carried out. Also, for the first 20 patients showing conversion to *RAS* wild-type in liquid biopsy during screening, at two time points, tumor material assessed locally, as well as a liquid biopsy sample should have been analysed comparatively for *RAS* mutation / wild-type to assess agreement between the analysis methods. This should have been done at baseline and once during screening when *RAS* wild-type was detected in liquid biopsy. For the second comparison tumor material of a new biopsy assessed locally should have been used, if possible. In cases of discordant *RAS* results between liquid and tumor biopsy, patients should not have been randomized. Overall, in at least 80% of patients a biopsy should have been taken to confirm *RAS* status in tissue of respective patients. However, if a patient had refused a new biopsy, he/she would have still been randomized and could have continued the study.

In addition, in the first 8 weeks after randomization, blood samples of the first 10 patients randomized into experimental arm A should have been taken more frequently: at weeks 2, 4, 6 and 8 instead of just weeks 4 and 8. If  $\geq 5$  of 10 patients in the experimental arm A would have shown *RAS* mutation within 4 weeks after randomization by liquid biopsy, the study would have been terminated prematurely, because, in this case, the effect of *RAS* conversion would not have seemed to be lasting long enough. This stopping rule was applied to the 4 patients randomized into arm A. Blood samples were taken at week 2, 4, 6 and 8. After 8 weeks all 4 patients still showed *RAS* wild-type.

Results of these analyses were reviewed by a DSMB and notified to the ethics committee together with recommendations of the DSMB regarding study conduct.

- 2) After 50 patients had been screened, the proportion of patients with conversion from *RAS* mutant to *RAS* wild-type should have been analysed and evaluated by the DSMB. If less than 50% of analysed patients showed conversion to *RAS* wild-type, the DSMB should have made recommendations regarding the conduct of the study. These should have been notified to the ethics committee.

### 9.3 Selection of Study Population

The selection of patients occurred through the investigator according to the inclusion and exclusion criteria after informing the patient written and orally about the study and after patient had signed the informed consent. No gender specific differences were expected concerning the efficacy and safety of the study treatment. Hence there was no preferred enrolment of men or women within this study. Pregnant or breastfeeding women were excluded from participation.

#### 9.3.1 Inclusion Criteria

Patients were included in the trial only if they met all the following criteria:

- Histologically confirmed, UICC stage IV adenocarcinoma of the left-sided colon or rectum with metastases (metastatic colorectal cancer), primarily non-resectable, confirmed *RAS* mutations proven in the primary tumor or metastasis (*KRAS* and *NRAS* exon 2, 3, 4)

- Age  $\geq$  18 years on day of signing informed consent
- No previous chemotherapy for metastatic disease (1 - 2 cycles FOLFIRI or mFOLFIRI are permitted before enrolment until *RAS* status is determined)
- Patients suitable for chemotherapy administration
- ECOG performance status 0-1
- Consent to liquid biopsy and mutation analysis
- Estimated life expectancy > 3 months
- Presence of at least one measurable reference lesion according to the RECIST 1.1 criteria (chest CT and abdominal CT 4 weeks or less before enrolment)
- Adequate bone marrow function defined as:
  - Leukocytes  $3.0 \times 10^9/L$  with neutrophils  $1.5 \times 10^9/L$
  - Thrombocytes  $100 \times 10^9/L$
  - Hemoglobin 9 g/dL
- Adequate hepatic function defined as: Serum bilirubin  $1.5 \times ULN$ , ALAT and ASAT  $2.5 \times ULN$  (in the presence of hepatic metastases, ALAT and ASAT  $5 \times ULN$ )
- Adequate renal function: Creatinine clearance  $\geq 50$  mL/min
- Adequate cardiac function defined as: normal ECG and echocardiogram with a left ventricular ejection fraction (LVEF) of 55%
- INR < 1.5 and aPTT <  $1.5 \times ULN$  (patients without anticoagulation). Therapeutic anticoagulation is allowed if INR and aPTT have remained stable within the therapeutic range for at least 2 weeks.
- Time interval of at least 6 months since last administration of any previous neoadjuvant/adjuvant chemotherapy or radiochemotherapy of the primary tumor in curative treatment intention
- Any relevant toxicities of prior treatments must have resolved to grade  $\leq 1$  according to the CTCAE (version 5), except alopecia
- Women of childbearing potential (WOCBP) should have a negative urine pregnancy test within 72 hours prior to receiving the first dose of study medication.
- Highly effective contraception for both male and female patients throughout the study and for at least 3 months after last dose of study medication administration if the risk of conception exists. Highly effective contraception has to be in line with the definition of the CTFG recommendation (see 17.5)
- Signed written informed consent and capacity to understand the informed consent

### 9.3.2 Exclusion criteria

Patients were excluded from the trial for any of the following reasons:

- Right sided mCRC
- Primarily resectable metastases
- Previous chemotherapy for the colorectal cancer with the exception of adjuvant treatment, completed at least 6 months before entering the study (1-2 cycles of FOLFIRI or mFOLFIRI are permitted before enrolment)
- Patients with known brain metastases
- Symptomatic peritoneal carcinosis
- Progressive disease before randomization
- History of acute or subacute intestinal occlusion, inflammatory bowel disease, immune colitis or chronic diarrhea
- Grade II heart failure (NYHA classification), Myocardial infarction, balloon angioplasty (PTCA) with or without stenting, and cerebral vascular accident/stroke within the past 12 months before enrolment, unstable angina pectoris, serious cardiac arrhythmia according to investigator's judgment requiring medication
- Medical or psychological impairments associated with restricted ability to give consent or not allowing conduct of the study
- Active infection with hepatitis B or C

- 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
- Uncontrolled hypertension
- Marked proteinuria (nephrotic syndrome)
- Arterial thromboembolism or severe hemorrhage within 6 months prior to randomization (with the exception of tumor bleeding before tumor resection surgery)
- Hemorrhagic diathesis or tendency towards thrombosis
- Participation in a clinical study or experimental drug treatment within 30 days prior to study
- Known hypersensitivity or allergic reaction to any of the study medications
- Severe, non-healing wounds, ulcers, bone fractures or an infection requiring systemic therapy
- Known history of alcohol or drug abuse
- Complete dihydropyrimidine dehydrogenase (DPD) deficiency (phenotyp and/or genotype test) (Patients with partial DPD deficiency may be included and should receive the first cycle with a reduced 5-FU dose. Dose reduction and escalation are at the discretion of the investigator and must be determined in the best interest of the patient.)
- Known glucuronidation deficiency (Gilbert's syndrome) (specific screening not required)
- Absent or restricted legal capacity
- For female patients only: Pregnancy (absence to be confirmed by  $\beta$ -HCG-test) or lactating

### 9.3.3 Removal of Patients from Therapy or Analysis

Each patient remained in the study until either the patient or the investigator decided that discontinuation of the study was the best for the respective patient.

Patients who discontinued the clinical study on their own by withdrawal of informed consent (at any time) or by patient preference and patients who were withdrawn by the investigator, for reasons other than disease progression, were defined as premature withdrawals.

Patients received study treatment until any of the following occurred:

- 3 years of study treatment
- Patient experienced PD according to RECIST v 1.1 criteria. Individual decision concerning discontinuation was performed at the discretion of the treating physician
- Patient experienced unacceptable toxicity or an adverse experience that, in the investigator's or sponsor's judgment, made continued administration of the study regimen an unacceptable risk
- Situations requiring a therapeutic intervention that was not permitted by the treatment plan
- Development of an intercurrent illness or situation which, in the judgement of the investigator, affected assessments of clinical status and study endpoints to a significant degree
- For WOCBP: Pregnancy
  - All WOCBP were be instructed to contact the investigator immediately if they suspected they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. The investigator immediately notified the delegated CRO (who informed the sponsor / coordinating investigator) in the event of a confirmed pregnancy in a patient or in a partner of a patient participating in the study.
- Request by the patient to stop the treatment
- Patient was considered by the investigator or the sponsor to be significantly noncompliant with the requirements of the protocol (e.g., patient becomes pregnant)
- Study was closed or terminated
- Patient lost to follow-up
- Investigator's decision
- At the specific request of the sponsor

In case of prolongation of any treatment delay beyond 28 days after the last administration of the chemotherapy as a result of delayed hematological recovery or/and non-hematological adverse events (AEs), permanent treatment discontinuation was decided after consultation with the coordinating investigator.

A temporary interruption in study medication due to an AE was not considered to be permanent discontinuation of investigational product.

The reason for discontinuing study treatment was clearly documented in the patient's medical record and recorded on the case report forms (CRF). Patients for whom the study treatment had been permanently discontinued, remained in the study unless they met the criteria for study withdrawal (below).

All patients with permanent treatment discontinuation (except for withdrawal of consent or loss to follow-up or death) were followed up as described.

### 9.3.4 Stopping or Suspending the Study

The sponsor could discontinue the study upon 30 days prior written notice. Study discontinuation was at the discretion of the following events:

- Medical or ethical reasons affecting the continued performance of the study (e.g. recommendations of DSMB)
- Difficulties in the recruitment of patients

In addition, the study could be discontinued at the discretion of the sponsor in the event of any or all of the following:

- Inefficacy of the study treatment
- Occurrence of AEs previously unknown in respect to their nature, severity, and duration, or unexpected incidence of known AEs

Safety data from the study was reviewed by the sponsor on a regular and ongoing basis in order to ensure the safety of the patients.

The regular end of study was defined as the last visit of the last patient, either at the end of study treatment or in the follow-up-period. Phone contact during the follow-up-period was regarded as a visit. A patient was considered as lost to follow-up if no contact could be established for 3 consecutive time points.

## 9.4 Treatments

### 9.4.1 Treatments administered

Patients with left-sided mCRC with mutant *RAS* were treated with FOLFIRI or mFOLFIRI before randomization phase as follows:

FOLFIRI (q14d):

- Irinotecan 180 mg/m<sup>2</sup> iv, 30 - 90 min on day 1
- Folinic acid (racemic) 400 mg/m<sup>2</sup> iv, 120 min on day 1
- 5-FU 400 mg/m<sup>2</sup> bolus on day 1
- 5-FU 2400 mg/m<sup>2</sup> iv over 46 h on day 1-2

OR

mFOLFIRI (q14d):

- Irinotecan 180 mg/m<sup>2</sup> iv, 30 - 90 min on day 1
- Folinic acid (racemic) 400 mg/m<sup>2</sup> iv, 120 min on day 1
- 5-FU 2400 mg/m<sup>2</sup> iv over 46 h on day 1-2

Patients with left-sided mCRC with conversion of mutant *RAS* within the first 4 months and without PD were assigned to one of the treatment arms:

**Experimental arm (switch arm):**

FOLFIRI (q14d) + cetuximab (q1w):

- Irinotecan 180 mg/m<sup>2</sup> iv, 30 - 90 min on day 1
- Folinic acid (racemic) 400 mg/m<sup>2</sup> iv, 120 min on day 1
- 5-FU 400 mg/m<sup>2</sup> bolus on day 1
- 5-FU 2400 mg/m<sup>2</sup> iv over 46 h on day 1-2
- Cetuximab initially 400 mg/m<sup>2</sup> as a 120 min infusion ( $\leq$  5 mg/min) on day 1; subsequently 250 mg/m<sup>2</sup> iv as a 60 min infusion every week ( $\leq$  10 mg/min)

OR

mFOLFIRI (q14d) + cetuximab (q1w):

- Irinotecan 180 mg/m<sup>2</sup> iv, 30 - 90 min on day 1
- Folinic acid (racemic) 400 mg/m<sup>2</sup> iv, 120 min on day 1
- 5-FU 2400 mg/m<sup>2</sup> iv over 46 h on day 1-2
- Cetuximab initially 400 mg/m<sup>2</sup> as a 120 min infusion ( $\leq$  5 mg/min) on day 1 subsequently 250 mg/m<sup>2</sup> iv as a 60 min infusion every week ( $\leq$  10 mg/min)

If *RAS* wild-type converted to *RAS* mutant: FOLFIRI or mFOLFIRI (q14d) as stated above.

If *RAS* mutant converted to *RAS* wild-type again: FOLFIRI or mFOLFIRI (q14d) + cetuximab q1w as stated above.

**Control arm:**

FOLFIRI (q14d):

- Irinotecan 180 mg/m<sup>2</sup> iv, 30 - 90 min on day 1
- Folinic acid (racemic) 400 mg/m<sup>2</sup> iv, 120 min on day 1
- 5-FU 400 mg/m<sup>2</sup> bolus on day 1
- 5-FU 2400 mg/m<sup>2</sup> iv over 46 h on day 1-2

OR

mFOLFIRI (q14d):

- Irinotecan 180 mg/m<sup>2</sup> iv, 30 - 90 min on day 1
- Folinic acid (racemic) 400 mg/m<sup>2</sup> iv, 120 min on day 1
- 5-FU 2400 mg/m<sup>2</sup> iv over 46 h on day 1-2

In case one of the substances had to be stopped due to toxicity, the others were continued, if tolerable for the patient.

**9.4.2 Identity of Investigational Products****9.4.2.1 Cetuximab****9.4.2.1.1 Preclinical Efficacy Pharmacology**

*In vitro* assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that express EGFR. No antitumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. In animal studies, the addition of cetuximab to irinotecan or irinotecan plus 5-FU, or the platinum-containing drugs, cisplatin and oxaliplatin, resulted in an increase in antitumor effects compared to chemotherapy alone (Investigator's Brochure Cetuximab, 2018).

#### 9.4.2.1.2 Clinical Efficacy Summary and RAS status

Cetuximab as a single agent or in combination with chemotherapy was investigated in 5 randomized controlled clinical studies and several supportive studies. The 5 randomized studies investigated a total of 3734 patients with metastatic colorectal cancer, in whom EGFR expression was detectable and who had an ECOG performance status of  $\leq 2$ . In all these studies, cetuximab was administered once a week with an initial dose of 400 mg/m<sup>2</sup> and 250 mg/m<sup>2</sup> subsequently.

CRYSTAL, a randomized study in patients with metastatic colorectal cancer who had not received prior treatment for metastatic disease, compared the combination of cetuximab and irinotecan plus infusional 5-fluorouracil/folinic acid to the same chemotherapy (FOLFIRI) given alone. Median PFS and OS was 8.9 and 19.9 months, respectively, for patients in the cetuximab arm, and 8.0 and 18.6 months, respectively, for patients receiving chemotherapy only.

The importance of *RAS* as a predictive marker for the efficacy of cetuximab treatment in mCRC was supported by other clinical trials. FIRE-3, an investigator-sponsored randomized clinical phase-III study, compared the treatment of FOLFIRI in combination with either cetuximab or bevacizumab in the 1<sup>st</sup>-line treatment of patients with *KRAS* exon 2 wild-type mCRC. The primary endpoint was objective response analysed by intention to treat. No significant difference was observed between the two treatment arms regarding the primary endpoint as well as PFS. However, median OS was 28.7 months (95% CI 24.0-36.6) in the cetuximab group compared with 25.0 months (22.7-27.6) in the bevacizumab group (HR 0.77, 95% CI 0.62-0.96;  $p=0.017$ ) [13]. Further post-hoc analyses on mutations other than *KRAS* exon 2 have been evaluated. Formalin-fixed paraffin-embedded (FFPE) tumor material of FIRE 3 patients was analysed for *KRAS* and *NRAS* exon 2, 3 and 4 mutations and for *BRAF* mutations. Taking into account only patients classified as wild-type without newly identified *RAS* and *BRAF* mutations ( $n=400$ ), median OS was higher in the FOLFIRI plus cetuximab group than the FOLFIRI plus bevacizumab group (33.1 months (95% CI 24.5–39.4) vs 25.0 months (CI 23.0–28.1); HR 0.70 (0.54–0.90);  $p=0.0059$ ). The objective response rate was higher in the cetuximab versus the bevacizumab arm (72.0% (95% CI 64.3–78.8) vs. 56.1% (48.3–63.6);  $p=0.0029$ ) (Stintzing, 2016).

Retrospective analyses of tumor material from different clinical trials investigating cetuximab concerning *KRAS* and *NRAS* exon 2, 3 and 4 mutations were performed. A majority of analysed tumor biopsies revealed a mutation in the exon 2 of the *KRAS* gene. However, it was shown retrospectively that patients with mCRC whose tumors had somatic mutations beyond *KRAS* exon 2, including *KRAS* exon 3 and 4 and *NRAS* exon 2, 3, and 4 mutations (new *RAS* mutation), also did not benefit from therapy with cetuximab (De Roock, 2010; Heinemann, 2014)

Nevertheless, it should be considered that there is an association between the proportion of *RAS*-mutated cancer cells in a tumor and the level of EGFR-targeted therapy resistance and that patients with other tumor *RAS* mutation signals between 0.1% and 5% may have benefited from the addition of cetuximab to FOLFIRI (Van Cutsem, 2015). Recently, retrospective analyses were conducted in patients with wild-type *RAS* mCRC from two phase III trials, CRYSTAL and FIRE-3, in which mCRC was subclassified as left-sided or right-sided. Patients in both clinical trials with left-sided CRC had a markedly better prognosis than those with right-sided CRC, especially if receiving FOLFIRI plus cetuximab (Tejpar, 2017).

#### 9.4.2.1.3 Pharmaceutical information

Pharmaceutical form: Erbitux 5 mg/ml was commercially available (Merck KGaA) as solution for infusion. Each mL of solution for infusion contained 5 mg cetuximab. Refer to the summary of product characteristics (SmPC) of Erbitux for information regarding the physical and chemical properties of Erbitux and a list of excipients.

Storage and stability: Shelf life was 4 years. Store in a refrigerator (2°C – 8°C). Chemical and physical in-use stability of Erbitux 5 mg/mL has been demonstrated for 48 hours at 25°C, if the solution is prepared as described. From a microbiological point of view, the product shall be used immediately after opening. If not used immediately, in-use storage times and conditions prior to



use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless opening has taken place in controlled and validated aseptic conditions.

Route of administration: Erbitux must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring is required during the infusion and for at least 1 hour after the end of infusion. Availability of resuscitation equipment must be ensured.

Prior to the first infusion, patients must receive premedication with an antihistamine and a corticosteroid at least 1 hour prior to administration of cetuximab. This premedication is recommended prior all subsequent infusions.

In all indications, Erbitux is administered once a week. The initial dose is 400 mg/m<sup>2</sup> body surface area. All subsequent weekly doses are 250 mg/m<sup>2</sup>. Erbitux 5 mg/mL is administered intravenously with an infusion pump, gravity drip or a syringe pump. The initial dose should be given slowly, and speed of infusion must not exceed 5 mg/min. The recommended infusion period is 120 minutes. For the subsequent weekly doses, the recommended infusion period is 60 minutes. The infusion rate must not exceed 10 mg/min.

Manufacturer: Merck Healthcare KGaA

#### 9.4.2.1.4 Licensed indication

- Treatment of patients with epidermal growth factor receptor (EGFR)-expressing, *RAS* wild-type metastatic colorectal cancer
  - In combination with irinotecan-based chemotherapy,
  - In 1<sup>st</sup>-line in combination with FOLFOX
  - As a single agent in patients who failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan
- Treatment of patients with squamous cell cancer of the head and neck
  - In combination with radiation therapy for locally advanced disease,
  - In combination with platinum-based chemotherapy for recurrent and/or metastatic disease.

#### 9.4.2.1.5 Contraindications

- Erbitux is contraindicated in patients with known severe (grade 3 or 4) hypersensitivity reactions to cetuximab
- The combination of Erbitux with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant *RAS* metastatic colorectal cancer or for whom *RAS* mCRC status is unknown.

#### 9.4.2.1.6 Clinical safety

Skin reactions (acneiform rash/acneiform dermatitis) are observed as the specific adverse reactions in the majority of patients, occurring at grade 3 or 4 in 15.7% of patients (Petrelli, 2018) Further notable side effects are hypomagnesaemia which occurs in more than 10% of patients (grade 3 - 4 hypomagnesaemia in 3% (Petrelli, 2018) and infusion related reactions, which occur with mild to moderate symptoms in more than 10% of patients and with severe symptoms in more than 1% of patients. An increased frequency of severe and sometimes fatal cardiovascular events and treatment emergent deaths has been observed in the treatment of non-small cell lung cancer, squamous cell carcinoma of the head and neck and colorectal carcinoma. Please refer to the current SmPC.

### 9.4.3 Method of Assigning Patients to Treatment groups

Patients with left sided mCRC with change in mutation status of *RAS* to wild-type in the first 16 weeks of screening were randomized in a 1:1-ratio to the experimental arm and the control arm.

#### 9.4.4 Dose Selection

There is limited experience with single doses higher than 400 mg/m<sup>2</sup> body surface area to date or weekly administrations of doses higher than 250 mg/m<sup>2</sup> body surface area. In clinical studies with doses up to 700 mg/m<sup>2</sup> given every 2 weeks the safety profile was consistent (Taberno, 2010).

#### 9.4.5 Selection and Timing of Dose for Each Patient

Patients in the experimental arm with change of mutant *RAS* to wild-type received cetuximab initially 400 mg/m<sup>2</sup> as a 120 min infusion on day 1; subsequently 250 mg/m<sup>2</sup> iv as a 60 min infusion every week. When changing back to mutant *RAS* in liquid biopsy, cetuximab was discontinued until changing back to *RAS* wild-type.

#### 9.4.6 Blinding

Not applicable.

#### 9.4.7 Prior and Concomitant Therapy

Any medications and treatments (other than those excluded by the clinical trial protocol) that were considered necessary for the patients' welfare and did not interfere with the trial drug could be given at the investigator's discretion.

All concomitant medication or medication administered within the 2 weeks preceding date of informed consent, during the study and 30 days after the last dose of trial treatment were recorded in the electronic case report forms (eCRF) including all prescription, over-the-counter (OTC), herbal supplements, and intravenous medications and fluids. The generic name of the medication was given along with the dose, duration, and indication of each drug.

The patient notified the investigational site about any new medications he/she took after the start of the study drug. Patients taking concomitant medications chronically maintained the same dose and dose schedule throughout the study if medically feasible.

Any additional concomitant therapy that became necessary during the trial and any relevant change to concomitant drugs was recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

All treatments that the investigator considered necessary for a patient's welfare could be administered at the discretion of the investigator in keeping with the community standards of medical care. This included resection of primary tumor / metastases in patients becoming eligible for surgery during study treatment.

Radiotherapy for treatment of bone metastases and drugs for treatment of adverse reactions of study treatment, anthroposophical and homeopathic medicinal products (e.g. mistletoe therapy) were permitted.

Any concomitant therapy intended for the treatment of primary tumor (except surgery) was prohibited during study therapy, including:

- Chemotherapy (other than the study treatment)
- Immunotherapy
- Targeted treatment (e.g. with small molecules)
- Radiation of primary tumor
- OTC medication
- Any other cytotoxic drugs

#### 9.4.8 Treatment Compliance

No patient diary was used in the study to assess treatment adherence

## 9.5 Efficacy and Safety Variables

### 9.5.1 Efficacy and Safety Measurements Assessed and Schedule of Assessment

Patients who had given their written informed consent were subjected to further assessment to verify the inclusion and exclusion criteria of the study.

Baseline examinations which had to be performed within 4 weeks before start of treatment, except laboratory parameters and urine pregnancy test ( $\beta$ -hCG), which had to be assessed within 3 days before registration:

- Provision of signed Informed Consent
- Assessment of demographic data, medical history
- Assessment of previous and concomitant medication within the last 2 weeks before signing of informed consent
- *RAS* mutation analysis on tumor tissue
- Blood sample (20 ml) for liquid biopsy
- CT-scan of abdomen, chest and pelvis to document baseline tumor status (in case of contraindications to CT scan, e.g. allergy to contrast medium, MRI should be performed); current TNM staging
- Vital signs: body temperature, heart rate, blood pressure, height and weight
- ECG
- Echocardiography
- ECOG performance status assessment
- Hematological and biochemical laboratory assessment including
  - Hemoglobin
  - Thrombocytes
  - Neutrophils
  - Electrolytes:  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$
  - Liver Function: ASAT, ALAT, alkaline phosphatase, GGT, bilirubin
  - Renal Function: urea, creatinine, creatinine-clearance
  - C-reactive CRP
  - CEA
  - CA-19-9
- Test for DPD deficiency as specified in the 'red-hand-letter' for 5-FU (i.v.), capecitabine- and tegafur-containing drugs, dated 04.06.2020:
  - Genotyping (4 variants of the DPYD genotype, namely c.1905+1G>A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3, are associated with a high risk for severe toxicities)
 and/or
  - Phenotyping (a blood uracil level between  $\geq 16$  and  $< 150$  ng/ml is an indicator of partial DPD deficiency, a blood uracil level  $\geq 150$  ng/ml is an indicator of complete DPD deficiency)
- Coagulation parameters: INR, aPTT
- Hepatitis B and C serology
- Females of childbearing potential: urine pregnancy test ( $\beta$ -hCG)
- Adverse events

Clinical examinations which had to be performed during Pre-randomization Phase for conversion to *RAS* wild-type (max. time period of 16 weeks from start of FOLFIRI):

Prior to every cycle (within 48 h before administration of study treatment):

- Hematological and biochemical laboratory assessment including
  - Hemoglobin
  - Thrombocytes
  - Neutrophils
  - Electrolytes:  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$

- Liver Function: ASAT, ALAT, alkaline phosphatase, GGT, bilirubin
- Renal Function: urea, creatinine, creatinine-clearance
- C-reactive CRP
- CEA
- CA-19-9

Prior the first cycle (within 72 h before administration of study treatment):

- Females of childbearing potential: urine pregnancy test ( $\beta$ -hCG)

Prior to administration of study treatment:

- Assessment of ECOG performance
- Survey of concomitant medication
- Vital signs: body temperature, heart rate, blood pressure, and weight

Every 2 weeks:

- Administration of study treatment (FOLFIRI or mFOLFIRI), Patients with partial DPD deficiency received the first cycle with a reduced 5-FU dose. Dose reduction and escalation were at the discretion of the investigator and were determined in the best interest of the patient.

Every 4 weeks:

- Females of childbearing potential: urine pregnancy test ( $\beta$ -hCG)

After every cycle:

- Assessment of adverse events. Adverse events were recorded according to NCI CTCAE v.5.0. Serious adverse events were reported within 24 h to Alcedis GmbH.

Every 8 weeks:

- Tumor assessment using CT-scan (in case of contraindications to CT scan, e.g. allergy to contrast medium, MRI should be performed) and classification of the response according to RECIST-Criteria V 1.1; the same method should be used throughout the study

At week 4, 8, 12 and 16 (until conversion to *RAS* wild-type):

- Blood sample (20 ml) for liquid biopsy
- If clinically indicated: ECG
- For patients without conversion to *RAS* wild-type by week 16, the 'end of study'-form was completed.
- Patients with conversion of *RAS* mutation to *RAS* wild-type, by  $\leq 8$  weeks or by  $> 8$  weeks, were randomized at week 8 or 16 respectively. Before randomization, the inclusion / exclusion criteria were checked.

**For the first 20 patients with *RAS* wild-type in liquid biopsy** a new tumor biopsy with *RAS* analysis was originally planned but not done due to the low number of patients recruited. Overall, in at least 80% of patients a biopsy should have been taken to confirm *RAS* status in tissue of respective patients.

Clinical examinations which had to be performed during treatment period (experimental arm):

Prior to every cycle (within 48 h before administration of study treatment):

- Hematological and biochemical laboratory assessment including
  - Hemoglobin
  - Thrombocytes
  - Neutrophils
  - Electrolytes:  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$
  - Liver Function: ASAT, ALAT, alkaline phosphatase, GGT, bilirubin
  - Renal Function: urea, creatinine, creatinine-clearance
  - C-reactive CRP
  - CEA

- CA-19-9

Prior to administration of study treatment:

- Assessment of ECOG performance
- Survey of concomitant medication
- Vital signs: body temperature, heart rate, blood pressure, and weight

Administration of study treatment:

- Cetuximab (every week) on day 1 and 8
- FOLFIRI (every 2 weeks) on day 1

After every administration of study treatment (d1 and d8):

- Assessment of adverse events. Adverse events were recorded according to NCI CTCAE v.5.0. Serious adverse events had to be reported within 24 h to Alcedis GmbH

Every 4 weeks:

- Females of childbearing potential: urine pregnancy test ( $\beta$ -hCG)

Every 2 weeks until week 8 (for the first 10 patients randomized to the experimental arm):

- Blood sample (20 ml) for liquid biopsy

Every 4 weeks until week 8 (for all other patients, unless otherwise recommended by DSMB):

- Blood sample (20 ml) for liquid biopsy

Every 8 weeks during the first year:

Tumor assessment using CT-scan (in case of contraindications to CT scan, e.g. allergy to contrast medium, MRI should be performed) and classification of the response according to RECIST-Criteria v1.1; the same method should be used throughout the study. If progression of disease was suspected for any reason at or between the 8-weekly evaluation visits, radiological confirmation is necessary, and a new scan had to be performed unless a scan taken no more than 14 days earlier was available.

- Blood sample (20 ml) for liquid biopsy

Every 12 weeks after the first year until end of study treatment:

- Tumor assessment using CT-scan (in case of contraindications to CT scan, e.g. allergy to contrast medium, MRI should be performed) and classification of the response according to RECIST-Criteria; the same method should be used throughout the study.

If progression of disease was suspected for any reason at or between the 12-weekly evaluation visits, radiological confirmation was necessary, and a new scan had to be performed unless a scan taken no more than 14 days earlier was available.

- Blood sample (20 ml) for liquid biopsy

If clinically indicated: ECG

Clinical Examinations during randomized Treatment Phase (control arm)

Prior to every cycle (within 48 h before administration of study treatment):

- Hematological and biochemical laboratory assessment including:
  - Hemoglobin
  - Thrombocytes
  - Neutrophils
  - Electrolytes:  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$
  - Liver Function: ASAT, ALAT, alkaline phosphatase, GGT, bilirubin
  - Renal Function: urea, creatinine, creatinine-clearance
  - C-reactive CRP
  - CEA

- CA-19-9

Prior to administration of study treatment:

- Assessment of ECOG performance
- Survey of concomitant medication
- Vital signs: body temperature, heart rate, blood pressure, and weight

Every 2 weeks:

- Administration of study treatment (FOLFIRI)

After every cycle:

- Assessment of adverse events. Adverse events were recorded according to NCI CTCAE v.5.0. Serious adverse events had to be reported within 24 h to Alcedis GmbH

Every 4 weeks:

- Females of childbearing potential: urine pregnancy test ( $\beta$ -hCG)

Every 8 weeks during the first year:

Tumor assessment using CT-scan (in case of contraindications to CT scan, e.g. allergy to contrast medium, MRI should be performed) and classification of the response according to RECIST-Criteria; the same method should be used throughout the study. If progression of disease was suspected for any reason at or between the 8-weekly evaluation visits, radiological confirmation was necessary, and a new scan had to be performed unless a scan taken no more than 14 days earlier was available.

Every 12 weeks after the first year until end of study treatment:

- Tumor assessment using CT-scan (in case of contraindications to CT scan, e.g. allergy to contrast medium, MRI should be performed) and classification of the response according to RECIST-Criteria; the same method should be used throughout the study.  
If progression of disease was suspected for any reason at or between the 12-weekly evaluation visits, radiological confirmation was necessary, and a new scan had to be performed unless a scan taken no more than 14 days earlier was available

Week 8 and 24:

- Blood sample (20 ml) for liquid biopsy

If clinically indicated: ECG

Final Examinations after the treatment phase:

Final examinations were performed **30±2 days** after last given medication.

- Hematological and biochemical laboratory assessment including
  - Hemoglobin
  - Thrombocytes
  - Neutrophils
  - Electrolytes: Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Ca<sup>2+</sup>
  - Liver Function: ASAT, ALAT, alkaline phosphatase, GGT, bilirubin
  - Renal Function: urea, creatinine, creatinine-clearance
  - C-reactive CRP
  - CEA
  - CA-19-9
- Assessment of adverse events. Adverse events were recorded according to NCI CTCAE v.5.0. Serious adverse events had to be reported within 24 h to the Alcedis GmbH
- If applicable: new tumor therapy
- Survival data
- Females of childbearing potential: urine pregnancy test ( $\beta$ -hCG)

Examinations during Follow-up Period:

The follow-up period lasted until the defined end of the study of a maximum of 36 months after last patient recruited. The following examinations were performed every 3 months after last treatment administration (if visit at the site was not possible, phone calls counted as visit):

- If applicable: new tumor therapy
- Survival data
- Adverse events: Final documentation of outcome of adverse events still ongoing at the End of Treatment Evaluation visit. Documentation of SAEs related to study treatment, until resolution or stabilization.

An overview of all clinical examinations is given in **Table 2**.

**Table 2:** Overview of clinical examinations

<b>Patients</b>	<b>All patients</b>		<b>Randomized patients (Experimental arm)</b>			<b>Randomized patients (Control arm)</b>			<b>End of therapy</b>	<b>Follow- up</b>
<b>Trial period</b>	Pre-Screening / Baseline	Pre-randomization (Screening) Phase (for conversion to RAS wild-type)	Switch arm (FOLFIRI/mFOLFIRI + cetuximab -> FOLFIRI/mFOLFIRI -> FOLFIRI/mFOLFIRI + cetuximab -> etc)			FOLFIRI/mFOLFIRI			Final Assessment	FU**
<b>Scheduling window</b>	-28 to -1 days	From Months 1 to 4	Every 2 weeks ± 3 days	Every 4 weeks ± 3 days	Every 8 / 12 weeks ± 3 days*	Every 2 weeks ± 3 days	Every 4 weeks ± 3 days	Every 8 / 12 weeks ± 3 days*	30± 2 days after last treatment	3 months ± 7 days
<b>Procedures / Assessments</b>										
Written informed consent	X									
Inclusion/Exclusion Criteria	X	X (before randomization)								
RAS mutation analysis on tumor tissue	X	X (New tumor biopsy at conversion, if possible, for the first 20 patients with conversion to RAS wild-type in liquid biopsy)***								
20 ml blood sample for liquid biopsy with RAS mutation analysis	X <sup>1</sup>	X <sup>2</sup>	X <sup>2</sup> (until week 8 for the first 10 patients)	X <sup>2</sup> (until week 8)	X <sup>2</sup> (from week 16 on)			X (week 8 / 24 only)		



<b>Patients</b>	<b>All patients</b>		<b>Randomized patients (Experimental arm)</b>			<b>Randomized patients (Control arm)</b>			<b>End of therapy</b>	<b>Follow- up</b>
<b>Trial period</b>	Pre-Screening / Baseline	Pre-randomization (Screening) Phase (for conversion to RAS wild-type)	Switch arm (FOLFIRI/mFOLFIRI + cetuximab -> FOLFIRI/mFOLFIRI -> FOLFIRI/mFOLFIRI + cetuximab -> etc)			FOLFIRI/mFOLFIRI			Final Assessment	FU**
<b>Scheduling window</b>	-28 to -1 days	From Months 1 to 4	Every 2 weeks $\pm$ 3 days	Every 4 weeks $\pm$ 3 days	Every 8 / 12 weeks $\pm$ 3 days*	Every 2 weeks $\pm$ 3 days	Every 4 weeks $\pm$ 3 days	Every 8 / 12 weeks $\pm$ 3 days*	30 $\pm$ 2 days after last treatment	3 months $\pm$ 7 days
<b>Procedures / Assessments</b>										
Vital signs <sup>3</sup>	X	X (before study treatment administration)	X			X				
Demographics and medical history / tumor characterization	X									
Previous and concomitant medication <sup>4</sup>	X									
ECOG performance status	X	X (before study treatment administration)	X			X				
ECG <sup>5</sup>	X	If clinically indicated	If clinically indicated			If clinically indicated				
Echocardiography	X									

Patients	All patients		Randomized patients (Experimental arm)			Randomized patients (Control arm)			End of therapy	Follow-up
Trial period	Pre-Screening / Baseline	Pre-randomization (Screening) Phase (for conversion to RAS wild-type)	Switch arm (FOLFIRI/mFOLFIRI + cetuximab -> FOLFIRI/mFOLFIRI -> FOLFIRI/mFOLFIRI + cetuximab -> etc)			FOLFIRI/mFOLFIRI			Final Assessment	FU**
Scheduling window	-28 to -1 days	From Months 1 to 4	Every 2 weeks ± 3 days	Every 4 weeks ± 3 days	Every 8 / 12 weeks ± 3 days*	Every 2 weeks ± 3 days	Every 4 weeks ± 3 days	Every 8 / 12 weeks ± 3 days*	30± 2 days after last treatment	3 months ± 7 days
Procedures / Assessments										
Tumor imaging examination <sup>6</sup>	X	X <sup>7</sup>			X			X		

Blood count <sup>8</sup>	X	X	X			X			X	
Biochemistry <sup>9</sup>	X	X	X			X			X	
Test for DPD deficiency	X <sup>15</sup>									
Coagulation parameters (INR, aPTT)	X									
Hepatitis B and C serology	X									
CEA and CA 19-9	X	X (every 2 weeks)	X			X			X	
β-HCG-test (for WOCBP) <sup>10</sup>	X (urine)	X (urine) (every 4 weeks)		X (urine)			X (urine)		X (urine)	
Administration of study treatment	X <sup>11</sup> (FOLFIRI/ mFOLFIRI)	X <sup>11</sup> (FOLFIRI/mFOLFIRI)	X <sup>12</sup>			X				
Adverse Events (AEs) / Serious adverse Events (SAEs) <sup>13</sup>	X	X (after every cycle)	X <sup>14</sup>			X			X	X (SAEs related to study treatment)
Change in or new concomitant medication		X (before study treatment administration)	X			X				
New tumor therapy									X	X
Survival data									X	X

\* Every 8 weeks during the first year, thereafter every 12 weeks up to end of study duration of 36 months

\*\* 3-monthly follow-up visits until end of study duration of 36 months; phone calls will count as study visits.

\*\*\* The results of *RAS* status, assessed locally, in tumor biopsy must be available within 10 days after the results of liquid biopsy become known. No randomization in case of different results for *RAS* status in tumor and liquid biopsy. 'End of study' form must be filled in for this case. Overall, in at least 80% of patients a biopsy should be taken to confirm *RAS* status in tissue of respective patients.

<sup>1</sup>) Blood samples from pre-screening/baseline will be analyzed only in cases with *RAS* wild-type in liquid biopsy at week 4 after starting FOLFIRI/mFOLFIRI. In patients who receive 1 -2 cycles FOLFIRI/mFOLFIRI in the pre-screening phase, the blood sample should be taken before administration of these cycles.

- 2a) Before randomization: Blood samples for liquid biopsy until detection of *RAS* wild-type at week 4, 8, 12 and 16 after starting FOLFIRI/mFOLFIRI .
- 2b) After randomization into the experimental arm: For the first 10 randomized patients only, blood samples for liquid biopsy at week 2, 4, 6 and 8 after starting FOLFIRI/mFOLFIRI; for subsequent patients at weeks 4 and 8; thereafter, for all patients, every 8 weeks for the first year, and every 12 weeks for the remaining study period. If receiving FOLFIRI/mFOLFIRI + cetuximab and disease progression is detected on CT and prior ctDNA analysis was wild-type, a single ctDNA analysis should be performed at the time of disease progression.
- 3) Body temperature, heart rate, blood pressure, weight and height (only at baseline)
- 4) Previous medication taken within the last 2 weeks before date of informed consent must be recorded.
- 5) If clinically indicated, more ECGs should be performed during study
- 6) CT scan: abdomen, chest and pelvis. In cases of contraindicated CT scan (e.g. contrast medium allergy) the MRI should be performed. The same method should be used throughout the study.
- 7) Every 8 weeks  $\pm$  3 days
- 8) Hemoglobin, thrombocytes, leukocytes, neutrophils (within 2 days before administration of study treatment)
- 9) Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup>, Ca<sup>2+</sup>, ASAT, ALAT, alkaline phosphatase, Gamma-glutamyl transferase (GGT), bilirubin, urea, creatinine, creatinine-clearance and C-reactive protein (CRP) (within 2 days before administration of study treatment)
- 10) Urine pregnancy test must be conducted for WOCBP; a negative result must be confirmed within 72 hours of first administration of study treatment
- 11) Every 2 weeks  $\pm$  3 days. 1-2 cycles of FOLFIRI / mFOLFIRI may be administered in the pre-screening period before the result of the *RAS* analysis is available. Patients with *RAS* mutation who fulfill all eligibility criteria will be enrolled into the pre-randomization phase. Patients with *RAS* wild-type are considered screening-failures and the blood sample will be discarded.
- 12) Cetuximab is administered every week
- 13) All (S)AEs that occur between the patient's first administration of study treatment until 30 days after discontinuation of study treatment, must be reported. All adverse events should be followed until resolution or stabilization. After the aforementioned time period the investigator should report any SAE which is believed to be related to study drug
- 14) Weekly during cetuximab therapy
- 15) Genotyping and/or phenotyping according to the 'red-hand-letter' for 5-FU (i.v.), capecitabine- and tegafur-containing drugs, dated 04.06.2020

A standardized eCRF was used for documentation of all study relevant parameters.

Routine laboratory assessments were performed at the local laboratory of the study site. Laboratory values as well as upper and lower limits of the respective laboratory were recorded in the eCRF.

All RAS analysis by liquid biopsy were performed at Immunological-Molecular Biological Laboratory of the Knappschaftskrankenhaus, Ruhr University Bochum by ddPCR.

#### **9.5.1.1 Primary Efficacy Measurement**

- Efficacy in terms of PFS according to RECIST v1.1

#### **9.5.1.2 Secondary Efficacy Measurements**

- Efficacy in terms of ORR determined by tumor assessment according to RECIST v1.1 after start of 1<sup>st</sup>-line treatment
- Efficacy in terms of OS from date of randomization
- Efficacy in terms of TFTS after randomization
- Efficacy in terms of Depth of response in terms of reduction of tumor mass after start of 1<sup>st</sup>-line treatment
- Efficacy in terms of PFS rate 1 year after date of randomization

#### **9.5.1.3 Safety – Adverse Events**

Investigators obtained information on AEs at each patient contact. The investigator was responsible for documenting all AEs that occurred during the study, including the duration and estimated severity in the eCRF.

AEs and their severity were reported according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. AEs were reported after informed consent has been given and until 30 days after last dose of study treatment. Afterwards, only AEs which were causally related to study treatment on the investigator's discretion were reported. All AEs had to be followed up until event was resolved or stabilization of the condition was achieved, or until end of study therapy (for AEs) and until end of study therapy + 30 days (for SAEs).

Prior to the statistical analysis, the AEs were coded using MedDRA Version 27.0.

All SAEs, whether related or unrelated to the study drug, had to be reported within 24 hours of becoming aware of the event by using the electronically available "Serious adverse events report" form.

#### **9.5.2 Appropriateness of Measurements**

All used efficacy or safety measures were standard or widely used in clinical studies.

#### **9.5.3 Pharmacokinetic and Pharmacodynamic Measurements**

Not applicable.

#### **9.5.4 Other Measures**

Not applicable.

### **9.6 Data Quality Assurance**

The investigator and the respective representative(s) signed the study protocol and thereby confirmed that they read and understood the protocol and aimed to work according to the protocol.

Each site had an on-site initiation visit by a clinical monitor appointed by Alcedis GmbH to ensure that investigators and study staff understood the study protocol and study-relevant procedures. Study personnel was trained in study procedures, medication handling and medication order, as well as documentation. Monitoring visits during the study conduct depended on patient recruitment and site performance. These visits were determined by the Alcedis monitor in consultation with the sponsor. Source Data Verification (SDV) was performed during monitoring visits in line with ICH GCP guidelines. All sites with at least one registered patient received an on-site close-out visit. Details are given in the Monitoring Plan which is available upon request.

Data for this study were collected by a web-based documentation system provided by Alcedis GmbH. Access authorization to the eCRF database was granted individually to investigators and further study personnel by means of user accounts. Data were entered at the study site into a validated eCRF, which enabled rapid processing and fast communication between trial site, monitor, data manager and sponsor. Data validation was performed automatically during data entry by means of electronic checks (eChecks to indicate missing or implausible data or range of values) as well as by manual checks (mChecks to verify the data's validity and plausibility).

The investigator ensured that the documented data was accurate and complete by electronically signing the documentation. All findings including clinical and laboratory data were recorded in the patient's medical record and in the eCRF. Each participating site reported their laboratory's standard values for hematology and blood chemistry into the eCRF. The respective laboratory institutions had to participate in an appropriate quality assurance program.

Toxicity was recorded in a standardized way according to NCI CTCAE v. 5.0 for categorization and grading. Evaluation of response efficacy was performed according to RECIST 1.1 standards.

The sponsor retained the right to undertake a quality audit in accordance with ICH-GCP guidelines at any time, particularly if any doubt arose about the quality of the documentation. In such an audit, as with an audit by the competent supervisory or health authorities, the authorized representatives involved were granted access to the originals of the patient files. The investigator guaranteed his full co-operation in the event of an audit. No audits or inspections were performed during this study.

## 9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

### 9.7.1 Statistical Analysis Plan

Due to the small number of patients enrolled (seven), the study was prematurely closed. Therefore, most analyses are provided as listings. Summary statistics of continuous variables like mean, standard deviation, and quantiles were not provided. Derived variables like ORR, OS, and PFS were given, and time-to-event analyses were done using Kaplan-Meier method. A swimmer plot showing the treatment and response timeline for each patient was created. Each listing shows the patient number, the arm into which the patient was randomized, and all relevant variables.

There was no differentiation between the analysis populations mentioned in Table 1 in the listings, figures, and tables of the final analysis.

Analysis concerning the primary objective:

- Listings containing RECIST assessments and observation of measurable and non-measurable lesions via CT
- Listing containing PFS, OS and TFTS
- Kaplan-Meier Plot for PFS

All AEs were ordered by patient number and summarized in listings.

### 9.7.2 Determination of Sample Size

Data from historical studies suggested the 12-months PFS rate of FOLFIRI in *RAS*-mutant mCRC to be in a range of 25-27%. In CRYSTAL study PFS-rate at 12 months of FOLFIRI + Cetuximab in left-sided *RAS* wild-type mCRC was 50% (HR = 0.56).

If the difference in PFS at 12 months between the experimental and control arms amounted to 20%, meaning an increase from 30% to 50% (Hazard ratio = 0.5757), 2 x 58 patients were planned

to be randomized and 107 PFS events would be needed if alpha error was 5% (0.05) and beta error was 20% (0.2). With a recruitment period of 18 months, a drop-out rate of 0.25% per month the 107 events were expected after a total follow-up time of 52 months assuming an exponential distribution.

Based on our data, the conversion rate would have been 80%. Assuming this conversion rate, 144 patients needed to be screened to achieve 116 patients for the randomization. The screening was planned to be continued until 116 patients were randomized.

## 9.8 Changes in the Conduct of the Study or Planned Analyses

There were several amendments of the study protocol. Changes made to the protocol during the conduct of the study are described in Section 3.1. An Amendment to the first Version of the study protocol was made according to the deficiency letter of the competent authority. The frequency of  $\beta$ -HCG tests in WOCBP was adapted in the visit schedule. The resection of the primary tumor and metastases was included in the section permitted concomitant medication/therapy.

Version 2.0 was set up according to the deficiency letter of the ethics committee including changes required for the competent authority. The originally planned treatment of the control group with FOLFIRI and bevacizumab was changed to monotherapy with FOLFIRI only because of the guidelines concerning *RAS*-mutated mCRC. Two stopping rules were included to increase patient safety and the visit schedule changed accordingly as well as interim analysis. Study timelines and wording were adjusted and the establishment of a Data Safety Monitoring Committee included in the protocol.

Information according to the appraisal letter of the ethics committee were inserted in version 2.1. The stopping rule was amended.

In March 2021 an adaption of some inclusion and exclusion criteria was made in version 3.0 of the study protocol. Previous chemotherapy with 1-2 cycles FOLFIRI or mFOLFIRI was permitted before enrolment and only patients with complete DPF deficiency were excluded from the study. It was allowed to administer mFOLFIRI as an alternative to FOLFIRI in the pre-randomization phase and the randomization phase. The visit schedule and corresponding sections were updated. A mistake in the section regarding the randomization timelines was corrected, the monitoring of vital signs during study treatment was specified.

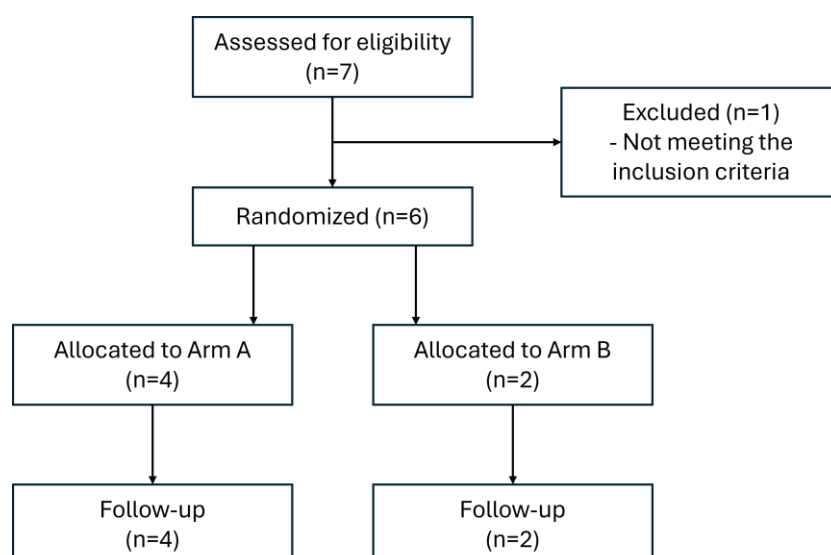
The statistical plan analysis plan was changed once in September 2024 after the last patient ended the study. Statistical methods were adapted, so PFS, OS and TSTS were graphically presented via Kaplan-Meier-plot and three figures were added.

## 10 STUDY PATIENTS

### 10.1 Disposition of Patients

Between September 2020 and July 2021, 129 patients were screened at 20 sites in Germany and one site in Austria. 122 patients were not eligible for participating in the study because of not meeting the inclusion/exclusion criteria. Main reasons were missing metastasis and right-sided tumor. Further reasons were previous palliative chemotherapy, *RAS* wild-type, refusal of participation in the study by the patient, second carcinoma or brain metastasis, first dose of FOLFIRI given although liquid-biopsy sample was not taken, patients with pending *RAS* status and high therapy pressure, primarily resectable mCRC and no measurable RECIST-lesion.

A total of six patients were randomized by four sites: Four patients into the experimental arm and two patients into the control arm. All patients received at least one dose of study medication and were included in the mITT and PP analysis sets. One patient was excluded before randomization because of violating the inclusion criterion '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)'. **Figure 2** shows the patient distribution.



**Figure 2:** Distribution of patients



## 10.2 Recruitment

Six patients were randomized (first patient in: March 2<sup>nd</sup>, 2021 / Last patient in: October 20<sup>th</sup>, 2021). The recruitment period was prematurely terminated due to the low number of eligible patients. Reasons were the Covid -19 Pandemic where patients had been protected against infection and unnecessary contacts and less preventive medical check-ups had been performed. Also study sites had been initiated later than planned because of strict regulations on staff and site visits during Covid-19 Pandemic.

The patients randomized were treated according to the protocol. Five out of six patients died before individual study duration of 36 months was reached, so the study was terminated when the last patient alive reached the individual study duration of 36 months.

## 10.3 Protocol Deviations

In all of the six randomized patients at least one protocol deviation was recorded.

One patient showed elevated liver enzymes at Baseline Lab Assessment due to liver metastases. After consultation of the national Coordinating Investigator and the Sponsor, the patient was included in the study.

Examinations were not performed according to protocol in 5 patients. For 2 patients, treatments, assessments and laboratory tests were not conducted according to protocol.

One patient received 500 mg/m<sup>2</sup> cetuximab as first infusion after randomization instead of 400 mg/m<sup>2</sup> as per protocol. Two patients did not receive cetuximab on day one and on day eight with 250 mg/m<sup>2</sup> but every 2 weeks with 500 mg/m<sup>2</sup> to reduce the burden for the patient to come in every week to every second week.

Several examinations and treatments were not conducted according to the protocol. The therapy of one patient was started without examination of DPD. Examinations and laboratory tests were not performed during randomization phase in three patients. For one patient tumor assessment and ECHO as well as laboratory tests at Baseline were performed too early.

The administration of the 2<sup>nd</sup> cycle was out of timeframe for one patient due to private reasons. End of treatment assessment was performed too late for two patients.

Follow-up visits for three patients which were planned three months after individual end of treatment were out of timeframe. The first and second restaging were both performed one day outside the timeframe for one patient. Liquid biopsies were taken at the wrong time points four times in this patient.

One patient showed conversion of RAS mutation to wild-type and should have been randomized at week eight but instead got randomized at week 12. For one patient a progress was detected via CT-scan, but treatment was not stopped after diagnosis. One patient showed a progress according to RECIST v1.1 that would have required end of treatment but was not considered as a progress after consultation of a radiologist. For one Patient therapy with cetuximab was continued although liquid biopsy showed RAS mutant.

**Table 3:** List of patients with Protocol deviations

Site No.	Patient No	Protocol Deviation
DE-01	MR-DE-01-01	Dosage of medication not according to protocol
DE-01	MR-DE-01-01	Formulation or administration of medication not according to protocol
DE-01	MR-DE-01-01	Examinations not performed according to protocol
DE-01	MR-DE-01-01	Required lab tests not according to protocol or not performed
DE-02	MR-DE-02-02	Dosage of medication not according to protocol
DE-02	MR-DE-02-02	Examinations not performed according to protocol
DE-02	MR-DE-02-01	Examinations not performed according to protocol
DE-02	MR-DE-02-01	Visit out of timeframe
DE-02	MR-DE-02-03	Cycle out of timeframe

DE-02	MR-DE-02-03	Assessment out of timeframe
DE-14	MR-DE-14-01	Tumor Assessment, ECHO, Coagulation, Tumormarker, Serologie not done within protocol window at Baseline
DE-14	MR-DE-14-01	Required lab tests not according to protocol or not performed
DE-14	MR-DE-14-01	Examinations not performed according to protocol
DE-14	MR-DE-14-01	Treatment period not stopped after diagnosis of progressive disease
DE-24	MR-DE-24-01	Examinations not performed according to protocol

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11 EFFICACY EVALUATION

11.1 Data Sets Analysed

**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.

Due to the small number of enrolled and randomized patients, analysis was not performed according to different data sets.

11.2 Demographic and Other Baseline Characteristics

The six randomized patients were between 41-80 years old and all Caucasian. One patient was female, the other participating patients were male. (Data source: Listing 4 of MoLiMoR\_Final\_TLF\_v1.0\_2024\_12\_06)

Four patients (experimental arm N=2, control arm: N=2) had an ECOG of 0 at Baseline. Two patients in the experimental arm had ECOG 1 at Baseline. (Data Source: Listing 14 of MoLiMoR\_Final\_TLF\_v1.0\_2024\_12\_06)

Five patients underwent a resection of the primary tumor before study inclusion, all of them had a resection status of R0 (Data Source: Listing 5.2. MoLiMoR\_Final\_TLF\_v1.0\_2024\_12\_06)

The time from baseline until first conversion to *RAS* wild-type ranged from 21 days to 64 days in the experimental arm and from 21 days to 29 days in the control arm (Table 4).

**Table 4:** Patients' first conversion to *RAS* wild-type

<i>Time from baseline sampling until first detection of RASwt [days]</i>									
	<i>N</i>	<i>Mean</i>	<i>STD</i>	<i>Min</i>	<i>Q1</i>	<i>Median</i>	<i>Q3</i>	<i>Max</i>	<i>NMiss</i>
<i>A</i>	4	43.00	20.31	21.00	26.00	43.50	60.00	64.00	0
<i>B</i>	2	25.00	5.66	21.00	21.00	25.00	29.00	29.00	0
<i>Total</i>	6	37.00	18.45	21.00	21.00	30.00	56.00	64.00	0

(Data source: Table 2 MoLiMoR\_Final\_TLF\_v1.0\_2024\_12\_06)

11.3 Measurements of treatment Compliance

Not applicable.

11.4 Efficacy Results

11.4.1 Primary Efficacy endpoint

The primary efficacy endpoint was the PFS of patients, defined as time between date of randomization until the date of progression according to RECIST v.1.1 criteria or date of death from

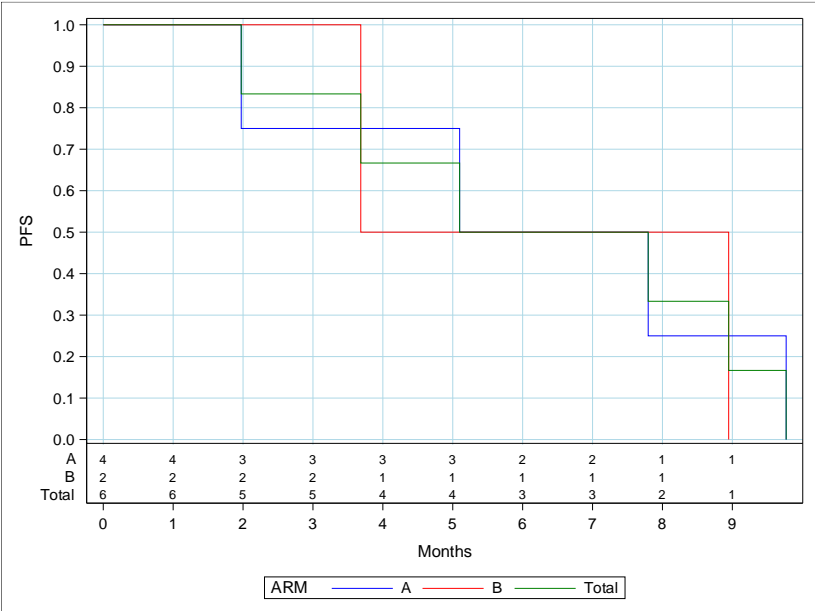
any cause, whichever occurred first. Details are shown in Listing 23.1 and Listing 23.2. of the MoLiMoR\_Final\_TLF\_v1.0\_2024\_12\_06.

PFS ranged from 1.97 to 9.77 months for the experimental treatment group and from 3.68 to 8.95 months in the control group. The median PFS in the experimental arm was 6.45 months, in the control arm the median PFS was 6.32 months; however, the small sample size of patients limited the statistical validity of this calculation (**Table 5**, Figure 3).

**Table 5:** Patients PFS

PFS [months]									
	N	Mean	STD	Min	Q1	Median	Q3	Max	NMiss
A	4	6.16	3.38	1.97	3.54	6.45	8.78	9.77	0
B	2	6.32	3.72	3.68	3.68	6.32	8.95	8.95	0
Total	6	6.21	3.11	1.97	3.68	6.45	8.95	9.77	0

(Data Source: Table 2.5 MoLiMoR\_PFS\_OS\_TFTS\_mean\_and\_more\_2024\_12\_19)



**Figure 3:** Progression-free survival (PFS) [months]  
(Data source: Figure 2 MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

11.4.2 Secondary Efficacy Endpoints

11.4.2.1 Objective Response rate (RECIST v1.1 criteria)

The objective response rate (ORR) was determined by tumor assessment according to RECIST v1.1 criteria which was performed by the investigators. The ORR was defined as patients with partial or complete response (PR + CR) in each treatment arm. Details can be found in listing 23.1 and 23.2 of the MoLiMoR\_Final\_TLF\_v1.0\_2024\_12\_06.

ORR was 75% and 50% in the experimental and control arm, respectively (Table 6).

Regarding the best response, no patient irrespective of treatment received a CR. Three patients in experimental arm achieved PR and one patient showed SD under treatment. In the control arm, one patient each showed PR and SD. All patients included in the study showed progressive disease as most recent response.

**Table 6:** ORR according to RECIST v1.1 criteria

<i>Responses according to RECIST v1.1 criteria including Overall response rate (ORR)</i>	<i>A [N,%]</i>	<i>B [N,%]</i>	<i>Total [N,%]</i>
Number of randomized patients	4 (100.00)	2 (100.00)	6 (100.00)
Most recent response			
Progressive disease (PD)	4 (100.00)	2 (100.00)	6 (100.00)
Best response			
Partial response (PR)	3 (75.00)	1 (50.00)	4 (66.67)
Stable disease (SD)	1 (25.00)	1 (50.00)	2 (33.33)
Overall response			
CR or PR (ORR)	3 (75.00)	1 (50.00)	4 (66.67)

(Data source: Table 3 MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

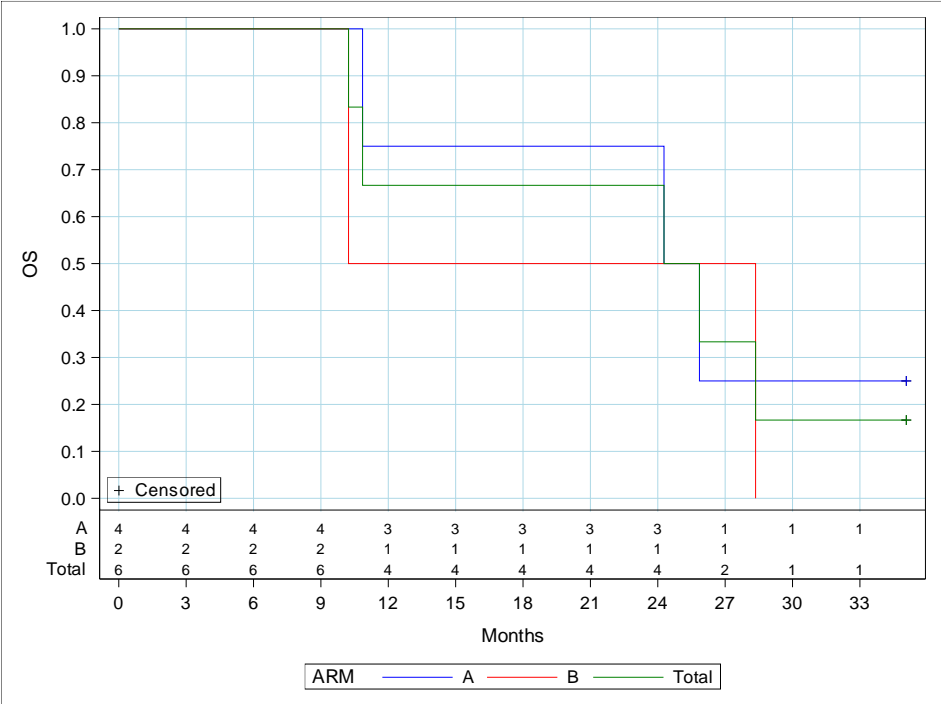
11.4.2.2 Overall Survival

OS was calculated from the date of randomization until death from any cause. OS in the experimental arm ranged from 10.86 to 35.07 months, in the control arm from 10.23 to 28.36 months. Median OS in the experimental arm was 25.07 months, in the control arm median OS was 19.29 months (Table 7, Figure 4), but due to the small sample size of patients, the statistical validity of this calculation is limited.

**Table 7:** Overall survival

<i>OS [months]</i>									
	<i>N</i>	<i>Mean</i>	<i>STD</i>	<i>Min</i>	<i>Q1</i>	<i>Median</i>	<i>Q3</i>	<i>Max</i>	<i>NMiss</i>
<i>A</i>	4	24.01	9.98	10.86	17.57	25.07	30.46	35.07	0
<i>B</i>	2	19.29	12.82	10.23	10.23	19.29	28.36	28.36	0
<i>Total</i>	6	22.44	9.93	10.23	10.86	25.07	28.36	35.07	0

(Data Source: Table 2.5 MoLiMoR\_PFS\_OS\_TFTS\_mean\_and\_more\_2024\_12\_19)



**Figure 4:** OS [months]  
(Data source: Figure 3 MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

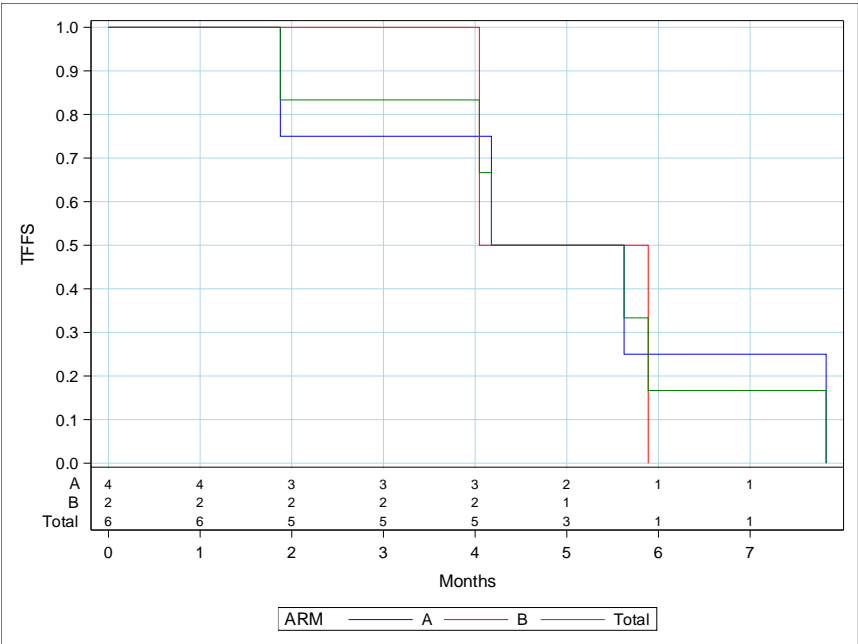
11.4.2.3 Time to failure of treatment strategy

The TFTS in the experimental arm ranged from 1.88 months to 7.83 months. The median TFTS was 4.90 months (Table 8, Figure 5). In the control arm, one patient had a failure of treatment strategy after 4.05 months, the other patient after 7.83 months. Calculated median TFTS was 4.97 months, but due to the small sample size of patients the statistical validity of this calculation is limited.

**Table 8:** Time to Failure of Treatment strategy

	TFTS [months]								
	<i>N</i>	<i>Mean</i>	<i>STD</i>	<i>Min</i>	<i>Q1</i>	<i>Median</i>	<i>Q3</i>	<i>Max</i>	<i>NMiss</i>
<i>A</i>	4	4.88	2.50	1.88	3.03	4.90	6.73	7.83	0
<i>B</i>	2	4.97	1.30	4.05	4.05	4.97	5.89	5.89	0
<i>Total</i>	6	4.91	2.02	1.88	4.05	4.90	5.89	7.83	0

Data Source: Table 2.5 MoLiMoR\_PFS\_OS\_TFTS\_mean\_and\_more\_2024\_12\_19



**Figure 5:** Time to failure of treatment strategy (TFTS) [months]  
(Data source: Figure 4 MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

11.4.3 Other Efficacy Endpoints

Originally, the analysis of PFS 1 year after randomization, the percentage of patients with metastasis resections and the Depth of Response (DpR) were planned as secondary endpoint analyses but were not analysed due to the small number of patients included in the study. Exploratory objectives were not analysed due to the same reason.

11.4.4 Post-hoc Analyses

Not applicable.

11.5 Statistical / Analytical Issues

11.5.1 Adjustments for Covariates

Not applicable.

11.5.2 Handling of Dropouts or Missing Data

Patients withdrawn from the study were not replaced. Missing data was not imputed.

11.5.3 Interim Analyses and Data Monitoring

No interim analyses were done due to the small number of participants. A Data Safety Monitoring Committee was established for this study but patient numbers that would have made a meeting necessary were not reached. A list of SAEs was submitted to the members of the committee for evaluation on a quarterly basis.

11.5.4 Multicentre Trials

Patients from all study centres were pooled and tabulated as single target group.

**11.5.5 Multiple Comparison / Multiplicity**

No multiple comparisons were performed due to the low number of patients.

**11.5.6 Use of an "Efficacy Subset" of patients**

The initially defined modified ITT set was used for analysis.

**11.5.7 Active-Control Studies Intended to Show Equivalence**

Not applicable.

**11.5.8 Examination of Subgroups**

No subgroups were analysed.

**11.5.9 Tabulation of Individual Response Data**

Due to the low number of patients participating in this clinical trial, all results were provided as listings of individual data. Therefore, no data according to analysis sets were shown in the final analysis. Listings including individual patient data are provided in section 12 of this final study report.

**11.6 Pharmacokinetic, Pharmacodynamic and other analyses results****11.6.1 Drug Dose, Drug Concentration, and Relationships to Response**

Not applicable.

**11.6.2 Drug-Drug and Drug-Disease Interactions**

Not applicable.

**11.6.3 Other Endpoints**

Not applicable.

**11.7 By Patient Displays**

Not applicable.

**11.8 Efficacy Result Summary**

All six patients included in the study were evaluable for efficacy analysis. The planned number of a total of 116 patients, 58 patients in the experimental and control arm each, was not achieved. The primary efficacy endpoint PFS ranged from 1.97 to 9.77 months in the experimental arm, in the control arm PFS ranged from 3.68 to 8.95 months. Due to the small number of patients, the explanatory power of the results is limited.

Neither in the experimental arm nor in the control arm CR was observed. In the experimental arm, three patients had PR, one patient showed SD as best response. In the control arm one patient showed PR, the other patient showed SD as best response. ORR in the experimental arm was 75%, in the control arm 50%. OS ranged from 10.86 to 35.07 months in the experimental arm, in the control arm, OS ranged from 10.23 to 28.36 months. Minimum TFTS was 1.88 months, maximum TFTS was 35.07 months in the experimental arm. in the control arm, TFTS ranged from 10.23 to 28.36 months.



The small number of patients also limited the explanatory power of the results for the secondary endpoints.

## 12 SAFETY EVALUATION

All patients who received at least one dose of the study treatment were included in the safety analysis set. The safety population was identical with the mITT set.

### 12.1 Extent of Exposure

All analysed patients received at least one cycle of the study treatment. Patients in the experimental group received Irinotecan 180 mg/m<sup>2</sup> as iv infusion over a time period of 20 to 90 minutes (see Listing 22.2. of MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06), 400 mg/m<sup>2</sup> Folinic acid as iv infusion over 120 minutes (see Listing 22.3. of MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06 and 2400 mg/m<sup>2</sup> 5-FU as iv infusion over 46 hours (see Listing 22.5. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06). Some patients received a 5-FU bolus of 400 mg/m<sup>2</sup> as defined in the schema for FOLFIRI (see Listing 22.4. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06) Cetuximab was administered initially with 400 mg/m<sup>2</sup> as iv infusion over 120 minutes and subsequently 250 mg/m<sup>2</sup> as iv infusion over 60 minutes on day 1 and 8. One patient did not receive cetuximab in standard dose every week but every two weeks according to patient's wish. Patients in treatment arm B received FOLFIRI or mFOLFIRI as explained above.

The number of cycles per patient are given in Listing 22.1 of MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06. Patients in treatment Arm A received between 10 and 20 cycles of study medication. Patients in treatment Arm B received 6 or 7 cycles of study treatment.

Main reason for end of treatment was Disease Progression occurring in three patients. One patient became available for resection. 2 patients ended the study treatment due to investigators decision. For details see Listing 25.1 of MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06.

All six patients had at least two follow up visits as in-house visit or as telephone call. Four patients received a new anticancer therapy after discontinuation of study treatment in the follow-up period. For details see Listing 26.1 of MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06.

The main reason for End of study was patient's death. Only one patient terminated the study regularly (Table 9).

Table 9: End of study

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					
						Grade	Term	Other	Death related disease if applicable	Date of withdrawal if applicable	Reason for withdrawal if applicable
MR-DE-01-01	A	17MAY22	Patient died	17MAY22	Adverse event related	5	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	mutated metastatic colorectal cancer			.
MR-DE-02-01	B	27OCT23	Patient died	27OCT23	Carcinoma related	.					.
MR-DE-02-02	A	11JUN24	Study closed / terminated	.	.	.					.
MR-DE-02-03	B	15MAY22	Patient died	15MAY22	Other: disease progression	.					.
MR-DE-14-01	A	28APR23	Patient died	28APR23	Other: unknown reason, no letter available	.					.
MR-DE-24-01	A	23OCT23	Patient died	27OCT23	Adverse event related	5	Gastric ulcer				.

(Data source: Listing 27 MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

In all six patients of the mITT at least one AE was recorded. A total of 78 AEs was reported, of these 47 were classified as treatment-related AEs. Three patients had AEs with a maximal grade of 2, one patient experienced AEs of grade 3. In two patients, the AEs had a fatal outcome. Both patients died due to the AEs. 50% of the patients experienced an SAE (Table 10).

Most frequently reported AEs were nausea (N=5), diarrhoea (N=4), fatigue and alopecia (N=3 each). (see Listings 4.2. and 4.3. of MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

Special AEs were predefined and included pregnancy and medication error. There were two cases of medication error reported as special AE. Once medication was overdosed, the other was a change in the schedule of medication administration. Both occurred in the same patient, both did not result in a serious AE.

Table 10: Adverse Events

Overview	Total [N,%]
Number of patients in mITT	6 (100.00)
Patients with any AE	6 (100.00)
Patients with AEs by maximal grade	
Grade 2	3 (50.00)
Grade 3	1 (16.67)

Overview	Total [N,%]
Grade 5	2 (33.33)
Number of AEs	78 (100.00)
Patients with treatment-related AEs	6 (100.00)
Number of treatment-related AEs	47 (60.26)
Patients with any SAE	3 (50.00)
Patients with SAEs by seriousness criteria	
Hospitalization	3 (50.00)
Death	2 (33.33)
Number of SAEs	4 (5.13)
Patients with any special AE	1 (16.67)
Patients with special AEs by speciality criteria	
Medication error	1 (16.67)
Number of special AEs	2 (2.56)
Patients with AEs leading to discontinuation	1 (16.67)
Number of AEs leading to discontinuation	2 (2.56)

(Data source: Table 4.1. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06

12.2.2      Display of Adverse Events

All AEs that occurred during the study are shown in Table 4.2 of the MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06 categorized in System Organ Classes (SOC), with Preferred Term (PT) and with NCI CTCAE grade. Table 4.3. of the MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06 shows the maximal NCI CTCAE grade per patient. All six patients included in the study, reported AEs of belonging to the SOC ‘gastrointestinal disorders’, five patients reported AEs belonging to the SOC ‘Investigations’..

12.2.3      Analysis of Adverse Events

The most frequently reported SOC’s were ‘Gastrointestinal disorders’ in patients of experimental and control group. Two AEs led to discontinuation of treatment with cetuximab, both AEs occurred in the same patient: ‘Nail infection’ out of the SOC ‘Infections and infestations’ and “Dermatitis acneiforme’. out of SOC ‘Skin and subcutaneous tissue disorders’. 70 AEs recovered without sequelae. Two patients had an AE of grade 5 (Colorectal cancer metastatic, SOC ‘Neoplasms benign, malignant and unspecified (incl cysts and polyps’, N=1 and Gastric ulcer, SOC ‘Gastrointestinal disorders’, N=1)

12.2.4      Listing of Adverse Events by Patient

A complete listing of all AEs per patient is available as listing 28.1. in the MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06.

## 12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

### 12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

#### 12.3.1.1 Deaths

Death was documented for 5 patients (experimental arm: N=3, control arm: N=2). Mutated, metastatic colorectal cancer and gastric ulcer (each in one patient of the experimental arm) were documented as reason for death. Both causes were recorded as AEs, the relation to study medication was assessed as unlikely. The other deaths were not documented as AE as they were outside the documentation period. Two patients died due to carcinoma, one patient died of unknown cause. (Data source: Listing 27 MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

#### 12.3.1.2 Other SAEs

A list of all SAEs is provided in Listing 28.2. of the MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06. There were four AEs classified as severe. All SAEs occurred in patients of the experimental arm. Two patients died as outcome of an SAE (see section 10.4.3), a relation to study medication was assessed as unlikely. One patient suffered from Ileus which was an SAE of grade 1 and was classified as serious because of hospitalization. Another patient suffered from hepatobiliary procedural complication classified as grade 1 and classified as serious due to hospitalization.

#### 12.3.1.3 Other Significant AEs

Not applicable.

### 12.3.2 Narratives of Deaths, Other SAEs, and Certain Other Significant AEs

**Table 11:** Narrative of Death MR-DE-01-01

Patient identifier	MR-DE-01-01				
Year of birth	1956				
Sex	Female				
Height (cm)	161				
Baseline weight (kg)	76				
Race	Caucasian				
Treatment arm	Experimental arm				
Start/stop of study treatment	Pre-randomization phase: first day first cycle April 30 <sup>th</sup> , 2021, first day last cycle June 14 <sup>th</sup> , 2021 Randomization phase: first day first cycle June 8 <sup>th</sup> , 2021, first day of the last cycle September 20 <sup>th</sup> , 2021				
Date of last dose of study drug before event	FOLFIRI/mFOLFIRI: September 20 <sup>th</sup> , 2021 Cetuximab: September 20 <sup>th</sup> , 2021				
Date of death	May 17 <sup>th</sup> , 2022				
Event Term	Start/stop date of the event	Severity	Event outcome	Relationship to study drug	Action taken with study drug
Colorectal cancer metastatic	Start date: unknown Stop date: May 17 <sup>th</sup> , 2022	Severe due to death	fatal	unlikely	No action taken
<b>EVENT SUMMARY:</b> This patient born in 1956 was initially diagnosed with CRC Stage I on May 1 <sup>st</sup> , 2020. The primary tumor was resected on May 7 <sup>th</sup> , 2020, with resection status R0.					

**Relevant medical history:**

- Phlebitis and thrombophlebitis of other sites
- Essential (primary) hypertension
- Predominantly allergic asthma

**Relevant concomitant medications:**

- Oxycodon
- Novaminsulfon
- Ibuprofen
- Heparin
- Vasopressoren

Event details: This patient ended the study treatment because she became eligible for resection of a liver metastasis on October 26<sup>th</sup>, 2021. During follow-up, a mass was found in the right lobe of the liver in April 2022. A hemihepatectomy was performed on April 28<sup>th</sup>, 2022. The patient was deeply sedated, mechanical ventilation and therapy with vasopressors was required. The amount of vasopressors was increased continuously. Plasmaseparation and haemodialysis were started. On May 7<sup>th</sup>, 2022 a CT-Thorax was performed which showed the occlusion of the portal vein and segmental pulmonary artery embolism. Application of OPAL dialysis was started. The circulatory instability of the patient worsened over time, increasing the need for vasopressors. Laboratory values showed hyperkalaemia on dialysis. Cause of the condition of the patient was acute hepatic insufficiency after hemihepatectomy. The residual volume of the liver was presumed sufficient but was functionally limited by previous chemotherapy. The patient died on May 17<sup>th</sup>, 2022.

**Table 12:** Narrative of death MR-DE-24-01

Patient identifier	MR-DE-24-01				
Year of birth	1941				
Sex	Male				
Height (cm)	175				
Baseline weight (kg)	72				
Race	Caucasian				
Treatment arm	A				
Start/stop of study treatment	Prerandomization phase: first day first cycle July 22 <sup>nd</sup> , 2021, first day last cycle September 29 <sup>th</sup> , 2021 Randomization phase: first day first cycle October 22 <sup>nd</sup> , 2022, first day last cycle February 28 <sup>th</sup> , 2022				
Date of last dose of study drug before event	FOLFIRI/mFOLFIRI: February 28 <sup>th</sup> , 2022 Cetuximab: February 14 <sup>th</sup> , 2022				
Date of death	October 27 <sup>th</sup> , 2023				
Event Term	Start/stop date of the event	Severity	Event outcome	Relationship to study drug	Action taken with study drug
Gastric ulcer	Start date: October 27 <sup>th</sup> , 2023 Stop date: October 27 <sup>th</sup> , 2023	Severe due to death	fatal	unlikely	No action taken
<b>EVENT SUMMARY:</b>					
This patient born in 1941 was initially diagnosed with mCRC on July 2 <sup>nd</sup> , 2021 The primary tumor was resected on June 28 <sup>th</sup> , 2021 with resection status R0.					
<b>Relevant medical history:</b>					
- Other gastritis					

## Relevant concomitant medications:

- Memantin
- Pantoprazol
- Novalgin
- Movicol
- Fragmin
- Scopoderm
- Practo Clyss
- Doxycyclin
- Minocyclin

Event details: This patient ended the study treatment due to progression of the disease. Last administration of study medication was on February 28<sup>th</sup>, 2022. A new tumor therapy with bevacizumab and Folfox was started as well as bevacizumab in combination with Longsurf which the patient decided to discontinue before his death. The patient was not hospitalized. An autopsy was performed, as reason for death gastric ulcer was documented in the eCRF. The autopsy letter was not available.

**Table 13:** Narrative of Death MR-DE-02-01

Patient identifier	MR-DE-02-01
Year of birth	1980
Sex	Male
Height (cm)	167
Baseline weight (kg)	93
Race	Caucasian
Treatment arm	Control arm
Start/stop of study treatment	Pre-randomization phase: first day first cycle April 26 <sup>th</sup> , 2021, first day last cycle June 9 <sup>th</sup> , 2021 Randomization phase: first day first cycle June 29 <sup>th</sup> , 2021, first day of the last cycle October 11 <sup>th</sup> , 2021
Date of death	October 27 <sup>th</sup> , 2023
Reason for death: Carcinoma related	
<b>SUMMARY:</b> This patient born in 1980 was initially diagnosed with CRC Stage IV on April 4 <sup>th</sup> , 2018. The primary tumor was resected on March 21 <sup>st</sup> , 2018 with resection status R0.  Relevant medical history: -  Relevant concomitant medications: <ul style="list-style-type: none"> <li>- Metamizol</li> <li>- Dexamethasone</li> <li>- Palladon acute</li> <li>- Pantoprazol</li> <li>- Olanzapin</li> <li>- Loperamid</li> <li>- Diltiazem</li> <li>- Akynzeo</li> <li>- Novalgin supp</li> <li>- Ibuprofen</li> </ul> <p>This patient ended the study treatment after 7 cycles of treatment in the randomization phase because of Investigator's decision. Best response during study treatment was PR. Ten AEs were reported during the study, all recovered without sequelae. Highest AE grade was 3. On March 16<sup>th</sup>, 2022, restaging showed progressive disease. No new tumor therapy was documented in</p>	

the eCRF. On April 1<sup>st</sup>, 2022, resection of liver metastases was performed. As last follow-up visit on October 27<sup>th</sup>, 2023, the death of the patient was reported.

**Table 14:** Narrative of Death MR-DE-02-03

Patient identifier	MR-DE-02-03
Year of birth	1970
Sex	Male
Height (cm)	186
Baseline weight (kg)	92
Race	Caucasian
Treatment arm	Control arm
Start/stop of study treatment	Pre-randomization phase: first day first cycle May 19 <sup>th</sup> , 2021, first day last cycle June 30 <sup>th</sup> , 2021 Randomization phase: first day first cycle July 14 <sup>th</sup> , 2021, first day of the last cycle September 29 <sup>th</sup> , 2021
Date of death	May 15 <sup>th</sup> , 2022
Reason for death: Disease progression	
<p><b>SUMMARY:</b> This patient born in 1980 was initially diagnosed with CRC Stage IV on April 30<sup>th</sup>, 2021. The primary tumor has not been resected before study inclusion.</p> <p>Relevant medical history:</p> <ul style="list-style-type: none"> <li>- Burn-out</li> <li>- Essential (primary) hypertension</li> <li>- Fatty (change of) liver, not elsewhere classified</li> <li>- Chronic nasopharyngitis</li> <li>- Fitting and adjustment of urinary device</li> <li>- Other specified disease of anus and rectum</li> </ul> <p>Relevant concomitant medications:</p> <ul style="list-style-type: none"> <li>- Candesartan</li> <li>- Pregabalin</li> <li>- Escitalopram</li> <li>- Loperamid</li> <li>- Dexamethason</li> <li>- Granisetron</li> <li>- Metoclopramid</li> <li>- Simeticon</li> <li>- Macrogol</li> <li>- Atropin</li> </ul> <p>This patient was randomized into the control group after four treatment cycles in the pre randomization phase. He was treated with 7 cycles in the randomized phase. Best response under study treatment was stable disease. Ten AEs were reported during the study, all of grade 1. Nine AEs recovered without sequelae; Bilirubin increase recovered with sequelae. Study treatment was ended because of disease progression, clinical progression and physician's decision. At the end of treatment evaluation visit in November 2021 ECOG performance status was 2. A new tumor therapy was started on November 8<sup>th</sup>, 2021, with FOLFOX6. The therapy was adjusted several times over the course of the treatment (December 10<sup>th</sup>, 2021, Bevacizumab; January 21<sup>st</sup>, 2022 – February 18<sup>th</sup>, 2022, Trifluridine/Tipiracil; March 4<sup>th</sup>, 2022 – May 6<sup>th</sup>, 2022, Sotorasib + Panitumumab). Three follow up visits were performed. On May 15<sup>th</sup>, 2022, the patient died due to progressive disease.</p>	

**Table 15:** Narrative of Death MR-DE-14-01

Patient identifier	MR-DE-14-01
Year of birth	1959
Sex	Male
Height (cm)	175
Baseline weight (kg)	89
Race	Caucasian
Treatment arm	Experimental arm
Start/stop of study treatment	Pre-randomization phase: first day first cycle December 29 <sup>th</sup> , 2020, first day last cycle February 23 <sup>rd</sup> , 2021 Randomization phase: first day first cycle March 9 <sup>th</sup> , 2021, first day of the last cycle July 3 <sup>rd</sup> , 2021
Date of death	May 15 <sup>th</sup> , 2022
Reason for death: Disease progression	
<p><b>SUMMARY:</b> This patient born in 1980 was initially diagnosed with CRC Stage IV on November 17<sup>th</sup>, 2020. The primary tumor was resected on December 2<sup>nd</sup>, 2020, with resection status R0.</p> <p>Relevant medical history:</p> <ul style="list-style-type: none"> <li>- Acute myocardial infarction, unspecified</li> <li>- Essential (primary) hypertension</li> <li>- Duodenal ulcer: Acute without haemorrhage or perforation</li> <li>- Other acute gastritis</li> <li>- Mixed hyperlipidaemia</li> <li>- Non-insulin dependent diabetes mellitus: without complications</li> </ul> <p>Relevant concomitant medications:</p> <ul style="list-style-type: none"> <li>- Ramipril</li> <li>- Pantoprazol</li> <li>- Nebivolol</li> <li>- Hydrochlorthiazid</li> <li>- Metoclopramid</li> <li>- Simvastatin</li> <li>- Metformin</li> <li>- ASS</li> <li>- Ranitidin</li> <li>- Fenistil</li> </ul> <p>This patient was randomized into the experimental arm after five treatment cycles in the pre randomization phase. He was treated with ten cycles in the randomized phase. Best response under study treatment was partial response. Eight AEs were reported during the study, highest grade of reported AEs was 2. Seven AEs recovered without sequelae; nausea was documented as ongoing. Study treatment was ended because of disease progression. At the end of treatment evaluation visit in December 2021 ECOG performance status was 0. A new tumor therapy with FOLFIRI was started on December 29<sup>th</sup>, 2021, and continued until January 18<sup>th</sup>, 2022. From July 5<sup>th</sup>, 2022, until December 8<sup>th</sup>, 2022, the patient was treated with Bevacizumab/FOLFOX. Six follow up visits were documented. On April 28<sup>th</sup>, 2023, the patient died. The reason maintained unknown as no letter was available</p>	



**Table 16:** Narrative of SAE MR-DE-14-01

Patient identifier	MR-DE-14-01				
Year of birth	1959				
Sex	Male				
Height (cm)	175				
Baseline weight (kg)	89				
Race	Caucasian				
Treatment arm	Experimental arm				
Start/stop of study treatment	Pre-randomization phase: first day first cycle December 29 <sup>th</sup> , 2020, first day last cycle February 23 <sup>rd</sup> , 2021 Randomization phase: first day first cycle March 9 <sup>th</sup> , 2021, first day of the last cycle July 13 <sup>th</sup> , 2021				
Date of last dose of study drug before event	FOLFIRI/mFOLFIRI: July 13 <sup>th</sup> , 2021 Cetuximab: April 27 <sup>th</sup> , 2021				
Date of death	May 15 <sup>th</sup> , 2023				
Event Term	Start/stop date of the event	Severity	Event outcome	Relationship to study drug	Action taken with study drug
Intraoperative hepatobiliary injury	Start date: August 16 <sup>th</sup> , 2021 Stop date: August 21 <sup>st</sup> , 2021	mild	Recovered without sequelae	No correlation	No action taken
<p><b>EVENT SUMMARY:</b></p> <p>This patient born in 1959 was initially diagnosed with CRC Stage IV on November 17<sup>th</sup>, 2020. The primary tumor was resected on December 2<sup>nd</sup>, 2020, with resection status R0.</p> <p>Relevant medical history:</p> <ul style="list-style-type: none"> <li>- Acute myocardial infarction in 2002</li> <li>- Essential (primary) hypertension</li> <li>- Duodenal ulcer (acute without haemorrhage or perforation)</li> <li>- Other acute gastritis</li> <li>- Mixed hyperlipidaemia</li> <li>- Non-insulin-dependent diabetes mellitus without complications</li> </ul> <p>Relevant concomitant medications:</p> <ul style="list-style-type: none"> <li>- Ramipril</li> <li>- Pantoprazol</li> <li>- Nebivolol</li> <li>- Hydrochlorothiazid</li> <li>- Metoclopramid</li> <li>- Simvastatin</li> <li>- Metformin</li> <li>- ASS</li> <li>- Ranitidin</li> <li>- Fenistil</li> </ul> <p>Event details: This patient was hospitalized for planned resection of liver metastases on August 15<sup>th</sup>, 2021, to August 23<sup>rd</sup>, 2021. In the surgery a minimal hepatobiliary injury occurred which was treated by stent implementation. The stent was removed in a standard procedure on September 16<sup>th</sup>, 2021.</p>					

**Table 17:** Narrative of SAE MR-DE-24-01

Patient identifier	MR-DE-24-01				
Year of birth	1941				
Sex	Male				
Height (cm)	175				
Baseline weight (kg)	72				
Race	Caucasian				
Treatment arm	A				
Start/stop of study treatment	Pre-randomization phase: first day first cycle July 22 <sup>nd</sup> , 2021, first day last cycle September 29 <sup>th</sup> , 2021 Randomization phase: first day first cycle October 22 <sup>nd</sup> , 2021, first day last cycle February 28 <sup>th</sup> , 2022				
Date of last dose of study drug before event	FOLFIRI/mFOLFIRI: September 29 <sup>th</sup> , 2021 Cetuximab: -				
Date of death (if applicable)	October 27 <sup>th</sup> , 2023				
Event Term	Start/stop date of the event	Severity	Event outcome	Relationship to study drug	Action taken with study drug
Ileus	Start date: October 6 <sup>th</sup> , 2021  Stop date: October 13 <sup>th</sup> , 2021	mild	Recovered without sequelae	No correlation	No action taken
<b>EVENT SUMMARY:</b> This patient born in 1941 was initially diagnosed with mCRC on July 2 <sup>nd</sup> , 2021. The primary tumor was resected on June 28 <sup>th</sup> , 2021, with resection status R0.  Relevant medical history: - Other gastritis  Relevant concomitant medications: - Pantoprazol - Novalgin - Movicol - Fragmin - Scopoderm - Practo Clyss - Doxycyclin - Minocyclin  Event details: This patient was hospitalized on October 8 <sup>th</sup> , 2021, with recurrent vomiting since October 6 <sup>th</sup> , 2021. Vital signs: temperature: 37.9°C, pO2 94%, weight 60kg, height 170cm. CT scan of the abdomen showed a mechanical ileus with calibre jump in the descending colon due to coprostasis. The patient was hospitalized and treated with Movicol for work-up for coprostasis. The patient recovered without sequelae from the event.					

### 12.3.3 Analysis and Discussion of Deaths, Other SAEs, and Other Significant AEs

Both SAEs of grade 5 were assessed as unlikely correlated to the study medication. The other 2 SAEs of lower grade were assessed as not correlated to study medication. No new safety issues for FOLFIRI and Cetuximab were identified during the course of the study

## 12.4 Clinical Laboratory Evaluation

### 12.4.1 Individual Laboratory Measurements by Patient and Abnormal Laboratory Value

Individual laboratory measurements by patient are available in the Listings 10, 16, 17.1., 17.2 in the MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06. These contain measurement of hematological and blood chemistry laboratory assessments as well as coagulation parameters.

Tumor marker assessments for each patient are available in Listing 18. as well as *RAS* mutation analyses on tumor tissue in Listing 19 and in liquid biopsy in Listing 20 in the MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06.

Before starting with the study treatment, a test for DPD deficiency was performed in two of the assigned patients and showed no deficiency for neither of the patients (Data source: Listing 11. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06).

Hepatitis serology was assessed at baseline, all six assigned patients showed negative serology for Hepatitis B and C (Data source: Listing 12. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06).

### 12.4.2 Evaluation of Laboratory Values

Because of the small number of patients, no analysis of the laboratory values was performed to compare Arm A to Arm B or individual patients. Detailed measurements for each patient can be found in the listings. No further analysis was conducted as this was not specified in the study protocol as study objective or in the Statistical Analysis Plan (SAP).

#### 12.4.2.1 Laboratory Values Over Time

Laboratory values over time are provided for each patient in the listings of MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06. No analysis of the laboratory values over time was conducted as this was not specified in the study protocol or in the SAP

#### 12.4.2.2 Individual Patient Changes in Laboratory Values

Not applicable.

#### 12.4.2.3 Individual Clinically Significant Abnormalities

Not applicable.

## 12.5 Vital Signs, Physical Examinations, and Other Observations Related to Safety

Results of physical examinations and vital signs can be found in the listings. Listing 8 of the MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06 shows the results of the echocardiography of every patient at baseline, Listing 13 shows the ECG assessment, the assessment of the ECOG performance status can be seen in Listing 14. Vital signs including weight, temperature, blood pressure and heartrate were raised at different times and listed in Listing 15. No comparison of the two treatment arms was performed due to the small number of patients. Furthermore, this was not specified in the study protocol or in the SAP.

## 12.6 Safety Result Summary

In total, 78 AEs were reported during the study, thereof 47 AEs were classified as related to study treatment by investigator's judgement. Two AEs resulted in death, both patients were in the experimental group. One patient died because of a gastric ulcer, the other from progression of carcinoma. Both SAEs were assessed as unlikely correlated to study medication. In general, most frequently reported AEs were nausea (N=5), diarrhoea (N=4), fatigue and alopecia (N=3 each).

Most reported AEs irrespective of the treatment arm belonged to SOC 'Gastrointestinal disorders' (N=6) and 'Investigations' (N=5).

A total of four SAEs was reported by three patients, all treated in the experimental arm. Two patients died because of a SAE, both were assessed as unlikely correlated to study medication. One patient experienced an AEs leading to discontinuation of Cetuximab (nail infection and Dermatitis acneiform). Dose reduction of 5-FU was done in one patient due to skin laceration.

Five patients (experimental arm: N=3, control arm: N=2) died. Reason of death was carcinoma (N=2), metastatic, mutated colorectal cancer (N=1), and gastric ulcer (N=1). For one death, the reason was unknown.

## 13 DISCUSSION AND OVERALL CONCLUSIONS

This multi-centre, randomized phase-II clinical study aimed to investigate the efficacy and safety of the adaption of adding cetuximab to 1<sup>st</sup>-line therapy with FOLFIRI after *RAS*-mutation status changed to wild-type and changing back to FOLFIRI, as required if *RAS*-mutation status changed to mutant.

The planned number of patients was not reached. The recruitment phase was terminated early. Only six patients were randomized (experimental arm: N=4, control arm: N=2). All randomized patients were evaluable for analysis of efficacy and safety. Due to the small number of evaluable patients the explanatory power of these results is limited.

The primary efficacy endpoint was PFS. In the experimental arm, PFS ranged from 1.97 to 9.77 months, in the control arm PFS ranged from 3.68 to 8.95 months.

Analysis of the secondary efficacy objectives (ORR, OS, TFTS) was not able to show differences between experimental and control group due to the limited data.

In total, 78 AEs in six patients were recorded during the study. NCI grade of the AEs ranged from 1 (N=57) to 5 (N=2). Four SAEs occurred in three patients. Mainly AEs in the SOC 'gastrointestinal disorders' and 'Investigations' were experienced which is in line with the toxicity profile of FOLFIRI and Cetuximab. No new safety issues for FOLFIRI and Cetuximab were identified during the course of the study.

In 2014, 61.000 people were diagnosed with CRC and a total of 25.5000 patients died due to CRC. In 2022, the number of people affected was roughly constant. The numbers are trending upwards, making clear that there is still a great unmet need for further development of CRC treatment, especially for advanced stages.

As today therapy of mCRC still depends on the individual state of health of the patient. The better the patient's general condition, the more intensive therapy can be. If possible, resection of the primary tumor and metastases should be attempted. Chemotherapy depends on the molecular pathological profile of the tumor. Patients in good general condition with left-sided mCRC with *RAS* wild-type should be treated with a chemotherapy doublet (e.g. FOLFIRI) and anti-EGFR therapy. Next to anti-EGFR therapy, other targeted therapies addressing other molecular groups were developed in the last decades such as anti-VEGF, therapies addressing BRAF V600E mutations, HER2 or ErBB2 amplifications. The development of resistance to targeted therapies is a major limitation in treatment of mCRC, thus the development of new strategies to overcome secondary drug resistance is very important. The approach of liquid biopsy-guided therapy, in which the *RAS* mutation status is analysed at regular intervals and the therapy is adjusted, as investigated in this study could be one solution for this problem. Analysis of ctDNA is component of further studies that investigate re-challenge therapy with anti-EGFR after development of resistance in previous therapies. The CRICKET trial showed higher rates of response (31%) for re-challenge therapy with anti-EGFR in patients without *RAS* mutations in ctDNA after the tumor developed resistance during previous treatment [Cremolini, 2018]. The results of the JACCRO CC-08 study suggest that the length of the cetuximab-free-interval has an impact on rechallenge therapy and that analysis of ctDNA may be more effective selecting patients for rechallenge therapy with anti-EGFR after development of resistance during previous therapy [Masuishi, 2020].

Future studies should continue to investigate the value of regular re-evaluation of *RAS* mutation status by liquid biopsy and subsequent adjustment of anti-EGFR therapy in patients with mCRC. The optimal timing for sample collection should also be an aspect of the research.

To address the problem of low patient recruitment in future studies, the study design should be kept as simple as possible. Consideration should be given to administering cetuximab at a once every-second-week dose of 500 mg/m<sup>2</sup> instead of 250 mg/m<sup>2</sup> on day 1 and day 8. The safety of this administration of cetuximab was assessed in a phase-I dose escalation study [Tabernero, 2010].

Another problem in this study was the time required to determine the *RAS* mutation status in patients with high therapy pressure. Faster molecular pathological analysis of samples could make these patients eligible for the study.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

Populations	[N,%]
Number of patients	7 (100.00)
Number of patients in analysis populations	
mITT=SP	6 (85.71)
PP	6 (85.71)
Number of patients in treatment arms	
A	4 (57.14)
B	2 (28.57)
Number of participating clinics	4 (100.00)

(Data source: Table 1 MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

Patient No.	Arm	Age [years]	Height [cm]	Weight [kg]	Sex	WOCBP	Ethnic origin	Protocol version at informed consent
MR-DE-01-01	A	65	161	76	Female	No	Caucasian / White	Version 3.0 (2021-03-09)
MR-DE-02-01	B	41	167	93	Male		Caucasian / White	Version 2.1 (2020-07-03)
MR-DE-02-02	A	67	176	125	Male		Caucasian / White	Version 3.0 (2021-03-09)
MR-DE-02-03	B	51	186	92	Male		Caucasian / White	Version 3.0 (2021-03-09)
MR-DE-14-01	A	62	175	89	Male		Caucasian / White	Version 2.1 (2020-07-03)
MR-DE-24-01	A	80	175	72	Male		Caucasian / White	Version 3.0 (2021-03-09)
MR-DE-24-02	Not assigned	69	.	.	Male		Missing	Version 3.0 (2021-03-09)

(Data source: Listing 4. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

Patient No.	Arm	Primary tumor resected before study inclusion	Date of resection	Resection status
MR-DE-01-01	A	Yes	07MAY20	R0
MR-DE-02-01	B	Yes	21MAR18	R0
MR-DE-02-02	A	Yes	23DEC16	R0
MR-DE-02-03	B	No	.	.
MR-DE-14-01	A	Yes	02DEC20	R0
MR-DE-24-01	A	Yes	28JUN21	R0

(Data source: Listing 5.2. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

14.2 Efficacy data

<i>Responses according to RECIST v1.1 criteria including Overall response rate (ORR)</i>	<i>A [N,%]</i>	<i>B [N,%]</i>	<i>Total [N,%]</i>
Number of randomized patients	4 (100.00)	2 (100.00)	6 (100.00)
Most recent response			
Progressive disease (PD)	4 (100.00)	2 (100.00)	6 (100.00)
Best response			
Partial response (PR)	3 (75.00)	1 (50.00)	4 (66.67)
Stable disease (SD)	1 (25.00)	1 (50.00)	2 (33.33)
Overall response			
CR or PR (ORR)	3 (75.00)	1 (50.00)	4 (66.67)

(Data source: Table 3 MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>RECIST assessment performed</i>	<i>Reason</i>	<i>Staging No.</i>	<i>Date of RECIST assessment</i>	<i>Number of metastases at beginning of the study</i>	<i>Sum of sizes [mm]</i>	<i>Overall assessment</i>	<i>Consultation with Administration Office has occurred</i>	<i>Comment</i>
MR-DE-01-01	A	Baseline	Yes		0	09APR21	1	70			
MR-DE-01-01	A	Pre-cycle 1	No	Other: not nessecary	.	.	.	.			
MR-DE-01-01	A	Pre-cycle 2	No	Other: not nessecary	.	.	.	.			
MR-DE-01-01	A	Pre-cycle 3	No	Other: not nessecary	.	.	.	.			
MR-DE-01-01	A	Pre-cycle 4	Yes	Regular Assessment due to study protocol	1	21JUN21	1	52	SD		
MR-DE-01-01	A	Cycle 1	No	Other: not necessary	.	.	.	.			
MR-DE-01-01	A	Cycle 2	No	Other: not necessary	.	.	.	.			
MR-DE-01-01	A	Cycle 3	No	Other: unnecessary	.	.	.	.			
MR-DE-01-01	A	Cycle 4	No	Other: unnecessary	.	.	.	.			
MR-DE-01-01	A	Cycle 5	Yes	Regular Assessment due to study protocol	2	20AUG21	1	43	PD	Yes	
MR-DE-01-01	A	Cycle 6	No	Other: unnecessary	.	.	.	.			
MR-DE-01-01	A	Cycle 7	No	Other: not necessary	.	.	.	.			
MR-DE-01-01	A	Cycle 8	No	Other: not necessary	.	.	.	.			
MR-DE-01-01	A	Cycle 9	No	Other: not necessary	.	.	.	.			
MR-DE-01-01	A	Cycle 10	No	Medical reason	.	.	.	.			
MR-DE-02-01	B	Baseline	Yes		0	16APR21	1	15			
MR-DE-02-01	B	Pre-cycle 1	No	Other: not necessary at that point of time	.	.	.	.			
MR-DE-02-01	B	Pre-cycle 2	No	Other: not necessary at that point of time	.	.	.	.			
MR-DE-02-01	B	Pre-cycle 3	No	Other: will be done on 16.06.2021	.	.	.	.			



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<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>RECIST assessment performed</i>	<i>Reason</i>	<i>Staging No.</i>	<i>Date of RECIST assessment</i>	<i>Number of metastases at beginning of the study</i>	<i>Sum of sizes [mm]</i>	<i>Overall assessment</i>	<i>Consultation with Administration Office has occurred</i>	<i>Comment</i>
MR-DE-02-01	B	Pre-cycle 4	Yes	Regular Assessment due to study protocol	1	16JUN21	1	8	PR		
MR-DE-02-01	B	Cycle 1	No	Other: not necessary at that cycle	.	.	.	.			
MR-DE-02-01	B	Cycle 2	No	Other: time point	.	.	.	.			
MR-DE-02-01	B	Cycle 3	No	Other: time point	.	.	.	.			
MR-DE-02-01	B	Cycle 4	Yes	Regular Assessment due to study protocol	2	23AUG21	1	7	PR		
MR-DE-02-01	B	Cycle 5	No	Other: time point	.	.	.	.			
MR-DE-02-01	B	Cycle 6	No	Other: in next cycle	.	.	.	.			
MR-DE-02-01	B	Cycle 7	Yes	Regular Assessment due to study protocol	3	18OCT21	1	8	PR		
MR-DE-02-01	B				4	14DEC21	1	7	PR		
MR-DE-02-01	B				5	16MAR22	1	42	PD		
MR-DE-02-02	A	Baseline	Yes		0	29APR21	23	58			
MR-DE-02-02	A	Pre-cycle 1	No	Other: not necessary at that point of time	.	.	.	.			
MR-DE-02-02	A	Pre-cycle 2	No	Other: not necessary at that point of time	.	.	.	.			
MR-DE-02-02	A	Pre-cycle 3	No	Other: not needed at the moment	.	.	.	.			
MR-DE-02-02	A	Pre-cycle 4	Yes	Regular Assessment due to study protocol	1	09JUL21	23	27	PR	Yes	
MR-DE-02-02	A	Cycle 1	No	Other: time point	.	.	.	.			
MR-DE-02-02	A	Cycle 2	No	Other: time point	.	.	.	.			
MR-DE-02-02	A	Cycle 3	No	Other: point of time	.	.	.	.			

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<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>RECIST assessment performed</i>	<i>Reason</i>	<i>Staging No.</i>	<i>Date of RECIST assessment</i>	<i>Number of metastases at beginning of the study</i>	<i>Sum of sizes [mm]</i>	<i>Overall assessment</i>	<i>Consultation with Administration Office has occurred</i>	<i>Comment</i>
MR-DE-02-02	A	Cycle 4	Yes	Regular Assessment due to study protocol	2	06SEP21	23	17	PR	Yes	
MR-DE-02-02	A	Cycle 5	No	Other: to be followed	.	.	.	.			
MR-DE-02-02	A	Cycle 6	No	Other: will be done	.	.	.	.			
MR-DE-02-02	A	Cycle 7	No	Other: wrong time point	.	.	.	.			
MR-DE-02-02	A	Cycle 8	Yes	Regular Assessment due to study protocol	3	08NOV21	23	17	PR	Yes	
MR-DE-02-02	A	Cycle 9	No	Other: done in prior cycle	.	.	.	.			
MR-DE-02-02	A	Cycle 10	No	Medical reason	.	.	.	.			
MR-DE-02-02	A				4	04MAY22	23	61	PD	Yes	
MR-DE-02-03	B	Baseline	Yes		0	10MAY21	23	88			
MR-DE-02-03	B	Pre-cycle 1	No	Other: not necessary at that point of time	.	.	.	.			
MR-DE-02-03	B	Pre-cycle 2	No	Other: not necessary at that point of time	.	.	.	.			
MR-DE-02-03	B	Pre-cycle 3	No	Other: not indicated today	.	.	.	.			
MR-DE-02-03	B	Pre-cycle 4	Yes	Regular Assessment due to study protocol	1	07JUL21	23	80	SD	Yes	
MR-DE-02-03	B	Cycle 1	No	Other: time point	.	.	.	.			
MR-DE-02-03	B	Cycle 2	No	Other: time point	.	.	.	.			
MR-DE-02-03	B	Cycle 3	No	Other: time point	.	.	.	.			
MR-DE-02-03	B	Cycle 4	No	Other: protocol	.	.	.	.			
MR-DE-02-03	B	Cycle 5	Yes	Regular Assessment due to study protocol	2	06SEP21	23	83	SD	Yes	

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>RECIST assessment performed</i>	<i>Reason</i>	<i>Staging No.</i>	<i>Date of RECIST assessment</i>	<i>Number of metastases at beginning of the study</i>	<i>Sum of sizes [mm]</i>	<i>Overall assessment</i>	<i>Consultation with Administration Office has occurred</i>	<i>Comment</i>
MR-DE-02-03	B	Cycle 6	Yes	Additional assessment (progress suspected)	3	28OCT21	23	91	PD	Yes	
MR-DE-14-01	A	Baseline	Yes		0	17NOV20	gt3	105			
MR-DE-14-01	A	Pre-cycle 1	No	Other: Performed in baseline	.	.		.			
MR-DE-14-01	A	Pre-cycle 2	No	Medical reason	.	.		.			
MR-DE-14-01	A	Pre-cycle 3	No	Other: as per protocol	.	.		.			
MR-DE-14-01	A	Pre-cycle 4	Yes	Regular Assessment due to study protocol	1	25FEB21	gt3	81	SD		
MR-DE-14-01	A	Pre-cycle 5	No	Other: as per protocol	.	.		.			
MR-DE-14-01	A	Cycle 1	No	Other: as per protocol	.	.		.			
MR-DE-14-01	A	Cycle 2	No	Other: as per protocol	.	.		.			
MR-DE-14-01	A	Cycle 3	No	Other: as per protocol	.	.		.			
MR-DE-14-01	A	Cycle 4	Yes	Regular Assessment due to study protocol	2	26APR21	gt3	48	PR		
MR-DE-14-01	A	Cycle 5	No	Other: as per protocol	.	.		.			
MR-DE-14-01	A	Cycle 6	No	Other: as per protocol	.	.		.			
MR-DE-14-01	A	Cycle 7	No	Other: as per protocol	.	.		.			
MR-DE-14-01	A	Cycle 8	Yes	Regular Assessment due to study protocol	3	21JUN21	gt3	40	PR		
MR-DE-14-01	A	Cycle 9	No	Other: as per protocol	.	.		.			
MR-DE-14-01	A	Cycle 10	No	Other: as per protocol	.	.		.			
MR-DE-14-01	A	Cycle 12	No	Other: therapy paused as per clinical routine	.	.		.			

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<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>RECIST assessment performed</i>	<i>Reason</i>	<i>Staging No.</i>	<i>Date of RECIST assessment</i>	<i>Number of metastases at beginning of the study</i>	<i>Sum of sizes [mm]</i>	<i>Overall assessment</i>	<i>Consultation with Administration Office has occurred</i>	<i>Comment</i>
MR-DE-14-01	A	Cycle 16	No	Other: medication paused as per local routine	.	.	.	.			
MR-DE-14-01	A	Cycle 18	Yes	Regular Assessment due to study protocol	4	26OCT21	gt3	73	PD		
MR-DE-14-01	A	Cycle 19	No	Other: as per protocol	.	.	.	.			
MR-DE-14-01	A	Cycle 20	No	Other: as per protocol	.	.	.	.			
MR-DE-24-01	A	Baseline	Yes		0	20JUL21	23	170			
MR-DE-24-01	A	Pre-cycle 1	No	Other: Direction every 8 weeks.	.	.	.	.			
MR-DE-24-01	A	Pre-cycle 2	No	Other: according to protocol every 8 weeks; next date Sept. 2021	.	.	.	.			
MR-DE-24-01	A	Pre-cycle 3	No	Other: Direction every 8 weeks.	.	.	.	.			
MR-DE-24-01	A	Pre-cycle 4	No	Other: Duration 8 weeks	.	.	.	.			
MR-DE-24-01	A	Pre-cycle 5	No	Other: Duration 8 weeks.	.	.	.	.			
MR-DE-24-01	A	Pre-cycle 6	Yes	Regular Assessment due to study protocol	1	21SEP21	23	114	PR		
MR-DE-24-01	A	Cycle 1	No	Medical reason	.	.	.	.			
MR-DE-24-01	A	Cycle 2	No	Other: lt. Protokoll: geplant 19.11.21	.	.	.	.			
MR-DE-24-01	A	Cycle 3	Yes	Regular Assessment due to study protocol	2	19NOV21	23	86	PR		
MR-DE-24-01	A	Cycle 4	No	Other: According to protocol	.	.	.	.			

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>RECIST assessment performed</i>	<i>Reason</i>	<i>Staging No.</i>	<i>Date of RECIST assessment</i>	<i>Number of metastases at beginning of the study</i>	<i>Sum of sizes [mm]</i>	<i>Overall assessment</i>	<i>Consultation with Administration Office has occurred</i>	<i>Comment</i>
MR-DE-24-01	A	Cycle 5	No	Other: Next Tumor Assessment will start 11.01.2022	.	.	.	.			
MR-DE-24-01	A	Cycle 6	No	Other: Lt. Protokoll	.	.	.	.			
MR-DE-24-01	A	Cycle 7	No	Other: Lt. Protokoll	.	.	.	.			
MR-DE-24-01	A	Cycle 8	Yes	Regular Assessment due to study protocol	3	26JAN22	23	66	PR		
MR-DE-24-01	A	Cycle 9	No	Other: ACCORDING TO THE PROTOCOL	.	.	.	.			
MR-DE-24-01	A	Cycle 10	No	Other: ACCORDING TO THE PROTOCOL	.	.	.	.			
MR-DE-24-01	A	Cycle 11	No	Other: ACCORDING TO THE PROTOCOL	.	.	.	.			
MR-DE-24-01	A	Cycle 12	Yes	Regular Assessment due to study protocol	4	23MAR22	23	94	PD		After consultation with the radiologist and Prof. Baraniskin, the RECIST evaluation should not be considered PD.
MR-DE-24-01	A	Cycle 13	No	Other: According to protocol	.	.	.	.			
MR-DE-24-01	A	Cycle 14	No	Other: According to the Protocol	.	.	.	.			
MR-DE-24-01	A	Cycle 15	No	Other: According to the protocol	.	.	.	.			
MR-DE-24-01	A	Cycle 16	Yes	Regular Assessment due to study protocol	4	23MAR22	23	94	PD		After consultation with the radiologist and Prof. Baraniskin, the RECIST evaluation should not be considered PD.

Patient No.	Arm	Point in time	RECIST assessment performed	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	Comment
MR-DE-24-01	A	Cycle 17	Yes	Regular Assessment due to study protocol	5	20MAY22	23	.			

(Data source: Listing 23.1. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

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-measureable lesions
MR-DE-01-01	A	0	09APR21	Abdominal wall	lobus caudatus	CT scan	45			
MR-DE-01-01	A	0	09APR21	Other	kindney superior pole	CT scan	25			
MR-DE-01-01	A	0	09APR21	Other	multiple little kidney lesionen	CT scan	.	Present		
MR-DE-01-01	A	1	21JUN21	Abdominal wall	lobus caudatus	CT scan	27		SD	CR
MR-DE-01-01	A	1	21JUN21	Other	kindney superior pole	CT scan	25		SD	CR
MR-DE-01-01	A	1	21JUN21	Other	multiple little kidney lesionen	CT scan	.	Absent	SD	CR
MR-DE-01-01	A	2	20AUG21	Lymph nodes iliacal	an Anastomose (IMA136/2)	CT scan	.	Present	PR	PD
MR-DE-01-01	A	2	20AUG21	Abdominal wall	lobus caudatus	CT scan	18		PR	PD
MR-DE-01-01	A	2	20AUG21	Other	kindney superior pole	CT scan	25		PR	PD
MR-DE-01-01	A	2	20AUG21	Other	multiple little kidney lesionen	CT scan	.	Present	PR	PD
MR-DE-02-01	B	0	16APR21	Liver	S6	CT scan	15			
MR-DE-02-01	B	0	16APR21	Liver	S4	CT scan	.	Present		
MR-DE-02-01	B	0	16APR21	Other	Met between M.c.d +thoracic wall	CT scan	.	Present		
MR-DE-02-01	B	1	16JUN21	Liver	S6	CT scan	8		PR	SD
MR-DE-02-01	B	1	16JUN21	Liver	S4	CT scan	.	Present	PR	SD
MR-DE-02-01	B	1	16JUN21	Other	Met between M.c.d +thoracic wall	CT scan	.	Present	PR	SD

<i>Patient No.</i>	<i>Arm</i>	<i>Staging No.</i>	<i>Date</i>	<i>Localization</i>	<i>Detailed information about localization</i>	<i>Method</i>	<i>Size of lesion if measurable [mm]</i>	<i>Tumor type if non-measurable</i>	<i>Assessment measurable lesions</i>	<i>Assessment non-measurable lesions</i>
MR-DE-02-01	B	2	23AUG21	Liver	S6	CT scan	7		PR	SD
MR-DE-02-01	B	2	23AUG21	Liver	S4	CT scan	.	Present	PR	SD
MR-DE-02-01	B	2	23AUG21	Other	Met between M.c.d +thoracic wall	CT scan	.	Present	PR	SD
MR-DE-02-01	B	3	18OCT21	Liver	S6	CT scan	8		PR	SD
MR-DE-02-01	B	3	18OCT21	Liver	S4	CT scan	.	Present	PR	SD
MR-DE-02-01	B	3	18OCT21	Other	Met between M.c.d +thoracic wall	CT scan	.	Present	PR	SD
MR-DE-02-01	B	4	14DEC21	Liver	S6	CT scan	7		PR	SD
MR-DE-02-01	B	4	14DEC21	Liver	S4	CT scan	.	Present	PR	SD
MR-DE-02-01	B	4	14DEC21	Other	Met between M.c.d +thoracic wall	CT scan	.	Present	PR	SD
MR-DE-02-01	B	5	16MAR22	Liver	S6	CT scan	7		PD	SD
MR-DE-02-01	B	5	16MAR22	Liver	S5/4b	CT scan	35		PD	SD
MR-DE-02-01	B	5	16MAR22	Liver	S4	CT scan	.	Present	PD	SD
MR-DE-02-01	B	5	16MAR22	Other	Met between M.c.d +thoracic wall	CT scan	.	Present	PD	SD
MR-DE-02-02	A	0	29APR21	Peritoneal	peritoneal nodes left	CT scan	31			
MR-DE-02-02	A	0	29APR21	Peritoneal	subphrenic	CT scan	27			
MR-DE-02-02	A	1	09JUL21	Peritoneal	peritoneal nodes left	CT scan	18		PR	
MR-DE-02-02	A	1	09JUL21	Peritoneal	subphrenic	CT scan	9		PR	
MR-DE-02-02	A	2	06SEP21	Peritoneal	peritoneal nodes left	CT scan	11		PR	
MR-DE-02-02	A	2	06SEP21	Peritoneal	subphrenic	CT scan	6		PR	
MR-DE-02-02	A	3	08NOV21	Peritoneal	peritoneal nodes left	CT scan	11		PR	
MR-DE-02-02	A	3	08NOV21	Peritoneal	subphrenic	CT scan	6		PR	
MR-DE-02-02	A	4	04MAY22	Peritoneal	peritoneal nodes left	CT scan	31		PD	
MR-DE-02-02	A	4	04MAY22	Peritoneal	subphrenic	CT scan	30		PD	
MR-DE-02-03	B	0	10MAY21	Liver	Seg III	CT scan	39			

<i>Patient No.</i>	<i>Arm</i>	<i>Staging No.</i>	<i>Date</i>	<i>Localization</i>	<i>Detailed information about localization</i>	<i>Method</i>	<i>Size of lesion if measurable [mm]</i>	<i>Tumor type if non-measurable</i>	<i>Assessment measurable lesions</i>	<i>Assessment non-measurable lesions</i>
MR-DE-02-03	B	0	10MAY21	Other	epigastric masses	CT scan	49			
MR-DE-02-03	B	0	10MAY21	Lung	left upper lung, lateral	CT scan	.	Present		
MR-DE-02-03	B	0	10MAY21	Lung	right upper lung	CT scan	.	Present		
MR-DE-02-03	B	1	07JUL21	Liver	Seg III	CT scan	35		SD	SD
MR-DE-02-03	B	1	07JUL21	Other	epigastric masses	CT scan	45		SD	SD
MR-DE-02-03	B	1	07JUL21	Lung	left upper lung, lateral	CT scan	.	Present	SD	SD
MR-DE-02-03	B	1	07JUL21	Lung	right upper lung	CT scan	.	Present	SD	SD
MR-DE-02-03	B	2	06SEP21	Liver	Seg III	CT scan	37		SD	SD
MR-DE-02-03	B	2	06SEP21	Other	epigastric masses	CT scan	46		SD	SD
MR-DE-02-03	B	2	06SEP21	Lung	left upper lung, lateral	CT scan	.	Present	SD	SD
MR-DE-02-03	B	2	06SEP21	Lung	right upper lung	CT scan	.	Present	SD	SD
MR-DE-02-03	B	3	28OCT21	Liver	Seg III	CT scan	41		SD	PD
MR-DE-02-03	B	3	28OCT21	Other	epigastric masses	CT scan	50		SD	PD
MR-DE-02-03	B	3	28OCT21	Lung	left upper lung, lateral	CT scan	.	Progradient	SD	PD
MR-DE-02-03	B	3	28OCT21	Lung	right upper lung	CT scan	.	Progradient	SD	PD
MR-DE-14-01	A	0	17NOV20	Liver	right lobe cranial	CT scan	56			
MR-DE-14-01	A	0	17NOV20	Liver	all segments	CT scan	.	Present		
MR-DE-14-01	A	0	17NOV20	Liver	Lobus caudatus	CT scan	49			
MR-DE-14-01	A	1	25FEB21	Liver	right lobe cranial	CT scan	46		SD	SD
MR-DE-14-01	A	1	25FEB21	Liver	Lobus caudatus	CT scan	35		SD	SD
MR-DE-14-01	A	1	25FEB21	Liver	all segments	CT scan	.	Present	SD	SD
MR-DE-14-01	A	2	26APR21	Liver	right lobe cranial	CT scan	29		PR	SD
MR-DE-14-01	A	2	26APR21	Liver	Lobus caudatus	CT scan	19		PR	SD
MR-DE-14-01	A	2	26APR21	Liver	all segments	CT scan	.	Present	PR	SD



<i>Patient No.</i>	<i>Arm</i>	<i>Staging No.</i>	<i>Date</i>	<i>Localization</i>	<i>Detailed information about localization</i>	<i>Method</i>	<i>Size of lesion if measurable [mm]</i>	<i>Tumor type if non-measurable</i>	<i>Assessment measurable lesions</i>	<i>Assessment non-measurable lesions</i>
MR-DE-14-01	A	3	21JUN21	Liver	right lobe cranial	CT scan	25		PR	SD
MR-DE-14-01	A	3	21JUN21	Liver	Lobus caudatus	CT scan	15		PR	SD
MR-DE-14-01	A	3	21JUN21	Liver	all segments	CT scan	.	Present	PR	SD
MR-DE-14-01	A	4	26OCT21	Lung	inferior lobe right	CT scan	.	Present	PD	PD
MR-DE-14-01	A	4	26OCT21	Lung	inferior lobe left	CT scan	.	Present	PD	PD
MR-DE-14-01	A	4	26OCT21	Liver	right lobe cranial	CT scan	43		PD	PD
MR-DE-14-01	A	4	26OCT21	Liver	Lobus caudatus	CT scan	30		PD	PD
MR-DE-14-01	A	4	26OCT21	Liver	all segments	CT scan	.	Present	PD	PD
MR-DE-24-01	A	0	20JUL21	Liver	Segment VII	CT scan	59			
MR-DE-24-01	A	0	20JUL21	Liver	Segment VIII	CT scan	111			
MR-DE-24-01	A	0	20JUL21	Liver	S2	CT scan	.	Present		
MR-DE-24-01	A	0	20JUL21	Liver	S5	CT scan	.	Present		
MR-DE-24-01	A	0	20JUL21	Liver	S3	CT scan	.	Present		
MR-DE-24-01	A	0	20JUL21	Liver	S6	CT scan	.	Present		
MR-DE-24-01	A	0	20JUL21	Liver	S7/8a	CT scan	.	Present		
MR-DE-24-01	A	0	20JUL21	Liver	S7/8b	CT scan	.	Present		
MR-DE-24-01	A	0	20JUL21	Liver	S9	CT scan	.	Present		
MR-DE-24-01	A	0	20JUL21	Liver	S10	CT scan	.	Present		
MR-DE-24-01	A	1	21SEP21	Liver	Segment VII	CT scan	38		PR	SD
MR-DE-24-01	A	1	21SEP21	Liver	Segment VIII	CT scan	76		PR	SD
MR-DE-24-01	A	1	21SEP21	Liver	S2	CT scan	.	Present	PR	SD
MR-DE-24-01	A	1	21SEP21	Liver	S5	CT scan	.	Present	PR	SD
MR-DE-24-01	A	1	21SEP21	Liver	S3	CT scan	.	Present	PR	SD
MR-DE-24-01	A	1	21SEP21	Liver	S6	CT scan	.	Present	PR	SD

<i>Patient No.</i>	<i>Arm</i>	<i>Staging No.</i>	<i>Date</i>	<i>Localization</i>	<i>Detailed information about localization</i>	<i>Method</i>	<i>Size of lesion if measurable [mm]</i>	<i>Tumor type if non-measurable</i>	<i>Assessment measurable lesions</i>	<i>Assessment non-measurable lesions</i>
MR-DE-24-01	A	1	21SEP21	Liver	S7/8a	CT scan	.	Present	PR	SD
MR-DE-24-01	A	1	21SEP21	Liver	S7/8b	CT scan	.	Present	PR	SD
MR-DE-24-01	A	1	21SEP21	Liver	S9	CT scan	.	Absent	PR	SD
MR-DE-24-01	A	1	21SEP21	Liver	S10	CT scan	.	Present	PR	SD
MR-DE-24-01	A	2	19NOV21	Liver	S5	CT scan	.	Absent	PR	SD
MR-DE-24-01	A	2	19NOV21	Liver	Segment VII	CT scan	33		PR	SD
MR-DE-24-01	A	2	19NOV21	Liver	Segment VIII	CT scan	53		PR	SD
MR-DE-24-01	A	2	19NOV21	Liver	S2	CT scan	.	Present	PR	SD
MR-DE-24-01	A	2	19NOV21	Liver	S3	CT scan	.	Present	PR	SD
MR-DE-24-01	A	2	19NOV21	Liver	S6	CT scan	.	Present	PR	SD
MR-DE-24-01	A	2	19NOV21	Liver	S7/8a	CT scan	.	Present	PR	SD
MR-DE-24-01	A	2	19NOV21	Liver	S9	CT scan	.	Absent	PR	SD
MR-DE-24-01	A	2	19NOV21	Liver	S10	CT scan	.	Absent	PR	SD
MR-DE-24-01	A	2	19NOV21	Liver	S7/8b	CT scan	.	Present	PR	SD
MR-DE-24-01	A	3	26JAN22	Liver	Segment VII	CT scan	25		PR	SD
MR-DE-24-01	A	3	26JAN22	Liver	Segment VIII	CT scan	41		PR	SD
MR-DE-24-01	A	3	26JAN22	Liver	S5	CT scan	.	Absent	PR	SD
MR-DE-24-01	A	3	26JAN22	Liver	S2	CT scan	.	Present	PR	SD
MR-DE-24-01	A	3	26JAN22	Liver	S3	CT scan	.	Present	PR	SD
MR-DE-24-01	A	3	26JAN22	Liver	S6	CT scan	.	Present	PR	SD
MR-DE-24-01	A	3	26JAN22	Liver	S7/8a	CT scan	.	Present	PR	SD
MR-DE-24-01	A	3	26JAN22	Liver	S7/8b	CT scan	.	Present	PR	SD
MR-DE-24-01	A	3	26JAN22	Liver	S9	CT scan	.	Absent	PR	SD
MR-DE-24-01	A	3	26JAN22	Liver	S10	CT scan	.	Absent	PR	SD

<i>Patient No.</i>	<i>Arm</i>	<i>Staging No.</i>	<i>Date</i>	<i>Localization</i>	<i>Detailed information about localization</i>	<i>Method</i>	<i>Size of lesion if measurable [mm]</i>	<i>Tumor type if non-measurable</i>	<i>Assessment measurable lesions</i>	<i>Assessment non-measurable lesions</i>
MR-DE-24-01	A	4	23MAR22	Liver	Segment VII	CT scan	40		PD	PD
MR-DE-24-01	A	4	23MAR22	Liver	Segment VIII	CT scan	54		PD	PD
MR-DE-24-01	A	4	23MAR22	Liver	S2	CT scan	.	Progredient	PD	PD
MR-DE-24-01	A	4	23MAR22	Liver	S3	CT scan	.	Progredient	PD	PD
MR-DE-24-01	A	4	23MAR22	Liver	S6	CT scan	.	Present	PD	PD
MR-DE-24-01	A	4	23MAR22	Liver	S7/8a	CT scan	.	Progredient	PD	PD
MR-DE-24-01	A	4	23MAR22	Liver	S7/8b	CT scan	.	Progredient	PD	PD
MR-DE-24-01	A	4	23MAR22	Liver	S9	CT scan	.	Absent	PD	PD
MR-DE-24-01	A	4	23MAR22	Liver	S10	CT scan	.	Absent	PD	PD
MR-DE-24-01	A	4	23MAR22	Liver	S5	CT scan	.	Absent	PD	PD
MR-DE-24-01	A	5	20MAY22	Missing		Missing	.			

(Data source: Listing 23.2. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

## 14.3 Safety data

### 14.3.1 Display of AEs

SOC	PT	NCI CTCAE grade				Total	
		1	2	3	5	N	%
Number of AEs		57	16	3	2	78	100.00
Blood and lymphatic system disorders		2	.	.	.	2	2.56
	Anaemia	2	.	.	.	2	2.56
Cardiac disorders		1	.	.	.	1	1.28
	Arrhythmia	1	.	.	.	1	1.28
Gastrointestinal disorders		18	6	1	1	26	33.33
	Constipation	2	1	.	.	3	3.85
	Diarrhoea	4	1	1	.	6	7.69
	Dyschezia	1	.	.	.	1	1.28
	Enteritis	1	.	.	.	1	1.28
	Flatulence	1	.	.	.	1	1.28
	Gastric ulcer	.	.	.	1	1	1.28
	Gastrooesophageal reflux disease	1	.	.	.	1	1.28
	Haemorrhoidal haemorrhage	1	.	.	.	1	1.28
	Ileus	1	.	.	.	1	1.28
	Nausea	5	2	.	.	7	8.97
	Vomiting	1	2	.	.	3	3.85
General disorders and administration site conditions		4	1	.	.	5	6.41
	Fatigue	3	.	.	.	3	3.85
	Pyrexia	1	1	.	.	2	2.56
Immune system disorders		1	.	.	.	1	1.28
	Hypersensitivity	1	.	.	.	1	1.28
Infections and infestations		2	3	.	.	5	6.41
	Anorectal infection	.	1	.	.	1	1.28
	Infection	.	1	.	.	1	1.28
	Nail infection	1	.	.	.	1	1.28
	Skin infection	1	.	.	.	1	1.28
	Urinary tract infection	.	1	.	.	1	1.28
Injury, poisoning and procedural complications		3	.	.	.	3	3.85
	Hepatobiliary procedural complication	1	.	.	.	1	1.28
	Overdose	1	.	.	.	1	1.28
	Skin laceration	1	.	.	.	1	1.28

SOC	PT	NCI CTCAE grade				Total	
		1	2	3	5	N	%
Investigations		5	4	1	.	10	12.82
	Alanine aminotransferase increased	2	1	.	.	3	3.85
	Aspartate aminotransferase increased	.	1	.	.	1	1.28
	Blood bilirubin increased	1	.	.	.	1	1.28
	Blood pressure abnormal	.	2	.	.	2	2.56
	C-reactive protein increased	2	.	.	.	2	2.56
	Gamma-glutamyltransferase increased	.	.	1	.	1	1.28
Metabolism and nutrition disorders		2	.	.	.	2	2.56
	Decreased appetite	2	.	.	.	2	2.56
Musculoskeletal and connective tissue disorders		1	1	1	.	3	3.85
	Pain in extremity	1	1	1	.	3	3.85
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		.	.	.	1	1	1.28
	Colorectal cancer metastatic	.	.	.	1	1	1.28
Nervous system disorders		4	.	.	.	4	5.13
	Anticholinergic syndrome	1	.	.	.	1	1.28
	Dysgeusia	1	.	.	.	1	1.28
	Parosmia	1	.	.	.	1	1.28
	Peripheral sensory neuropathy	1	.	.	.	1	1.28
Psychiatric disorders		2	.	.	.	2	2.56
	Nightmare	1	.	.	.	1	1.28
	Stress	1	.	.	.	1	1.28
Renal and urinary disorders		1	.	.	.	1	1.28
	Renal failure	1	.	.	.	1	1.28
Reproductive system and breast disorders		1	.	.	.	1	1.28
	Pelvic pain	1	.	.	.	1	1.28
Respiratory, thoracic and mediastinal disorders		2	.	.	.	2	2.56
	Cough	1	.	.	.	1	1.28
	Hiccups	1	.	.	.	1	1.28
Skin and subcutaneous tissue disorders		8	.	.	.	8	10.26
	Alopecia	3	.	.	.	3	3.85
	Dermatitis acneiform	2	.	.	.	2	2.56
	Night sweats	1	.	.	.	1	1.28
	Pruritus	2	.	.	.	2	2.56
Surgical and medical procedures		1	.	.	.	1	1.28

SOC	PT	NCI CTCAE grade				Total	
		1	2	3	5	N	%
Vascular disorders	Therapy change	1	.	.	.	1	1.28
		.	1	.	.	1	1.28
	Embolism	.	1	.	.	1	1.28

(Data source: Table 4.2. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

SOC	PT	Maximum NCI CTCAE grade				Total	
		1	2	3	5	N	%
Number of patients with any AE		.	3	1	2	6	100.00
Blood and lymphatic system disorders		2	.	.	.	2	33.33
	Anaemia	2	.	.	.	2	33.33
Cardiac disorders		1	.	.	.	1	16.67
	Arrhythmia	1	.	.	.	1	16.67
Gastrointestinal disorders		3	1	1	1	6	100.00
	Constipation	2	1	.	.	3	50.00
	Diarrhoea	3	.	1	.	4	66.67
	Dyschezia	1	.	.	.	1	16.67
	Enteritis	1	.	.	.	1	16.67
	Flatulence	1	.	.	.	1	16.67
	Gastric ulcer	.	.	.	1	1	16.67
	Gastrooesophageal reflux disease	1	.	.	.	1	16.67
	Haemorrhoidal haemorrhage	1	.	.	.	1	16.67
	Ileus	1	.	.	.	1	16.67
	Nausea	3	2	.	.	5	83.33
	Vomiting	.	2	.	.	2	33.33
General disorders and administration site conditions		2	1	.	.	3	50.00
	Fatigue	3	.	.	.	3	50.00
	Pyrexia	1	1	.	.	2	33.33
Immune system disorders		1	.	.	.	1	16.67
	Hypersensitivity	1	.	.	.	1	16.67
Infections and infestations		.	3	.	.	3	50.00
	Anorectal infection	.	1	.	.	1	16.67
	Infection	.	1	.	.	1	16.67
	Nail infection	1	.	.	.	1	16.67
	Skin infection	1	.	.	.	1	16.67
	Urinary tract infection	.	1	.	.	1	16.67
Injury, poisoning and procedural complications		3	.	.	.	3	50.00

SOC	PT	Maximum NCI CTCAE grade				Total	
		1	2	3	5	N	%
Investigations	Hepatobiliary procedural complication	1	.	.	.	1	16.67
	Overdose	1	.	.	.	1	16.67
	Skin laceration	1	.	.	.	1	16.67
		3	1	1	.	5	83.33
	Alanine aminotransferase increased	1	1	.	.	2	33.33
	Aspartate aminotransferase increased	.	1	.	.	1	16.67
	Blood bilirubin increased	1	.	.	.	1	16.67
	Blood pressure abnormal	.	1	.	.	1	16.67
	C-reactive protein increased	2	.	.	.	2	33.33
	Gamma-glutamyltransferase increased	.	.	1	.	1	16.67
Metabolism and nutrition disorders		1	.	.	.	1	16.67
	Decreased appetite	1	.	.	.	1	16.67
Musculoskeletal and connective tissue disorders		.	.	1	.	1	16.67
	Pain in extremity	.	.	1	.	1	16.67
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		.	.	.	1	1	16.67
	Colorectal cancer metastatic	.	.	.	1	1	16.67
Nervous system disorders		2	.	.	.	2	33.33
	Anticholinergic syndrome	1	.	.	.	1	16.67
	Dysgeusia	1	.	.	.	1	16.67
	Parosmia	1	.	.	.	1	16.67
	Peripheral sensory neuropathy	1	.	.	.	1	16.67
Psychiatric disorders		2	.	.	.	2	33.33
	Nightmare	1	.	.	.	1	16.67
	Stress	1	.	.	.	1	16.67
Renal and urinary disorders		1	.	.	.	1	16.67
	Renal failure	1	.	.	.	1	16.67
Reproductive system and breast disorders		1	.	.	.	1	16.67
	Pelvic pain	1	.	.	.	1	16.67
Respiratory, thoracic and mediastinal disorders		2	.	.	.	2	33.33
	Cough	1	.	.	.	1	16.67
	Hiccups	1	.	.	.	1	16.67
Skin and subcutaneous tissue disorders		4	.	.	.	4	66.67
	Alopecia	3	.	.	.	3	50.00

SOC	PT	Maximum NCI CTCAE grade				Total	
		1	2	3	5	N	%
Surgical and medical procedures	Dermatitis acneiform	2	.	.	.	2	33.33
	Night sweats	1	.	.	.	1	16.67
	Pruritus	1	.	.	.	1	16.67
	Therapy change	1	.	.	.	1	16.67
	Embolism	.	1	.	.	1	16.67
Vascular disorders		.	1	.	.	1	16.67

(Data source: Table 4.3. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)



*Terminology according to CTCAE  
version 5*

<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-01-01	A	5	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	mutated metastatic colorectal cancer	Colorectal cancer metastatic	.	.	Fatal (AE resulted in death)	Yes	5-FU	Unlikely	Treatment continued without Change	Yes
MR-DE-01-01	A	5	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	mutated metastatic colorectal cancer	Colorectal cancer metastatic	.	.	Fatal (AE resulted in death)	Yes	Cetuximab	Unlikely	Not applicable	Yes
MR-DE-01-01	A	5	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	mutated metastatic colorectal cancer	Colorectal cancer metastatic	.	.	Fatal (AE resulted in death)	Yes	Folinic acid	Unlikely	Treatment continued without Change	Yes
MR-DE-01-01	A	5	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	mutated metastatic colorectal cancer	Colorectal cancer metastatic	.	.	Fatal (AE resulted in death)	Yes	Irinotecan	Unlikely	Treatment continued without Change	Yes
MR-DE-01-01	A	1	Injury, poisoning and procedural complications - Other, specify	overdose	Overdose	28JUN21	28JUN21	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-01-01	A	1	Injury, poisoning and procedural complications - Other, specify	overdose	Overdose	28JUN21	28JUN21	Recovered without sequelae	Yes	Cetuximab	Definitely	Not applicable	No

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-01-01	A	1	Injury, poisoning and procedural complications - Other, specify	overdose	Overdose	28JUN21	28JUN21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-01-01	A	1	Injury, poisoning and procedural complications - Other, specify	overdose	Overdose	28JUN21	28JUN21	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No
MR-DE-01-01	A	1	Nausea		Nausea	05JUL21	08JUL21	Recovered without sequelae	Yes	5-FU	Possibly	Treatment continued without Change	No
MR-DE-01-01	A	1	Nausea		Nausea	05JUL21	08JUL21	Recovered without sequelae	Yes	Cetuximab	Possibly	Treatment continued without Change	No
MR-DE-01-01	A	1	Nausea		Nausea	05JUL21	08JUL21	Recovered without sequelae	Yes	Folinic acid	Possibly	Treatment continued without Change	No
MR-DE-01-01	A	1	Nausea		Nausea	05JUL21	08JUL21	Recovered without sequelae	Yes	Irinotecan	Possibly	Treatment continued without Change	No
MR-DE-01-01	A	1	Injury, poisoning and procedural complications - Other, specify	medicatio n dose changed	Therapy change	12JUL21	20SEP2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-01-01	A	1	Injury, poisoning and procedural complications - Other, specify	medicatio n dose changed	Therapy change	12JUL21	20SEP2 1	Recovered without sequelae	Yes	Cetuximab	Definitely	Not applicable	No
MR-DE-01-01	A	1	Injury, poisoning and procedural complications - Other, specify	medicatio n dose changed	Therapy change	12JUL21	20SEP2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-01-01	A	1	Injury, poisoning and procedural complications - Other, specify	medicatio n dose changed	Therapy change	12JUL21	20SEP2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No
MR-DE-01-01	A	2	Nausea		Nausea	19JUL21	26JUL21	Recovered without sequelae	Yes	5-FU	Possibly	Treatment continued without Change	No
MR-DE-01-01	A	2	Nausea		Nausea	19JUL21	26JUL21	Recovered without sequelae	Yes	Cetuximab	Possibly	Treatment continued without Change	No
MR-DE-01-01	A	2	Nausea		Nausea	19JUL21	26JUL21	Recovered without sequelae	Yes	Folinic acid	Possibly	Treatment continued without Change	No
MR-DE-01-01	A	2	Nausea		Nausea	19JUL21	26JUL21	Recovered without sequelae	Yes	Irinotecan	Possibly	Treatment continued without Change	No

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-01-01	A	1	Diarrhea		Diarrhoea	02AUG2 1	06AUG2 1	Recovered without sequelae	Yes	5-FU	Unlikely	Treatment continued without Change	No
MR-DE-01-01	A	1	Diarrhea		Diarrhoea	02AUG2 1	06AUG2 1	Recovered without sequelae	Yes	Cetuximab	Unlikely	Treatment continued without Change	No
MR-DE-01-01	A	1	Diarrhea		Diarrhoea	02AUG2 1	06AUG2 1	Recovered without sequelae	Yes	Folinic acid	Unlikely	Treatment continued without Change	No
MR-DE-01-01	A	1	Diarrhea		Diarrhoea	02AUG2 1	06AUG2 1	Recovered without sequelae	Yes	Irinotecan	Unlikely	Treatment continued without Change	No
MR-DE-02-01	B	1	Nausea		Nausea	28APR2 1	15OCT2 1	Recovered without sequelae	Yes	5-FU	Probably	Treatment continued without Change	Yes
MR-DE-02-01	B	1	Nausea		Nausea	28APR2 1	15OCT2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-01	B	1	Nausea		Nausea	28APR2 1	15OCT2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-01	B	1	Nausea		Nausea	28APR2 1	15OCT2 1	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	Yes
MR-DE-02-01	B	3	Pain in extremity		Pain in extremity	28APR2 1	14AUG2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-02-01	B	3	Pain in extremity		Pain in extremity	28APR2 1	14AUG2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-01	B	3	Pain in extremity		Pain in extremity	28APR2 1	14AUG2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-01	B	3	Pain in extremity		Pain in extremity	28APR2 1	14AUG2 1	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	Yes
MR-DE-02-01	B	2	Vomiting		Vomiting	28APR2 1	01JUN21	Recovered without sequelae	Yes	5-FU	Probably	Treatment continued without Change	Yes
MR-DE-02-01	B	2	Vomiting		Vomiting	28APR2 1	01JUN21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-01	B	2	Vomiting		Vomiting	28APR2 1	01JUN21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-01	B	2	Vomiting		Vomiting	28APR2 1	01JUN21	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	Yes
MR-DE-02-01	B	2	Diarrhea		Diarrhoea	01MAY2 1	15OCT2 1	Recovered without sequelae	Yes	5-FU	Probably	Treatment continued without Change	Yes
MR-DE-02-01	B	2	Diarrhea		Diarrhoea	01MAY2 1	15OCT2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-01	B	2	Diarrhea		Diarrhoea	01MAY2 1	15OCT2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-01	B	2	Diarrhea		Diarrhoea	01MAY2 1	15OCT2 1	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	Yes
MR-DE-02-01	B	1	Vomiting		Vomiting	02JUN21	01AUG2 1	Recovered without sequelae	Yes	5-FU	Probably	Treatment continued without Change	Yes
MR-DE-02-01	B	1	Vomiting		Vomiting	02JUN21	01AUG2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-01	B	1	Vomiting		Vomiting	02JUN21	01AUG2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-01	B	1	Vomiting		Vomiting	02JUN21	01AUG21	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	Yes
MR-DE-02-01	B	1	Alanine aminotransferase increased		Alanine aminotransferase increased	09JUN21	14JUN21	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	1	Alanine aminotransferase increased		Alanine aminotransferase increased	09JUN21	14JUN21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-01	B	1	Alanine aminotransferase increased		Alanine aminotransferase increased	09JUN21	14JUN21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	1	Alanine aminotransferase increased		Alanine aminotransferase increased	09JUN21	14JUN21	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	No
MR-DE-02-01	B	1	Anemia		Anaemia	09JUN21	13DEC21	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	1	Anemia		Anaemia	09JUN21	13DEC21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-01	B	1	Anemia		Anaemia	09JUN21	13DEC21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-01	B	1	Anemia		Anaemia	09JUN21	13DEC21	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	No
MR-DE-02-01	B	2	Alanine aminotransferase increased		Alanine aminotransferase increased	15JUN21	13JUL21	Recovered without sequelae	Yes	5-FU	Unlikely	Treatment continued without Change	No
MR-DE-02-01	B	2	Alanine aminotransferase increased		Alanine aminotransferase increased	15JUN21	13JUL21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-01	B	2	Alanine aminotransferase increased		Alanine aminotransferase increased	15JUN21	13JUL21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	2	Alanine aminotransferase increased		Alanine aminotransferase increased	15JUN21	13JUL21	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	2	Aspartate aminotransferase increased		Aspartate aminotransferase increased	15JUN21	13JUL21	Recovered without sequelae	Yes	5-FU	Unlikely	Treatment continued without Change	No
MR-DE-02-01	B	2	Aspartate aminotransferase increased		Aspartate aminotransferase increased	15JUN21	13JUL21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-01	B	2	Aspartate aminotransferase increased		Aspartate aminotransferase increased	15JUN21	13JUL21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No



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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-01	B	2	Aspartate aminotransferase increased		Aspartate aminotransfere se increased	15JUN21	13JUL21	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	3	GGT increased		Gamma- glutamyltransf erase increased	15JUN21	15OCT2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	3	GGT increased		Gamma- glutamyltransf erase increased	15JUN21	15OCT2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-01	B	3	GGT increased		Gamma- glutamyltransf erase increased	15JUN21	15OCT2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	3	GGT increased		Gamma- glutamyltransf erase increased	15JUN21	15OCT2 1	Recovered without sequelae	Yes	Irinotecan	Definitely	Treatment continued without Change	No
MR-DE-02-01	B	3	Diarrhea		Diarrhoea	29JUN21	15JUL21	Recovered without sequelae	Yes	5-FU	Probably	Treatment continued without Change	Yes
MR-DE-02-01	B	3	Diarrhea		Diarrhoea	29JUN21	15JUL21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes

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Patient No.	Arm	Grade	Term	Other	PT according to MedDRA	Start date	End date	Outcome	Study treatment started	Study treatment component	Causal relationship suspected	Action taken	Event treated with medication
MR-DE-02-01	B	3	Diarrhea		Diarrhoea	29JUN21	15JUL21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-01	B	3	Diarrhea		Diarrhoea	29JUN21	15JUL21	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	Yes
MR-DE-02-01	B	2	Nausea		Nausea	29JUN21	15JUL21	Recovered without sequelae	Yes	5-FU	Probably	Treatment continued without Change	Yes
MR-DE-02-01	B	2	Nausea		Nausea	29JUN21	15JUL21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-01	B	2	Nausea		Nausea	29JUN21	15JUL21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-01	B	2	Nausea		Nausea	29JUN21	15JUL21	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	Yes
MR-DE-02-01	B	1	Anorexia		Decreased appetite	30JUN21	15OCT21	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	1	Anorexia		Decreased appetite	30JUN21	15OCT21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-01	B	1	Anorexia		Decreased appetite	30JUN21	15OCT2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	1	Anorexia		Decreased appetite	30JUN21	15OCT2 1	Recovered without sequelae	Yes	Irinotecan	Possibly	Treatment continued without Change	No
MR-DE-02-01	B	1	General disorders and administration site conditions - Other, specify	Inappeten ce	Decreased appetite	30JUN21	15OCT2 1	Recovered without sequelae	Yes	5-FU	Probably	Treatment continued without Change	No
MR-DE-02-01	B	1	General disorders and administration site conditions - Other, specify	Inappeten ce	Decreased appetite	30JUN21	15OCT2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-01	B	1	General disorders and administration site conditions - Other, specify	Inappeten ce	Decreased appetite	30JUN21	15OCT2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	1	General disorders and administration site conditions - Other, specify	Inappeten ce	Decreased appetite	30JUN21	15OCT2 1	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	No
MR-DE-02-01	B	1	Fatigue		Fatigue	01JUL21	15OCT2 1	Recovered without sequelae	Yes	5-FU	Probably	Treatment continued without Change	No

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-01	B	1	Fatigue		Fatigue	01JUL21	15OCT2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-01	B	1	Fatigue		Fatigue	01JUL21	15OCT2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	1	Fatigue		Fatigue	01JUL21	15OCT2 1	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	No
MR-DE-02-01	B	1	Peripheral sensory neuropathy		Peripheral sensory neuropathy	13JUL21	29OCT2 1	Recovered without sequelae	Yes	5-FU	Probably	Treatment continued without Change	No
MR-DE-02-01	B	1	Peripheral sensory neuropathy		Peripheral sensory neuropathy	13JUL21	29OCT2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-01	B	1	Peripheral sensory neuropathy		Peripheral sensory neuropathy	13JUL21	29OCT2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	1	Peripheral sensory neuropathy		Peripheral sensory neuropathy	13JUL21	29OCT2 1	Recovered without sequelae	Yes	Irinotecan	Definitely	Treatment continued without Change	No
MR-DE-02-01	B	1	Hiccups		Hiccups	17JUL21	28OCT2 1	Recovered without sequelae	Yes	5-FU	Possibly	Treatment continued without Change	No

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-01	B	1	Hiccups		Hiccups	17JUL21	28OCT21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-01	B	1	Hiccups		Hiccups	17JUL21	28OCT21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	1	Hiccups		Hiccups	17JUL21	28OCT21	Recovered without sequelae	Yes	Irinotecan	Possibly	Treatment continued without Change	No
MR-DE-02-01	B	2	Pain in extremity		Pain in extremity	15AUG21	10OCT21	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-02-01	B	2	Pain in extremity		Pain in extremity	15AUG21	10OCT21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-01	B	2	Pain in extremity		Pain in extremity	15AUG21	10OCT21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-01	B	2	Pain in extremity		Pain in extremity	15AUG21	10OCT21	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	Yes
MR-DE-02-01	B	1	Alopecia		Alopecia	27SEP21	11OCT21	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-01	B	1	Alopecia		Alopecia	27SEP2 1	11OCT2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-01	B	1	Alopecia		Alopecia	27SEP2 1	11OCT2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-01	B	1	Alopecia		Alopecia	27SEP2 1	11OCT2 1	Recovered without sequelae	Yes	Irinotecan	Possibly	Treatment continued without Change	No
MR-DE-02-01	B	1	Pain in extremity		Pain in extremity	11OCT2 1	15OCT2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-02-01	B	1	Pain in extremity		Pain in extremity	11OCT2 1	15OCT2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-01	B	1	Pain in extremity		Pain in extremity	11OCT2 1	15OCT2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-01	B	1	Pain in extremity		Pain in extremity	11OCT2 1	15OCT2 1	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	Yes
MR-DE-02-02	A	1	Nausea		Nausea	19MAY2 1	21MAY2 1	Recovered without sequelae	Yes	5-FU	Possibly	Treatment continued without Change	No

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-02	A	1	Nausea		Nausea	19MAY2 1	21MAY2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-02	A	1	Nausea		Nausea	19MAY2 1	21MAY2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Nausea		Nausea	19MAY2 1	21MAY2 1	Recovered without sequelae	Yes	Irinotecan	Possibly	Treatment continued without Change	No
MR-DE-02-02	A	1	Nervous system disorders - Other, specify	Nightmare	Nightmare	19MAY2 1	21MAY2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Nervous system disorders - Other, specify	Nightmare	Nightmare	19MAY2 1	21MAY2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-02	A	1	Nervous system disorders - Other, specify	Nightmare	Nightmare	19MAY2 1	21MAY2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Nervous system disorders - Other, specify	Nightmare	Nightmare	19MAY2 1	21MAY2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Alopecia		Alopecia	02JUN21	12OCT2 1	Recovered without sequelae	Yes	5-FU	Unlikely	Treatment continued without Change	No

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-02	A	1	Alopecia		Alopecia	02JUN21	12OCT21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-02	A	1	Alopecia		Alopecia	02JUN21	12OCT21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Alopecia		Alopecia	02JUN21	12OCT21	Recovered without sequelae	Yes	Irinotecan	Possibly	Treatment continued without Change	No
MR-DE-02-02	A	1	Diarrhea		Diarrhoea	15JUN21	16JUN21	Recovered without sequelae	Yes	5-FU	Possibly	Treatment continued without Change	No
MR-DE-02-02	A	1	Diarrhea		Diarrhoea	15JUN21	16JUN21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-02	A	1	Diarrhea		Diarrhoea	15JUN21	16JUN21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Diarrhea		Diarrhoea	15JUN21	16JUN21	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	No
MR-DE-02-02	A	1	Allergic reaction		Hypersensitivity	29JUN21	29JUN21	Recovered without sequelae	Yes	5-FU	Unlikely	Treatment continued without Change	No



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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-02	A	1	Allergic reaction		Hypersensitivit y	29JUN21	29JUN21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-02	A	1	Allergic reaction		Hypersensitivit y	29JUN21	29JUN21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Allergic reaction		Hypersensitivit y	29JUN21	29JUN21	Recovered without sequelae	Yes	Irinotecan	Definitely	Treatment continued without Change	No
MR-DE-02-02	A	2	Cardiac disorders - Other, specify	derailed blood pressure	Blood pressure abnormal	29JUN21	29JUN21	Recovered without sequelae	Yes	5-FU	Probably	Treatment continued without Change	Yes
MR-DE-02-02	A	2	Cardiac disorders - Other, specify	derailed blood pressure	Blood pressure abnormal	29JUN21	29JUN21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-02	A	2	Cardiac disorders - Other, specify	derailed blood pressure	Blood pressure abnormal	29JUN21	29JUN21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-02	A	2	Cardiac disorders - Other, specify	derailed blood pressure	Blood pressure abnormal	29JUN21	29JUN21	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	Yes
MR-DE-02-02	A	1	Gastroesophageal reflux disease		Gastrooesoph ageal reflux disease	29JUN21	22NOV2 1	Recovered without sequelae	Yes	5-FU	Possibly	Treatment continued without Change	Yes

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-02	A	1	Gastroesophageal reflux disease		Gastrooesoph ageal reflux disease	29JUN21	22NOV2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-02	A	1	Gastroesophageal reflux disease		Gastrooesoph ageal reflux disease	29JUN21	22NOV2 1	Recovered without sequelae	Yes	Folinic acid	Possibly	Treatment continued without Change	Yes
MR-DE-02-02	A	1	Gastroesophageal reflux disease		Gastrooesoph ageal reflux disease	29JUN21	22NOV2 1	Recovered without sequelae	Yes	Irinotecan	Possibly	Treatment continued without Change	Yes
MR-DE-02-02	A	2	Cardiac disorders - Other, specify	derailed blood pressure	Blood pressure abnormal	20JUL21	20JUL21	Recovered without sequelae	Yes	5-FU	Possibly	Treatment continued without Change	Yes
MR-DE-02-02	A	2	Cardiac disorders - Other, specify	derailed blood pressure	Blood pressure abnormal	20JUL21	20JUL21	Recovered without sequelae	Yes	Cetuximab	No correlation	Treatment continued without Change	Yes
MR-DE-02-02	A	2	Cardiac disorders - Other, specify	derailed blood pressure	Blood pressure abnormal	20JUL21	20JUL21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-02	A	2	Cardiac disorders - Other, specify	derailed blood pressure	Blood pressure abnormal	20JUL21	20JUL21	Recovered without sequelae	Yes	Irinotecan	Possibly	Treatment continued without Change	Yes

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-02	A	1	Renal and urinary disorders - Other, specify	renal failure	Renal failure	20JUL21	27JUL21	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Renal and urinary disorders - Other, specify	renal failure	Renal failure	20JUL21	27JUL21	Recovered without sequelae	Yes	Cetuximab	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Renal and urinary disorders - Other, specify	renal failure	Renal failure	20JUL21	27JUL21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Renal and urinary disorders - Other, specify	renal failure	Renal failure	20JUL21	27JUL21	Recovered without sequelae	Yes	Irinotecan	Definitely	Treatment continued without Change	No
MR-DE-02-02	A	1	Gastrointestinal disorders - Other, specify	burn when defecating	Dyschezia	10AUG21	16NOV21	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Gastrointestinal disorders - Other, specify	burn when defecating	Dyschezia	10AUG21	16NOV21	Recovered without sequelae	Yes	Cetuximab	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Gastrointestinal disorders - Other, specify	burn when defecating	Dyschezia	10AUG21	16NOV21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-02	A	1	Gastrointestinal disorders - Other, specify	burn when defecating	Dyschezia	10AUG2 1	16NOV2 1	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	No
MR-DE-02-02	A	1	Rash acneiform		Dermatitis acneiform	10AUG2 1	22NOV2 1	Recovered without sequelae	Yes	5-FU	Unlikely	Treatment continued without Change	Yes
MR-DE-02-02	A	1	Rash acneiform		Dermatitis acneiform	10AUG2 1	22NOV2 1	Recovered without sequelae	Yes	Cetuximab	Definitely	Treatment continued without Change	Yes
MR-DE-02-02	A	1	Rash acneiform		Dermatitis acneiform	10AUG2 1	22NOV2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-02	A	1	Rash acneiform		Dermatitis acneiform	10AUG2 1	22NOV2 1	Recovered without sequelae	Yes	Irinotecan	Unlikely	Treatment continued without Change	Yes
MR-DE-02-02	A	1	Constipation		Constipation	15AUG2 1	10SEP2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-02-02	A	1	Constipation		Constipation	15AUG2 1	10SEP2 1	Recovered without sequelae	Yes	Cetuximab	No correlation	Treatment continued without Change	Yes

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-02	A	1	Constipation		Constipation	15AUG2 1	10SEP2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-02	A	1	Constipation		Constipation	15AUG2 1	10SEP2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	Yes
MR-DE-02-02	A	2	Thromboembolic event		Embolism	06SEP2 1	.	Ongoing	Yes	5-FU	Probably	Treatment continued without Change	Yes
MR-DE-02-02	A	2	Thromboembolic event		Embolism	06SEP2 1	.	Ongoing	Yes	Cetuximab	Probably	Treatment continued without Change	Yes
MR-DE-02-02	A	2	Thromboembolic event		Embolism	06SEP2 1	.	Ongoing	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-02	A	2	Thromboembolic event		Embolism	06SEP2 1	.	Ongoing	Yes	Irinotecan	Probably	Treatment continued without Change	Yes
MR-DE-02-02	A	1	Diarrhea		Diarrhoea	07OCT2 1	08OCT2 1	Recovered without sequelae	Yes	5-FU	Unlikely	Treatment continued without Change	Yes

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-02	A	1	Diarrhea		Diarrhoea	07OCT2 1	08OCT2 1	Recovered without sequelae	Yes	Cetuximab	Unlikely	Treatment continued without Change	Yes
MR-DE-02-02	A	1	Diarrhea		Diarrhoea	07OCT2 1	08OCT2 1	Recovered without sequelae	Yes	Folinic acid	Unlikely	Treatment continued without Change	Yes
MR-DE-02-02	A	1	Diarrhea		Diarrhoea	07OCT2 1	08OCT2 1	Recovered without sequelae	Yes	Irinotecan	Unlikely	Treatment continued without Change	Yes
MR-DE-02-02	A	1	Hemorrhoidal hemorrhage		Haemorrhoidal haemorrhage	29OCT2 1	31OCT2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Hemorrhoidal hemorrhage		Haemorrhoidal haemorrhage	29OCT2 1	31OCT2 1	Recovered without sequelae	Yes	Cetuximab	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Hemorrhoidal hemorrhage		Haemorrhoidal haemorrhage	29OCT2 1	31OCT2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Hemorrhoidal hemorrhage		Haemorrhoidal haemorrhage	29OCT2 1	31OCT2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-02	A	1	Alanine aminotransferase increased		Alanine aminotransfera se increased	16NOV2 1	04JAN23	Recovered without sequelae	Yes	5-FU	Possibly	Not applicable	No
MR-DE-02-02	A	1	Alanine aminotransferase increased		Alanine aminotransfera se increased	16NOV2 1	04JAN23	Recovered without sequelae	Yes	Cetuximab	No correlation	Treatment continued without Change	No
MR-DE-02-02	A	1	Alanine aminotransferase increased		Alanine aminotransfera se increased	16NOV2 1	04JAN23	Recovered without sequelae	Yes	Folinic acid	No correlation	Not applicable	No
MR-DE-02-02	A	1	Alanine aminotransferase increased		Alanine aminotransfera se increased	16NOV2 1	04JAN23	Recovered without sequelae	Yes	Irinotecan	Definitely	Not applicable	No
MR-DE-02-03	B	1	General disorders and administration site conditions - Other, specify	anticholine rgic syndrom due to irinotecan	Anticholinergic syndrome	19MAY2 1	19MAY2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-02-03	B	1	General disorders and administration site conditions - Other, specify	anticholine rgic syndrom due to irinotecan	Anticholinergic syndrome	19MAY2 1	19MAY2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-03	B	1	General disorders and administration site conditions - Other, specify	anticholine rgic syndrom due to irinotecan	Anticholinergic syndrome	19MAY2 1	19MAY2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-03	B	1	General disorders and administration site conditions - Other, specify	anticholine rgic syndrom due to irinotecan	Anticholinergic syndrome	19MAY2 1	19MAY2 1	Recovered without sequelae	Yes	Irinotecan	Definitely	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Nausea		Nausea	20MAY2 1	29SEP2 1	Recovered without sequelae	Yes	5-FU	Probably	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Nausea		Nausea	20MAY2 1	29SEP2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-03	B	1	Nausea		Nausea	20MAY2 1	29SEP2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Nausea		Nausea	20MAY2 1	29SEP2 1	Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Fatigue		Fatigue	21MAY2 1	20OCT2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Fatigue		Fatigue	21MAY2 1	20OCT2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No



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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-03	B	1	Fatigue		Fatigue	21MAY2 1	20OCT2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Fatigue		Fatigue	21MAY2 1	20OCT2 1	Recovered without sequelae	Yes	Irinotecan	Possibly	Treatment continued without Change	No
MR-DE-02-03	B	1	Diarrhea		Diarrhoea	01JUN21	08NOV2 1	Recovered without sequelae	Yes	5-FU	Definitely	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Diarrhea		Diarrhoea	01JUN21	08NOV2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-03	B	1	Diarrhea		Diarrhoea	01JUN21	08NOV2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Diarrhea		Diarrhoea	01JUN21	08NOV2 1	Recovered without sequelae	Yes	Irinotecan	Definitely	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Anemia		Anaemia	02JUN21	31JAN22	Recovered without sequelae	Yes	5-FU	Definitely	Treatment continued without Change	No
MR-DE-02-03	B	1	Anemia		Anaemia	02JUN21	31JAN22	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No

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MR-DE-02-03	B	1	Anemia		Anaemia	02JUN21	31JAN22	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Anemia		Anaemia	02JUN21	31JAN22	Recovered without sequelae	Yes	Irinotecan	Definitely	Treatment continued without Change	No
MR-DE-02-03	B	1	Hepatobiliary disorders - Other, specify	Bilirubin increased	Blood bilirubin increased	02JUN21	08NOV2 1	Recovered with sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Hepatobiliary disorders - Other, specify	Bilirubin increased	Blood bilirubin increased	02JUN21	08NOV2 1	Recovered with sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-03	B	1	Hepatobiliary disorders - Other, specify	Bilirubin increased	Blood bilirubin increased	02JUN21	08NOV2 1	Recovered with sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Hepatobiliary disorders - Other, specify	Bilirubin increased	Blood bilirubin increased	02JUN21	08NOV2 1	Recovered with sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Alopecia		Alopecia	09JUN21	08NOV2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Alopecia		Alopecia	09JUN21	08NOV2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-03	B	1	Alopecia		Alopecia	09JUN21	08NOV21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Alopecia		Alopecia	09JUN21	08NOV21	Recovered without sequelae	Yes	Irinotecan	Definitely	Treatment continued without Change	No
MR-DE-02-03	B	1	Pruritus		Pruritus	16JUN21	30JUN21	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Pruritus		Pruritus	16JUN21	30JUN21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-03	B	1	Pruritus		Pruritus	16JUN21	30JUN21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Pruritus		Pruritus	16JUN21	30JUN21	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Cough		Cough	30JUL21	08NOV21	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Cough		Cough	30JUL21	08NOV21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No

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Patient No.	Arm	Grade	Term	Other	PT according to MedDRA	Start date	End date	Outcome	Study treatment started	Study treatment component	Causal relationship suspected	Action taken	Event treated with medication
MR-DE-02-03	B	1	Cough		Cough	30JUL21	08NOV21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Cough		Cough	30JUL21	08NOV21	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Fever		Pyrexia	30JUL21	08NOV21	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Fever		Pyrexia	30JUL21	08NOV21	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-03	B	1	Fever		Pyrexia	30JUL21	08NOV21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Fever		Pyrexia	30JUL21	08NOV21	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Pruritus		Pruritus	04AUG21	15MAY22	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Pruritus		Pruritus	04AUG21	15MAY22	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-03	B	1	Pruritus		Pruritus	04AUG2 1	15MAY2 2	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Pruritus		Pruritus	04AUG2 1	15MAY2 2	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Constipation		Constipation	15SEP2 1	02NOV2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Constipation		Constipation	15SEP2 1	02NOV2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-03	B	1	Constipation		Constipation	15SEP2 1	02NOV2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Constipation		Constipation	15SEP2 1	02NOV2 1	Recovered without sequelae	Yes	Irinotecan	Possibly	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Dysgeusia		Dysgeusia	15SEP2 1	02NOV2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Dysgeusia		Dysgeusia	15SEP2 1	02NOV2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No

*Terminology according to CTCAE  
version 5*

<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-03	B	1	Dysgeusia		Dysgeusia	15SEP2 1	02NOV2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Dysgeusia		Dysgeusia	15SEP2 1	02NOV2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Flatulence		Flatulence	15SEP2 1	29SEP2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Flatulence		Flatulence	15SEP2 1	29SEP2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-03	B	1	Flatulence		Flatulence	15SEP2 1	29SEP2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Flatulence		Flatulence	15SEP2 1	29SEP2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	Yes
MR-DE-02-03	B	1	General disorders and administration site conditions - Other, specify	dysosmia	Parosmia	15SEP2 1	02NOV2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No

*Terminology according to CTCAE  
version 5*

<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-03	B	1	General disorders and administration site conditions - Other, specify	dysosmia	Parosmia	15SEP2 1	02NOV2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-03	B	1	General disorders and administration site conditions - Other, specify	dysosmia	Parosmia	15SEP2 1	02NOV2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	General disorders and administration site conditions - Other, specify	dysosmia	Parosmia	15SEP2 1	02NOV2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	General disorders and administration site conditions - Other, specify	Night sweat	Night sweats	01OCT2 1	02NOV2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	General disorders and administration site conditions - Other, specify	Night sweat	Night sweats	01OCT2 1	02NOV2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-03	B	1	General disorders and administration site conditions - Other, specify	Night sweat	Night sweats	01OCT2 1	02NOV2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	General disorders and administration site conditions - Other, specify	Night sweat	Night sweats	01OCT2 1	02NOV2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No

*Terminology according to CTCAE  
version 5*

<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-03	B	1	Cardiac disorders - Other, specify	Cardiac stutter under stress	Stress	10OCT2 1	02NOV2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Cardiac disorders - Other, specify	Cardiac stutter under stress	Arrhythmia	10OCT2 1	02NOV2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Cardiac disorders - Other, specify	Cardiac stutter under stress	Stress	10OCT2 1	02NOV2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-03	B	1	Cardiac disorders - Other, specify	Cardiac stutter under stress	Arrhythmia	10OCT2 1	02NOV2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-03	B	1	Cardiac disorders - Other, specify	Cardiac stutter under stress	Stress	10OCT2 1	02NOV2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Cardiac disorders - Other, specify	Cardiac stutter under stress	Arrhythmia	10OCT2 1	02NOV2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Cardiac disorders - Other, specify	Cardiac stutter under stress	Stress	10OCT2 1	02NOV2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No



*Terminology according to CTCAE  
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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-03	B	1	Cardiac disorders - Other, specify	Cardiac stutter under stress	Arrhythmia	10OCT2 1	02NOV2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No
MR-DE-02-03	B	1	Pelvic pain		Pelvic pain	10OCT2 1	03DEC2 1	Recovered with sequelae	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Pelvic pain		Pelvic pain	10OCT2 1	03DEC2 1	Recovered with sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-02-03	B	1	Pelvic pain		Pelvic pain	10OCT2 1	03DEC2 1	Recovered with sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-02-03	B	1	Pelvic pain		Pelvic pain	10OCT2 1	03DEC2 1	Recovered with sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	Yes
MR-DE-02-03	B	2	Anorectal infection		Anorectal infection	26OCT2 1	29OCT2 1	Recovered without sequelae	Yes	5-FU	No correlation	Not applicable	No
MR-DE-02-03	B	2	Anorectal infection		Anorectal infection	26OCT2 1	29OCT2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	No
MR-DE-02-03	B	2	Anorectal infection		Anorectal infection	26OCT2 1	29OCT2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Not applicable	No

*Terminology according to CTCAE  
version 5*

<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-02-03	B	2	Anorectal infection		Anorectal infection	26OCT2 1	29OCT2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Not applicable	No
MR-DE-14-01	A	1	Nausea		Nausea	29DEC2 0	.	Ongoing	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-14-01	A	1	Nausea		Nausea	29DEC2 0	.	Ongoing	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-14-01	A	1	Nausea		Nausea	29DEC2 0	.	Ongoing	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-14-01	A	1	Nausea		Nausea	29DEC2 0	.	Ongoing	Yes	Irinotecan	Probably	Treatment continued without Change	Yes
MR-DE-14-01	A	1	Fatigue		Fatigue	23MAR2 1	.	Recovered without sequelae	Yes	5-FU	Probably	Treatment continued without Change	No
MR-DE-14-01	A	1	Fatigue		Fatigue	23MAR2 1	.	Recovered without sequelae	Yes	Cetuximab	No correlation	Treatment continued without Change	No
MR-DE-14-01	A	1	Fatigue		Fatigue	23MAR2 1	.	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No

*Terminology according to CTCAE  
version 5*

<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-14-01	A	1	Fatigue		Fatigue	23MAR2 1		Recovered without sequelae	Yes	Irinotecan	Probably	Treatment continued without Change	No
MR-DE-14-01	A	1	Nail infection		Nail infection	07APR2 1	01JUN21	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-14-01	A	1	Nail infection		Nail infection	07APR2 1	01JUN21	Recovered without sequelae	Yes	Cetuximab	Definitely	Permanently discontinued	No
MR-DE-14-01	A	1	Nail infection		Nail infection	07APR2 1	01JUN21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No
MR-DE-14-01	A	1	Nail infection		Nail infection	07APR2 1	01JUN21	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No
MR-DE-14-01	A	1	Rash acneiform		Dermatitis acneiform	07APR2 1	01JUN21	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	No
MR-DE-14-01	A	1	Rash acneiform		Dermatitis acneiform	07APR2 1	01JUN21	Recovered without sequelae	Yes	Cetuximab	Definitely	Permanently discontinued	No
MR-DE-14-01	A	1	Rash acneiform		Dermatitis acneiform	07APR2 1	01JUN21	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	No

*Terminology according to CTCAE  
version 5*

<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-14-01	A	1	Rash acneiform		Dermatitis acneiform	07APR2 1	01JUN21	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	No
MR-DE-14-01	A	1	Intraoperative hepatobiliary injury		Hepatobiliary procedural complication	16AUG2 1	21SEP2 1	Recovered without sequelae	Yes	5-FU	No correlation	Not applicable	No
MR-DE-14-01	A	1	Intraoperative hepatobiliary injury		Hepatobiliary procedural complication	16AUG2 1	21SEP2 1	Recovered without sequelae	Yes	Cetuximab	No correlation	Not applicable	No
MR-DE-14-01	A	1	Intraoperative hepatobiliary injury		Hepatobiliary procedural complication	16AUG2 1	21SEP2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Not applicable	No
MR-DE-14-01	A	1	Intraoperative hepatobiliary injury		Hepatobiliary procedural complication	16AUG2 1	21SEP2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Not applicable	No
MR-DE-14-01	A	2	Infections and infestations - Other, specify	fever episod	Pyrexia	16SEP2 1	21SEP2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-14-01	A	2	Infections and infestations - Other, specify	fever episod	Pyrexia	16SEP2 1	21SEP2 1	Recovered without sequelae	Yes	Cetuximab	No correlation	Not applicable	Yes
MR-DE-14-01	A	2	Infections and infestations - Other, specify	fever episod	Pyrexia	16SEP2 1	21SEP2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes

*Terminology according to CTCAE  
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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-14-01	A	2	Infections and infestations - Other, specify	fever episod	Pyrexia	16SEP2 1	21SEP2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	Yes
MR-DE-14-01	A	2	Gastrointestinal disorders - Other, specify	Infection	Infection	11NOV2 1	29NOV2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-14-01	A	2	Gastrointestinal disorders - Other, specify	Infection	Infection	11NOV2 1	29NOV2 1	Recovered without sequelae	Yes	Cetuximab	No correlation	Not applicable	Yes
MR-DE-14-01	A	2	Gastrointestinal disorders - Other, specify	Infection	Infection	11NOV2 1	29NOV2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-14-01	A	2	Gastrointestinal disorders - Other, specify	Infection	Infection	11NOV2 1	29NOV2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	Yes
MR-DE-14-01	A	1	Infections and infestations - Other, specify	CRP increase without symptoms	C-reactive protein increased	06DEC2 1	08DEC2 1	Recovered without sequelae	Yes	5-FU	Possibly	Treatment continued without Change	Yes
MR-DE-14-01	A	1	Infections and infestations - Other, specify	CRP increase without symptoms	C-reactive protein increased	06DEC2 1	08DEC2 1	Recovered without sequelae	Yes	Cetuximab	No correlation	Treatment continued without Change	Yes

*Terminology according to CTCAE  
version 5*

<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-14-01	A	1	Infections and infestations - Other, specify	CRP increase without symptoms	C-reactive protein increased	06DEC2 1	08DEC2 1	Recovered without sequelae	Yes	Folinic acid	Possibly	Treatment continued without Change	Yes
MR-DE-14-01	A	1	Infections and infestations - Other, specify	CRP increase without symptoms	C-reactive protein increased	06DEC2 1	08DEC2 1	Recovered without sequelae	Yes	Irinotecan	Possibly	Treatment continued without Change	Yes
MR-DE-24-01	A	2	Constipation		Constipation	.	13JUL21	Recovered with sequelae	No	5-FU	Missing	Missing	Yes
MR-DE-24-01	A	2	Constipation		Constipation	.	13JUL21	Recovered with sequelae	No	Cetuximab	Missing	Missing	Yes
MR-DE-24-01	A	2	Constipation		Constipation	.	13JUL21	Recovered with sequelae	No	Folinic acid	Missing	Missing	Yes
MR-DE-24-01	A	2	Constipation		Constipation	.	13JUL21	Recovered with sequelae	No	Irinotecan	Missing	Missing	Yes
MR-DE-24-01	A	1	Skin infection		Skin infection	.	.	Ongoing	No	5-FU	Missing	Missing	Yes
MR-DE-24-01	A	1	Skin infection		Skin infection	.	.	Ongoing	No	Cetuximab	Missing	Missing	Yes
MR-DE-24-01	A	1	Skin infection		Skin infection	.	.	Ongoing	No	Folinic acid	Missing	Missing	Yes
MR-DE-24-01	A	1	Skin infection		Skin infection	.	.	Ongoing	No	Irinotecan	Missing	Missing	Yes
MR-DE-24-01	A	2	Vomiting		Vomiting	25AUG2 1	20SEP2 1	Recovered with sequelae	Yes	5-FU	Unlikely	Treatment continued without Change	Yes

*Terminology according to CTCAE  
version 5*

<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-24-01	A	2	Vomiting		Vomiting	25AUG2 1	20SEP2 1	Recovered with sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-24-01	A	2	Vomiting		Vomiting	25AUG2 1	20SEP2 1	Recovered with sequelae	Yes	Folinic acid	Unlikely	Treatment continued without Change	Yes
MR-DE-24-01	A	2	Vomiting		Vomiting	25AUG2 1	20SEP2 1	Recovered with sequelae	Yes	Irinotecan	Unlikely	Treatment continued without Change	Yes
MR-DE-24-01	A	1	Ileus		Ileus	06OCT2 1	13OCT2 1	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-24-01	A	1	Ileus		Ileus	06OCT2 1	13OCT2 1	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-24-01	A	1	Ileus		Ileus	06OCT2 1	13OCT2 1	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-24-01	A	1	Ileus		Ileus	06OCT2 1	13OCT2 1	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	Yes
MR-DE-24-01	A	1	Skin and subcutaneous tissue disorders - Other, specify	Skin on the fingertips is torn	Skin laceration	07DEC2 1	.	Ongoing	Yes	5-FU	Probably	Dose reduced	Yes

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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-24-01	A	1	Skin and subcutaneous tissue disorders - Other, specify	Skin on the fingertips is torn	Skin laceration	07DEC2 1	.	Ongoing	Yes	Cetuximab	No correlation	Treatment continued without Change	Yes
MR-DE-24-01	A	1	Skin and subcutaneous tissue disorders - Other, specify	Skin on the fingertips is torn	Skin laceration	07DEC2 1	.	Ongoing	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-24-01	A	1	Skin and subcutaneous tissue disorders - Other, specify	Skin on the fingertips is torn	Skin laceration	07DEC2 1	.	Ongoing	Yes	Irinotecan	No correlation	Treatment continued without Change	Yes
MR-DE-24-01	A	1	Small intestinal mucositis		Enteritis	30MAR2 2	11APR2 2	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-24-01	A	1	Small intestinal mucositis		Enteritis	30MAR2 2	11APR2 2	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-24-01	A	1	Small intestinal mucositis		Enteritis	30MAR2 2	11APR2 2	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-24-01	A	1	Small intestinal mucositis		Enteritis	30MAR2 2	11APR2 2	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	Yes



*Terminology according to CTCAE  
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<i>Patient No.</i>	<i>Arm</i>	<i>Grade</i>	<i>Term</i>	<i>Other</i>	<i>PT according to MedDRA</i>	<i>Start date</i>	<i>End date</i>	<i>Outcome</i>	<i>Study treatment started</i>	<i>Study treatment component</i>	<i>Causal relationship suspected</i>	<i>Action taken</i>	<i>Event treated with medicati on</i>
MR-DE-24-01	A	1	Investigations - Other, specify	CRP (increased ) 9.9 mg/dl; Norm 0.3- 0.5 mg/dl	C-reactive protein increased	07JUN22	21JUN22	Recovered without sequelae	Yes	5-FU	No correlation	Treatment continued without Change	Yes
MR-DE-24-01	A	1	Investigations - Other, specify	CRP (increased ) 9.9 mg/dl; Norm 0.3- 0.5 mg/dl	C-reactive protein increased	07JUN22	21JUN22	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes
MR-DE-24-01	A	1	Investigations - Other, specify	CRP (increased ) 9.9 mg/dl; Norm 0.3- 0.5 mg/dl	C-reactive protein increased	07JUN22	21JUN22	Recovered without sequelae	Yes	Folinic acid	No correlation	Treatment continued without Change	Yes
MR-DE-24-01	A	1	Investigations - Other, specify	CRP (increased ) 9.9 mg/dl; Norm 0.3- 0.5 mg/dl	C-reactive protein increased	07JUN22	21JUN22	Recovered without sequelae	Yes	Irinotecan	No correlation	Treatment continued without Change	Yes
MR-DE-24-01	A	2	Urinary tract infection		Urinary tract infection	05OCT2 3	.	Recovered without sequelae	Yes	5-FU	Missing	Missing	Yes
MR-DE-24-01	A	2	Urinary tract infection		Urinary tract infection	05OCT2 3	.	Recovered without sequelae	Yes	Cetuximab	Missing	Missing	Yes

Terminology according to CTCAE version 5													
Patient No.	Arm	Grade	Term	Other	PT according to MedDRA	Start date	End date	Outcome	Study treatment started	Study treatment component	Causal relationship suspected	Action taken	Event treated with medication
MR-DE-24-01	A	2	Urinary tract infection		Urinary tract infection	05OCT23		Recovered without sequelae	Yes	Folinic acid	Missing	Missing	Yes
MR-DE-24-01	A	2	Urinary tract infection		Urinary tract infection	05OCT23		Recovered without sequelae	Yes	Irinotecan	Missing	Missing	Yes
MR-DE-24-01	A	5	Gastric ulcer		Gastric ulcer	27OCT23		Fatal (AE resulted in death)	Yes	5-FU	Unlikely	Unknown	No
MR-DE-24-01	A	5	Gastric ulcer		Gastric ulcer	27OCT23		Fatal (AE resulted in death)	Yes	Cetuximab	Unlikely	Unknown	No
MR-DE-24-01	A	5	Gastric ulcer		Gastric ulcer	27OCT23		Fatal (AE resulted in death)	Yes	Folinic acid	Unlikely	Unknown	No
MR-DE-24-01	A	5	Gastric ulcer		Gastric ulcer	27OCT23		Fatal (AE resulted in death)	Yes	Irinotecan	Unlikely	Treatment continued without Change	No

(Data source: Listing 28.1. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06).

14.3.2 Listings of Deaths, SAEs, Other Significant AEs

Terminology according to CTCAE version 5										
Patient No.	Arm	Grade	Term	Other	PT according to MedDRA	Start date	Serious AE	Reason for classification as serious	Special event	Reason for classification as special
MR-DE-01-01	A	5	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	mutated metastatic colorectal cancer	Colorectal cancer metastatic	.	Yes	Death, Hospitalization	No	
MR-DE-01-01	A	1	Injury, poisoning and procedural complications - Other, specify	overdose	Overdose	28JUN21	No		Yes	Medication Error
MR-DE-01-01	A	1	Injury, poisoning and procedural complications - Other, specify	medication dose changed	Therapy change	12JUL21	No		Yes	Medication Error
MR-DE-14-01	A	1	Intraoperative hepatobiliary injury		Hepatobiliary procedural complication	16AUG21	Yes	Hospitalization	No	
MR-DE-24-01	A	1	Ileus		Ileus	06OCT21	Yes	Hospitalization	No	
MR-DE-24-01	A	5	Gastric ulcer		Gastric ulcer	27OCT23	Yes	Death	No	

(Data source: Listing 28.2. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

14.3.3 Narratives of Deaths, SAEs, Other Significant AEs

Narratives of Deaths, SAEs and other significant AEs are shown in Section **Fehler!**  
**Verweisquelle konnte nicht gefunden werden..**

14.3.4 Laboratory Values (by-patient listing), Vital signs, physical examinations

<i>Patient No.</i>	<i>Arm</i>	<i>Echocardiography performed</i>	<i>Reason if no</i>	<i>Date of echocardiography</i>	<i>LVEF [%]</i>	<i>Clinical significance</i>
MR-DE-01-01	A	Yes		30APR21	64	Normal
MR-DE-02-01	B	Yes		20APR21	60	Normal
MR-DE-02-02	A	Yes		11MAY21	60	Normal
MR-DE-02-03	B	Yes		12MAY21	60	Normal
MR-DE-14-01	A	Yes		18NOV20	55	Normal
MR-DE-24-01	A	Yes		14JUL21	60	Normal

(Data source: Listing 8. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

<i>Patient No.</i>	<i>Arm</i>	<i>Coagulation done</i>	<i>Reason if no</i>	<i>Date of coagulation sampling</i>	<i>INR</i>	<i>PTT [s]</i>
MR-DE-01-01	A	Yes		30APR21	1.03	39.9
MR-DE-02-01	B	Yes		20APR21	1.00	28.1
MR-DE-02-02	A	Yes		11MAY21	1.10	31.2
MR-DE-02-03	B	Yes		12MAY21	1.00	26.2
MR-DE-14-01	A	Yes		06DEC20	1.00	30.5
MR-DE-24-01	A	Yes		13JUL21	1.08	37.3

(Data source: Listing 10. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

<i>Patient No.</i>	<i>Arm</i>	<i>Test for DPD deficiency performed</i>	<i>Reason if no</i>	<i>Date of DPD deficiency test</i>	<i>Test result</i>
MR-DE-01-01	A	Missing			.
MR-DE-02-01	B	Missing			.
MR-DE-02-02	A	Missing			.
MR-DE-02-03	B	Yes		07MAY21	No deficiency
MR-DE-14-01	A	Missing			.
MR-DE-24-01	A	Yes		15JUL21	No deficiency
MR-DE-24-02	Not assigned	Missing			.

(Data source: Listing 11. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

<i>Patient No.</i>	<i>Arm</i>	<i>Serological tests performed</i>	<i>Reason if no</i>	<i>Date of serological tests</i>	<i>Hepatitis B</i>	<i>Hepatitis C</i>
MR-DE-01-01	A	Yes		30APR21	Negative	Negative
MR-DE-02-01	B	Yes		20APR21	Negative	Negative

<i>Patient No.</i>	<i>Arm</i>	<i>Serological tests performed</i>	<i>Reason if no</i>	<i>Date of serological tests</i>	<i>Hepatitis B</i>	<i>Hepatitis C</i>
MR-DE-02-02	A	Yes		11MAY21	Negative	Negative
MR-DE-02-03	B	Yes		12MAY21	Negative	Negative
MR-DE-14-01	A	Yes		08DEC20	Negative	Missing
MR-DE-24-01	A	Yes		13JUL21	Negative	Negative

(Data source: Listing 12. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06).

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>ECG performed</i>	<i>Reason if no</i>	<i>Date of ECG</i>	<i>Clinical significance</i>
MR-DE-01-01	A	Baseline	Yes		30APR21	Normal
MR-DE-02-01	B	Baseline	Yes		20APR21	Normal
MR-DE-02-02	A	Baseline	Yes		11MAY21	Normal
MR-DE-02-03	B	Baseline	Yes		12MAY21	Normal
MR-DE-14-01	A	Baseline	Yes		16DEC20	Not clinically significant
MR-DE-24-01	A	Baseline	Yes		14JUL21	Normal
MR-DE-24-01	A	Pre-cycle 1	Yes		14JUL21	Normal

(Data source: Listing 13. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06).

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Date of ECOG evaluation</i>	<i>ECOG performance status</i>
MR-DE-01-01	A	Baseline	30APR21	1
MR-DE-01-01	A	Pre-cycle 1	30APR21	1
MR-DE-01-01	A	Pre-cycle 2	14MAY21	0
MR-DE-01-01	A	Pre-cycle 3	31MAY21	0
MR-DE-01-01	A	Pre-cycle 4	14JUN21	0
MR-DE-01-01	A	Cycle 1	28JUN21	0
MR-DE-01-01	A	Cycle 2	08JUL21	0
MR-DE-01-01	A	Cycle 3	26JUL21	0
MR-DE-01-01	A	Cycle 4	09AUG21	0
MR-DE-01-01	A	Cycle 5	23AUG21	0
MR-DE-01-01	A	Cycle 6	06SEP21	0
MR-DE-01-01	A	Cycle 7	20SEP21	0
MR-DE-01-01	A	EOT	26OCT21	1
MR-DE-01-01	A	Follow-up 1	03MAR22	0
MR-DE-01-01	A	Follow-up 2	17MAY22	5
MR-DE-02-01	B	Baseline	20APR21	0
MR-DE-02-01	B	Pre-cycle 1	26APR21	0
MR-DE-02-01	B	Pre-cycle 2	10MAY21	0
MR-DE-02-01	B	Pre-cycle 3	26MAY21	0
MR-DE-02-01	B	Pre-cycle 4	09JUN21	1
MR-DE-02-01	B	Cycle 1	29JUN21	0
MR-DE-02-01	B	Cycle 2	13JUL21	1
MR-DE-02-01	B	Cycle 3	02AUG21	1
MR-DE-02-01	B	Cycle 4	16AUG21	0
MR-DE-02-01	B	Cycle 5	13SEP21	0
MR-DE-02-01	B	Cycle 6	27SEP21	0
MR-DE-02-01	B	Cycle 7	11OCT21	0
MR-DE-02-01	B	EOT	13DEC21	0
MR-DE-02-01	B	Follow-up 1	16MAR22	0
MR-DE-02-01	B	Follow-up 2	04JUL22	0
MR-DE-02-01	B	Follow-up 3	18OCT22	0
MR-DE-02-01	B	Follow-up 4	10FEB23	0
MR-DE-02-01	B	Follow-up 5	08MAY23	0
MR-DE-02-01	B	Follow-up 6	20JUL23	1
MR-DE-02-01	B	Follow-up 7	27OCT23	5
MR-DE-02-02	A	Baseline	11MAY21	0
MR-DE-02-02	A	Pre-cycle 1	18MAY21	0
MR-DE-02-02	A	Pre-cycle 2	01JUN21	0
MR-DE-02-02	A	Pre-cycle 3	15JUN21	0

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Date of ECOG evaluation</i>	<i>ECOG performance status</i>
MR-DE-02-02	A	Pre-cycle 4	29JUN21	0
MR-DE-02-02	A	Cycle 1	20JUL21	0
MR-DE-02-02	A	Cycle 1	27JUL21	0
MR-DE-02-02	A	Cycle 2	03AUG21	0
MR-DE-02-02	A	Cycle 2	10AUG21	0
MR-DE-02-02	A	Cycle 3	17AUG21	0
MR-DE-02-02	A	Cycle 3	24AUG21	0
MR-DE-02-02	A	Cycle 4	31AUG21	0
MR-DE-02-02	A	Cycle 4	07SEP21	0
MR-DE-02-02	A	Cycle 5	14SEP21	0
MR-DE-02-02	A	Cycle 5	21SEP21	0
MR-DE-02-02	A	Cycle 6	28SEP21	0
MR-DE-02-02	A	Cycle 6	05OCT21	0
MR-DE-02-02	A	Cycle 7	12OCT21	0
MR-DE-02-02	A	Cycle 7	19OCT21	0
MR-DE-02-02	A	Cycle 8	26OCT21	1
MR-DE-02-02	A	Cycle 8	02NOV21	1
MR-DE-02-02	A	Cycle 9	09NOV21	0
MR-DE-02-02	A	Cycle 9	16NOV21	0
MR-DE-02-02	A	Cycle 10	23NOV21	0
MR-DE-02-02	A	Cycle 10	30NOV21	0
MR-DE-02-02	A	EOT	29DEC21	1
MR-DE-02-02	A	Follow-up 1	22MAR22	0
MR-DE-02-02	A	Follow-up 2	04MAY22	0
MR-DE-02-02	A	Follow-up 3	10AUG22	0
MR-DE-02-02	A	Follow-up 4	08NOV22	0
MR-DE-02-02	A	Follow-up 5	10FEB23	0
MR-DE-02-02	A	Follow-up 6	05MAY23	0
MR-DE-02-02	A	Follow-up 7	29AUG23	0
MR-DE-02-02	A	Follow-up 8	07NOV23	0
MR-DE-02-02	A	Follow-up 9	01FEB24	1
MR-DE-02-02	A	Follow-up 10	30APR24	0
MR-DE-02-02	A	Follow-up 11	11JUN24	0
MR-DE-02-03	B	Baseline	12MAY21	0
MR-DE-02-03	B	Pre-cycle 1	19MAY21	0
MR-DE-02-03	B	Pre-cycle 2	02JUN21	0
MR-DE-02-03	B	Pre-cycle 3	16JUN21	1
MR-DE-02-03	B	Pre-cycle 4	30JUN21	0
MR-DE-02-03	B	Cycle 1	14JUL21	0

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Date of ECOG evaluation</i>	<i>ECOG performance status</i>
MR-DE-02-03	B	Cycle 2	04AUG21	1
MR-DE-02-03	B	Cycle 3	18AUG21	0
MR-DE-02-03	B	Cycle 4	01SEP21	1
MR-DE-02-03	B	Cycle 5	15SEP21	0
MR-DE-02-03	B	Cycle 6	29SEP21	1
MR-DE-02-03	B	EOT	08NOV21	2
MR-DE-02-03	B	Follow-up 1	31JAN22	2
MR-DE-02-03	B	Follow-up 2	21MAR22	2
MR-DE-02-03	B	Follow-up 3	03MAY22	3
MR-DE-14-01	A	Baseline	29DEC20	0
MR-DE-14-01	A	Pre-cycle 1	29DEC20	0
MR-DE-14-01	A	Pre-cycle 2	12JAN21	0
MR-DE-14-01	A	Pre-cycle 3	26JAN21	0
MR-DE-14-01	A	Pre-cycle 4	09FEB21	0
MR-DE-14-01	A	Pre-cycle 5	23FEB21	0
MR-DE-14-01	A	Cycle 1	09MAR21	0
MR-DE-14-01	A	Cycle 1	16MAR21	0
MR-DE-14-01	A	Cycle 2	23MAR21	0
MR-DE-14-01	A	Cycle 2	30MAR21	0
MR-DE-14-01	A	Cycle 3	07APR21	0
MR-DE-14-01	A	Cycle 3	14APR21	0
MR-DE-14-01	A	Cycle 4	20APR21	0
MR-DE-14-01	A	Cycle 4	27APR21	0
MR-DE-14-01	A	Cycle 5	04MAY21	0
MR-DE-14-01	A	Cycle 6	18MAY21	0
MR-DE-14-01	A	Cycle 7	01JUN21	0
MR-DE-14-01	A	Cycle 8	15JUN21	0
MR-DE-14-01	A	Cycle 9	29JUN21	0
MR-DE-14-01	A	Cycle 10	13JUL21	0
MR-DE-14-01	A	Cycle 18	03NOV21	0
MR-DE-14-01	A	Cycle 19	17NOV21	0
MR-DE-14-01	A	Cycle 20	01DEC21	0
MR-DE-14-01	A	EOT	15DEC21	0
MR-DE-14-01	A	Follow-up 1	18JAN22	2
MR-DE-14-01	A	Follow-up 2	28MAR22	2
MR-DE-14-01	A	Follow-up 3	05JUL22	1
MR-DE-14-01	A	Follow-up 4	27SEP22	1
MR-DE-14-01	A	Follow-up 5	09JAN23	2
MR-DE-14-01	A	Follow-up 6	28APR23	5



<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Date of ECOG evaluation</i>	<i>ECOG performance status</i>
MR-DE-24-01	A	Baseline	13JUL21	1
MR-DE-24-01	A	Pre-cycle 1	22JUL21	1
MR-DE-24-01	A	Pre-cycle 2	05AUG21	1
MR-DE-24-01	A	Pre-cycle 3	18AUG21	1
MR-DE-24-01	A	Pre-cycle 4	01SEP21	1
MR-DE-24-01	A	Pre-cycle 5	15SEP21	1
MR-DE-24-01	A	Pre-cycle 6	29SEP21	1
MR-DE-24-01	A	Cycle 1	21OCT21	1
MR-DE-24-01	A	Cycle 1	29OCT21	1
MR-DE-24-01	A	Cycle 2	03NOV21	1
MR-DE-24-01	A	Cycle 2	10NOV21	1
MR-DE-24-01	A	Cycle 3	17NOV21	1
MR-DE-24-01	A	Cycle 3	24NOV21	1
MR-DE-24-01	A	Cycle 4	01DEC21	1
MR-DE-24-01	A	Cycle 4	08DEC21	1
MR-DE-24-01	A	Cycle 5	15DEC21	1
MR-DE-24-01	A	Cycle 5	22DEC21	1
MR-DE-24-01	A	Cycle 6	29DEC21	1
MR-DE-24-01	A	Cycle 6	05JAN22	1
MR-DE-24-01	A	Cycle 7	12JAN22	1
MR-DE-24-01	A	Cycle 7	19JAN22	1
MR-DE-24-01	A	Cycle 8	31JAN22	1
MR-DE-24-01	A	Cycle 9	14FEB22	1
MR-DE-24-01	A	Cycle 10	28FEB22	1
MR-DE-24-01	A	Cycle 11	14MAR22	1
MR-DE-24-01	A	Cycle 12	28MAR22	0
MR-DE-24-01	A	Cycle 13	13APR22	1
MR-DE-24-01	A	Cycle 14	25APR22	1
MR-DE-24-01	A	Cycle 15	09MAY22	1
MR-DE-24-01	A	Cycle 16	23MAY22	1
MR-DE-24-01	A	Cycle 17	08JUN22	1
MR-DE-24-01	A	EOT	14JUN22	1
MR-DE-24-01	A	Follow-up 1	15SEP22	1
MR-DE-24-01	A	Follow-up 2	13DEC22	1
MR-DE-24-01	A	Follow-up 3	07MAR23	2
MR-DE-24-01	A	Follow-up 4	23MAY23	2
MR-DE-24-01	A	Follow-up 5	25AUG23	2

(Data source: Listing 14. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

MoLiMoR

Clinical Study Report

EudraCT-No. 2019-003714-14

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Vital signs examined</i>	<i>Reason if no</i>	<i>Date of examination</i>	<i>Weight [kg]</i>	<i>Temperature [°C]</i>	<i>Blood pressure (systolic) [mmHg]</i>	<i>Blood pressure (diastolic) [mmHg]</i>	<i>Heartrate [per min]</i>
MR-DE-01-01	A	Baseline	Yes		30APR21	76	35.0	122	81	60
MR-DE-01-01	A	Pre-cycle 1	Yes		30APR21	76	35.0	122	81	60
MR-DE-01-01	A	Pre-cycle 2	Yes			76	.	140	80	68
MR-DE-01-01	A	Pre-cycle 3	Yes		31MAY21	71	.	130	70	71
MR-DE-01-01	A	Pre-cycle 4	Yes		14JUN21	71	.	100	60	68
MR-DE-01-01	A	Cycle 1	Yes		28JUN21	71	.	90	60	74
MR-DE-01-01	A	Cycle 2	Yes		12JUL21	71	.	110	70	64
MR-DE-01-01	A	Cycle 3	Yes		26JUL21	71	.	100	70	80
MR-DE-01-01	A	Cycle 4	Yes		09AUG21	71	.	90	60	64
MR-DE-01-01	A	Cycle 5	Yes		23AUG21	71	.	90	60	53
MR-DE-01-01	A	Cycle 6	No	Missed by site		.	.	.	.	.
MR-DE-01-01	A	Cycle 7	Yes		20SEP21	72	.	90	60	56
MR-DE-02-01	B	Baseline	Yes		20APR21	93	36.8	110	80	80
MR-DE-02-01	B	Pre-cycle 1	Yes		26APR21	93	36.1	130	95	68
MR-DE-02-01	B	Pre-cycle 2	Yes		10MAY21	93	36.7	134	86	92
MR-DE-02-01	B	Pre-cycle 3	Yes		26MAY21	92	36.3	120	85	72
MR-DE-02-01	B	Pre-cycle 4	Yes		09JUN21	89	36.5	110	80	76
MR-DE-02-01	B	Cycle 1	Yes		29JUN21	92	36.4	120	80	82
MR-DE-02-01	B	Cycle 2	Yes		13JUL21	92	36.5	115	75	92
MR-DE-02-01	B	Cycle 3	Yes		02AUG21	90	36.3	110	80	88
MR-DE-02-01	B	Cycle 4	Yes		16AUG21	90	36.7	110	70	82
MR-DE-02-01	B	Cycle 5	Yes		13SEP21	90	36.4	122	82	83
MR-DE-02-01	B	Cycle 6	Yes		27SEP21	90	36.5	120	80	85
MR-DE-02-01	B	Cycle 7	Yes		11OCT21	94	36.2	125	85	94
MR-DE-02-02	A	Baseline	Yes		11MAY21	125	36.1	180	100	94

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Vital signs examined</i>	<i>Reason if no</i>	<i>Date of examination</i>	<i>Weight [kg]</i>	<i>Temperature [°C]</i>	<i>Blood pressure (systolic) [mmHg]</i>	<i>Blood pressure (diastolic) [mmHg]</i>	<i>Heartrate [per min]</i>
MR-DE-02-02	A	Pre-cycle 1	Yes		18MAY21	125	36.9	178	93	76
MR-DE-02-02	A	Pre-cycle 2	Yes		01JUN21	125	36.8	190	109	76
MR-DE-02-02	A	Pre-cycle 3	Yes		15JUN21	124	36.7	153	89	105
MR-DE-02-02	A	Pre-cycle 4	Yes		29JUN21	125	36.5	170	90	85
MR-DE-02-02	A	Cycle 1	Yes		20JUL21	125	36.8	190	110	85
MR-DE-02-02	A	Cycle 1	Yes		27JUL21	125	36.7	147	85	82
MR-DE-02-02	A	Cycle 2	Yes		03AUG21	125	36.9	164	81	84
MR-DE-02-02	A	Cycle 2	Yes		10AUG21	125	37.4	143	73	96
MR-DE-02-02	A	Cycle 3	Yes		17AUG21	125	36.9	175	90	96
MR-DE-02-02	A	Cycle 3	Yes		24AUG21	125	36.9	130	70	88
MR-DE-02-02	A	Cycle 4	Yes		31AUG21	125	36.7	124	73	78
MR-DE-02-02	A	Cycle 4	Yes		07SEP21	125	36.6	160	90	97
MR-DE-02-02	A	Cycle 5	Yes		14SEP21	125	36.8	160	80	86
MR-DE-02-02	A	Cycle 5	Yes		21SEP21	125	36.5	150	80	84
MR-DE-02-02	A	Cycle 6	Yes		28SEP21	125	36.6	155	80	68
MR-DE-02-02	A	Cycle 6	Yes		05OCT21	125	36.6	180	70	84
MR-DE-02-02	A	Cycle 7	Yes		12OCT21	125	36.6	154	82	82
MR-DE-02-02	A	Cycle 7	Yes		19OCT21	125	36.6	153	75	90
MR-DE-02-02	A	Cycle 8	Yes		26OCT21	125	36.5	157	85	76
MR-DE-02-02	A	Cycle 8	Yes		02NOV21	125	36.7	160	80	94
MR-DE-02-02	A	Cycle 9	Yes		09NOV21	125	36.3	133	78	86
MR-DE-02-02	A	Cycle 9	Yes		16NOV21	125	36.6	144	80	90
MR-DE-02-02	A	Cycle 10	Yes		23NOV21	125	36.6	150	90	95
MR-DE-02-02	A	Cycle 10	Yes		30NOV21	125	36.6	145	80	76
MR-DE-02-03	B	Baseline	Yes		12MAY21	92	36.3	145	95	90

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Vital signs examined</i>	<i>Reason if no</i>	<i>Date of examination</i>	<i>Weight [kg]</i>	<i>Temperature [°C]</i>	<i>Blood pressure (systolic) [mmHg]</i>	<i>Blood pressure (diastolic) [mmHg]</i>	<i>Heartrate [per min]</i>
MR-DE-02-03	B	Pre-cycle 1	Yes		19MAY21	91	36.9	145	100	90
MR-DE-02-03	B	Pre-cycle 2	Yes		02JUN21	89	36.5	125	80	84
MR-DE-02-03	B	Pre-cycle 3	Yes		16JUN21	89	36.4	120	80	92
MR-DE-02-03	B	Pre-cycle 4	Yes		30JUN21	88	36.4	135	80	65
MR-DE-02-03	B	Cycle 1	Yes		14JUL21	86	36.3	125	85	78
MR-DE-02-03	B	Cycle 2	Yes		04AUG21	86	36.6	140	95	76
MR-DE-02-03	B	Cycle 3	Yes		18AUG21	85	36.3	145	100	84
MR-DE-02-03	B	Cycle 4	Yes		01SEP21	84	36.6	120	80	93
MR-DE-02-03	B	Cycle 5	Yes		15SEP21	84	36.4	145	100	87
MR-DE-02-03	B	Cycle 6	Yes		29SEP21	84	36.6	120	80	93
MR-DE-14-01	A	Baseline	Yes		29DEC20	89	36.5	100	60	65
MR-DE-14-01	A	Pre-cycle 1	Yes		29DEC20	89	36.5	100	60	65
MR-DE-14-01	A	Pre-cycle 2	Yes		12JAN21	88	34.7	120	70	67
MR-DE-14-01	A	Pre-cycle 3	Yes		26JAN21	87	35.1	110	70	67
MR-DE-14-01	A	Pre-cycle 4	Yes		09FEB21	88	36.0	105	70	74
MR-DE-14-01	A	Pre-cycle 5	Yes		23FEB21	88	36.0	110	60	68
MR-DE-14-01	A	Cycle 1	Yes		09MAR21	88	35.7	105	70	73
MR-DE-14-01	A	Cycle 1	Yes		16MAR21	.	.	120	80	74
MR-DE-14-01	A	Cycle 2	Yes		23MAR21	89	35.6	90	60	74
MR-DE-14-01	A	Cycle 2	Yes		30MAR21	.	.	130	70	61
MR-DE-14-01	A	Cycle 3	Yes		07APR21	88	35.7	120	80	72
MR-DE-14-01	A	Cycle 3	Yes		14APR21	88	.	120	80	78
MR-DE-14-01	A	Cycle 4	Yes		20APR21	89	36.7	130	80	84
MR-DE-14-01	A	Cycle 4	Yes		27APR21	89	.	120	80	74
MR-DE-14-01	A	Cycle 5	Yes		04MAY21	88	35.6	120	70	85

MoLiMoR

Clinical Study Report

EudraCT-No. 2019-003714-14

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Vital signs examined</i>	<i>Reason if no</i>	<i>Date of examination</i>	<i>Weight [kg]</i>	<i>Temperature [°C]</i>	<i>Blood pressure (systolic) [mmHg]</i>	<i>Blood pressure (diastolic) [mmHg]</i>	<i>Heartrate [per min]</i>
MR-DE-14-01	A	Cycle 6	Yes		18MAY21	89	35.2	120	70	77
MR-DE-14-01	A	Cycle 7	Yes		01JUN21	88	.	130	70	79
MR-DE-14-01	A	Cycle 8	Yes		15JUN21	90	.	130	70	68
MR-DE-14-01	A	Cycle 9	Yes		29JUN21	93	36.9	140	80	83
MR-DE-14-01	A	Cycle 10	Yes		13JUL21	94	.	140	80	77
MR-DE-14-01	A	Cycle 18	Yes		03NOV21	93	.	120	80	68
MR-DE-14-01	A	Cycle 19	Yes		17NOV21	91	.	140	70	67
MR-DE-14-01	A	Cycle 20	Yes		01DEC21	91	.	150	60	74
MR-DE-24-01	A	Baseline	Yes		13JUL21	72	35.9	120	70	71
MR-DE-24-01	A	Pre-cycle 1	Yes		22JUL21	53	35.9	127	70	71
MR-DE-24-01	A	Pre-cycle 2	No	Missed by site	.	.	.	.	.	.
MR-DE-24-01	A	Pre-cycle 3	Yes		18AUG21	63	35.9	90	60	59
MR-DE-24-01	A	Pre-cycle 4	Yes		01SEP21	63	35.8	115	65	72
MR-DE-24-01	A	Pre-cycle 5	No	Missed by site	.	.	.	.	.	.
MR-DE-24-01	A	Pre-cycle 6	No	Missed by site	.	.	.	.	.	.
MR-DE-24-01	A	Cycle 1	Yes		21OCT21	61	34.4	120	70	52
MR-DE-24-01	A	Cycle 1	Yes		29OCT21	58	36.5	150	80	64
MR-DE-24-01	A	Cycle 2	Yes		03NOV21	58	35.7	110	75	80
MR-DE-24-01	A	Cycle 2	Yes		10NOV21	58	35.6	110	80	80
MR-DE-24-01	A	Cycle 3	Yes		17NOV21	55	34.6	105	85	50
MR-DE-24-01	A	Cycle 3	Yes		24NOV21	61	36.0	125	70	76
MR-DE-24-01	A	Cycle 4	Yes		01DEC21	57	36.0	120	70	65
MR-DE-24-01	A	Cycle 4	Yes		08DEC21	59	36.2	120	70	63
MR-DE-24-01	A	Cycle 5	Yes		15DEC21	59	36.2	120	70	63
MR-DE-24-01	A	Cycle 5	Yes		22DEC21	57	35.8	110	80	76

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Vital signs examined</i>	<i>Reason if no</i>	<i>Date of examination</i>	<i>Weight [kg]</i>	<i>Temperature [°C]</i>	<i>Blood pressure (systolic) [mmHg]</i>	<i>Blood pressure (diastolic) [mmHg]</i>	<i>Heartrate [per min]</i>
MR-DE-24-01	A	Cycle 6	Yes		29DEC21	58	35.6	110	60	62
MR-DE-24-01	A	Cycle 6	Yes		05JAN22	59	36.2	110	60	61
MR-DE-24-01	A	Cycle 7	Yes		12JAN22	59	35.5	110	60	65
MR-DE-24-01	A	Cycle 7	Yes		19JAN22	59	36.2	110	60	61
MR-DE-24-01	A	Cycle 8	Yes		31JAN22	59	36.0	115	95	85
MR-DE-24-01	A	Cycle 9	Yes		14FEB22	62	36.5	120	75	80
MR-DE-24-01	A	Cycle 10	Yes		28FEB22	63	36.5	110	60	63
MR-DE-24-01	A	Cycle 11	Yes		14MAR22	63	35.8	110	90	97
MR-DE-24-01	A	Cycle 12	Yes		28MAR22	64	35.7	120	80	60
MR-DE-24-01	A	Cycle 13	Yes		13APR22	64	36.6	115	75	70
MR-DE-24-01	A	Cycle 14	Yes		25APR22	66	36.0	130	80	72
MR-DE-24-01	A	Cycle 15	Yes		09MAY22	65	36.7	120	65	68
MR-DE-24-01	A	Cycle 16	Yes		23MAY22	64	36.2	110	75	70
MR-DE-24-01	A	Cycle 17	Yes		08JUN22	64	36.2	110	75	70

(Data source: Listing 14. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory hematology done</i>	<i>Reason if no</i>	<i>Date of hematology sampling</i>	<i>Hemoglobin [g/dL]</i>	<i>Platelets [10<sup>9</sup>/L]</i>	<i>Leukocytes [10<sup>9</sup>/L]</i>	<i>Neutrophils (total) [10<sup>9</sup>/L]</i>
MR-DE-01-01	A	Baseline	Yes		30APR21	12.20	201.0	5.40	3.105
MR-DE-01-01	A	Pre-cycle 1	No	Other: same like baseline	.	.	.	.	.
MR-DE-01-01	A	Pre-cycle 2	Yes		14MAY21	11.30	199.0	4.30	2.230
MR-DE-01-01	A	Pre-cycle 3	Yes		31MAY21	11.50	202.0	4.50	2.370
MR-DE-01-01	A	Pre-cycle 4	Yes		14JUN21	11.60	196.0	4.10	2.240

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory hematology done</i>	<i>Reason if no</i>	<i>Date of hematology sampling</i>	<i>Hemoglobin [g/dL]</i>	<i>Platelets [10<sup>9</sup>/L]</i>	<i>Leukocytes [10<sup>9</sup>/L]</i>	<i>Neutrophils (total) [10<sup>9</sup>/L]</i>
MR-DE-01-01	A	Cycle 1	Yes		28JUN21	11.20	171.0	4.40	2.500
MR-DE-01-01	A	Cycle 2	Yes		08JUL21	11.40	229.0	3.00	1.280
MR-DE-01-01	A	Cycle 3	Yes		23JUL21	11.20	223.0	4.40	2.720
MR-DE-01-01	A	Cycle 4	Yes		06AUG21	11.10	199.0	6.90	4.990
MR-DE-01-01	A	Cycle 5	Yes		20AUG21	11.30	193.0	6.00	4.350
MR-DE-01-01	A	Cycle 6	Yes		03SEP21	12.00	204.0	4.10	2.560
MR-DE-01-01	A	Cycle 7	Yes		17SEP21	11.90	177.0	3.60	2.170
MR-DE-01-01	A	Cycle 8	Yes		04OCT21	11.30	177.0	3.20	1.560
MR-DE-01-01	A	Cycle 9	Yes		25OCT21	12.20	188.0	4.90	.
MR-DE-01-01	A	Cycle 10	Yes		02NOV21	11.70	213.0	4.30	.
MR-DE-01-01	A	EOT	Yes		25OCT21	12.20	188.0	4.90	.
MR-DE-02-01	B	Baseline	Yes		20APR21	16.40	268.0	6.61	3.200
MR-DE-02-01	B	Pre-cycle 1	Yes		26APR21	15.30	251.0	5.45	2.610
MR-DE-02-01	B	Pre-cycle 2	Yes		10MAY21	14.30	253.0	4.71	.
MR-DE-02-01	B	Pre-cycle 3	Yes		26MAY21	14.20	220.0	4.64	1.860
MR-DE-02-01	B	Pre-cycle 4	Yes		09JUN21	10.90	273.0	4.98	3.020
MR-DE-02-01	B	Cycle 1	Yes		29JUN21	13.30	224.0	4.73	1.670
MR-DE-02-01	B	Cycle 2	Yes		13JUL21	12.40	183.0	4.75	2.550
MR-DE-02-01	B	Cycle 3	Yes		02AUG21	13.30	224.0	4.53	1.410
MR-DE-02-01	B	Cycle 4	Yes		16AUG21	12.60	189.0	4.81	2.340
MR-DE-02-01	B	Cycle 5	Yes		13SEP21	14.00	215.0	6.25	3.090
MR-DE-02-01	B	Cycle 6	Yes		27SEP21	13.30	188.0	5.07	2.370
MR-DE-02-01	B	Cycle 7	Yes		11OCT21	12.50	193.0	4.89	2.250

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory hematology done</i>	<i>Reason if no</i>	<i>Date of hematology sampling</i>	<i>Hemoglobin [g/dL]</i>	<i>Platelets [10<sup>9</sup>/L]</i>	<i>Leukocytes [10<sup>9</sup>/L]</i>	<i>Neutrophils (total) [10<sup>9</sup>/L]</i>
MR-DE-02-01	B	EOT	Yes		13DEC21	15.40	244.0	6.23	3.180
MR-DE-02-02	A	Baseline	Yes		11MAY21	17.20	343.0	11.80	7.660
MR-DE-02-02	A	Pre-cycle 1	Yes		18MAY21	16.50	296.0	8.82	5.640
MR-DE-02-02	A	Pre-cycle 2	Yes		01JUN21	15.60	286.0	5.78	2.480
MR-DE-02-02	A	Pre-cycle 3	Yes		15JUN21	15.20	241.0	6.99	.
MR-DE-02-02	A	Pre-cycle 4	Yes		29JUN21	14.90	234.0	6.41	3.000
MR-DE-02-02	A	Cycle 1	Yes		20JUL21	15.90	316.0	7.11	3.740
MR-DE-02-02	A	Cycle 2	Yes		03AUG21	15.70	317.0	7.52	4.160
MR-DE-02-02	A	Cycle 3	Yes		17AUG21	16.50	280.0	6.39	3.140
MR-DE-02-02	A	Cycle 4	Yes		31AUG21	15.80	263.0	5.89	2.390
MR-DE-02-02	A	Cycle 5	Yes		14SEP21	15.60	341.0	5.25	1.650
MR-DE-02-02	A	Cycle 6	Yes		28SEP21	15.20	299.0	5.91	2.840
MR-DE-02-02	A	Cycle 7	Yes		12OCT21	15.30	288.0	6.82	3.410
MR-DE-02-02	A	Cycle 8	Yes		26OCT21	16.10	272.0	6.72	1.350
MR-DE-02-02	A	Cycle 9	Yes		09NOV21	15.70	262.0	6.52	3.450
MR-DE-02-02	A	Cycle 10	Yes		23NOV21	17.20	251.0	10.11	5.840
MR-DE-02-02	A	EOT	Yes		29DEC21	17.20	328.0	10.08	5.670
MR-DE-02-03	B	Baseline	Yes		12MAY21	14.50	215.0	9.58	7.160
MR-DE-02-03	B	Pre-cycle 1	Yes		19MAY21	14.10	245.0	9.78	7.000
MR-DE-02-03	B	Pre-cycle 2	Yes		02JUN21	13.10	180.0	4.00	1.980
MR-DE-02-03	B	Pre-cycle 3	Yes		16JUN21	12.80	173.0	4.30	2.070
MR-DE-02-03	B	Pre-cycle 4	Yes		29JUN21	12.30	313.0	3.81	1.890
MR-DE-02-03	B	Cycle 1	Yes		14JUL21	12.40	266.0	4.08	1.960



<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory hematology done</i>	<i>Reason if no</i>	<i>Date of hematology sampling</i>	<i>Hemoglobin [g/dL]</i>	<i>Platelets [10<sup>9</sup>/L]</i>	<i>Leukocytes [10<sup>9</sup>/L]</i>	<i>Neutrophils (total) [10<sup>9</sup>/L]</i>
MR-DE-02-03	B	Cycle 2	Yes		04AUG21	12.40	385.0	7.24	4.370
MR-DE-02-03	B	Cycle 3	Yes		18AUG21	12.30	297.0	5.81	3.680
MR-DE-02-03	B	Cycle 4	Yes		30AUG21	12.50	298.0	5.54	3.320
MR-DE-02-03	B	Cycle 5	Yes		15SEP21	12.50	315.0	4.74	2.200
MR-DE-02-03	B	Cycle 6	Yes		29SEP21	11.80	348.0	3.04	0.890
MR-DE-02-03	B	EOT	Yes		08NOV21	11.90	365.0	10.29	7.550
MR-DE-14-01	A	Baseline	Yes		29DEC20	15.04	204.2	7.12	73.670
MR-DE-14-01	A	Pre-cycle 1	Yes		29DEC20	15.04	204.2	7.12	73.670
MR-DE-14-01	A	Pre-cycle 2	Yes		12JAN21	14.23	198.1	6.49	73.930
MR-DE-14-01	A	Pre-cycle 3	Yes		26JAN21	14.56	150.7	6.70	70.950
MR-DE-14-01	A	Pre-cycle 4	Yes		09FEB21	13.70	179.9	6.07	61.380
MR-DE-14-01	A	Pre-cycle 5	Yes		23FEB21	13.25	158.9	5.68	68.880
MR-DE-14-01	A	Cycle 1	Yes		09MAR21	13.50	166.5	5.30	66.910
MR-DE-14-01	A	Cycle 2	Yes		23MAR21	14.28	172.7	7.89	73.510
MR-DE-14-01	A	Cycle 3	Yes		07APR21	14.10	172.0	4.50	.
MR-DE-14-01	A	Cycle 4	Yes		20APR21	14.71	154.6	4.33	64.570
MR-DE-14-01	A	Cycle 5	Yes		04MAY21	14.68	177.3	4.63	65.630
MR-DE-14-01	A	Cycle 6	Yes		18MAY21	14.14	164.4	3.86	55.090
MR-DE-14-01	A	Cycle 7	Yes		01JUN21	13.56	196.0	4.96	56.510
MR-DE-14-01	A	Cycle 8	Yes		15JUN21	13.23	151.6	4.32	51.960
MR-DE-14-01	A	Cycle 9	Yes		29JUN21	13.37	152.2	4.43	61.150
MR-DE-14-01	A	Cycle 10	Yes		13JUL21	13.74	128.5	5.63	63.730
MR-DE-14-01	A	Cycle 12	No	Other: therapy paused as per clinical routine	.	.	.	.	.

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory hematology done</i>	<i>Reason if no</i>	<i>Date of hematology sampling</i>	<i>Hemoglobin [g/dL]</i>	<i>Platelets [10<sup>9</sup>/L]</i>	<i>Leukocytes [10<sup>9</sup>/L]</i>	<i>Neutrophils (total) [10<sup>9</sup>/L]</i>
MR-DE-14-01	A	Cycle 16	No	Other: medication paused as per local routine	.	.	.	.	.
MR-DE-14-01	A	Cycle 18	Yes		03NOV21	13.45	179.9	7.60	71.180
MR-DE-14-01	A	Cycle 19	Yes		17NOV21	13.48	229.2	6.58	68.720
MR-DE-14-01	A	Cycle 20	Yes		29NOV21	13.61	186.0	7.59	70.940
MR-DE-14-01	A	EOT	Yes		15DEC21	16.38	189.6	7.44	71.690
MR-DE-24-01	A	Baseline	Yes		13JUL21	12.00	397.0	7.94	72.100
MR-DE-24-01	A	Pre-cycle 1	Yes		22JUL21	11.10	296.0	5.68	64.000
MR-DE-24-01	A	Pre-cycle 2	Yes		05AUG21	10.60	279.0	5.00	81.000
MR-DE-24-01	A	Pre-cycle 3	Yes		18AUG21	12.10	226.0	4.60	66.100
MR-DE-24-01	A	Pre-cycle 4	Yes		31AUG21	12.60	275.0	5.10	61.800
MR-DE-24-01	A	Pre-cycle 5	Yes		14SEP21	12.40	240.0	5.68	62.500
MR-DE-24-01	A	Pre-cycle 6	Yes		28SEP21	12.60	268.0	5.39	61.700
MR-DE-24-01	A	Cycle 1	Yes		21OCT21	12.10	403.0	6.11	62.900
MR-DE-24-01	A	Cycle 2	Yes		02NOV21	12.50	256.0	3.72	55.400
MR-DE-24-01	A	Cycle 3	Yes		16NOV21	13.10	256.0	4.36	58.200
MR-DE-24-01	A	Cycle 4	Yes		30NOV21	13.40	227.0	4.31	27.400
MR-DE-24-01	A	Cycle 5	Yes		14DEC21	12.20	252.0	6.27	70.400
MR-DE-24-01	A	Cycle 6	Yes		28DEC21	12.70	243.0	6.01	67.100
MR-DE-24-01	A	Cycle 7	Yes		11JAN22	13.10	212.0	6.31	64.400
MR-DE-24-01	A	Cycle 8	Yes		28JAN22	13.00	235.0	5.83	59.900
MR-DE-24-01	A	Cycle 9	Yes		11FEB22	12.60	225.0	4.68	57.400
MR-DE-24-01	A	Cycle 10	Yes		25FEB22	12.50	238.0	4.56	54.200
MR-DE-24-01	A	Cycle 11	Yes		11MAR22	12.60	256.0	3.97	57.600

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory hematology done</i>	<i>Reason if no</i>	<i>Date of hematology sampling</i>	<i>Hemoglobin [g/dL]</i>	<i>Platelets [10<sup>9</sup>/L]</i>	<i>Leukocytes [10<sup>9</sup>/L]</i>	<i>Neutrophils (total) [10<sup>9</sup>/L]</i>
MR-DE-24-01	A	Cycle 12	Yes		25MAR22	12.00	254.0	4.18	61.000
MR-DE-24-01	A	Cycle 13	Yes		08APR22	11.90	242.0	3.65	47.700
MR-DE-24-01	A	Cycle 14	Yes		22APR22	12.60	253.0	3.77	51.700
MR-DE-24-01	A	Cycle 15	Yes		06MAY22	12.50	195.0	13.33	81.100
MR-DE-24-01	A	Cycle 16	Yes		20MAY22	11.50	288.0	4.36	67.100
MR-DE-24-01	A	Cycle 17	Yes		07JUN22	11.80	218.0	8.27	67.800
MR-DE-24-01	A	EOT	No	Other: The last blood collection was 10.06.2022 control to AE.Next collection will be planed for 21.06.2022.	.	.	.	.	.

(Data source: Listing 16. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory blood chemistry done</i>	<i>Reason if no</i>	<i>Date of chemistry sampling</i>	<i>Sodium [mval/L]</i>	<i>Potassium [mmol/L]</i>	<i>Magnesium [mmol/L]</i>	<i>Calcium [mmol/L]</i>	<i>ASAT [U/L]</i>
MR-DE-01-01	A	Baseline	Yes		30APR21	141	3.81	1.90	2.37	39.7
MR-DE-01-01	A	Pre-cycle 1	No	Other: same like baseline	.	.	.	.	.	.
MR-DE-01-01	A	Pre-cycle 2	Yes		14MAY21	141	3.32	.	.	27.6
MR-DE-01-01	A	Pre-cycle 3	Yes		31MAY21	141	3.84	.	.	35.8
MR-DE-01-01	A	Pre-cycle 4	Yes		14JUN21	143	4.15	.	.	22.6
MR-DE-01-01	A	Cycle 1	Yes		28JUN21	144	3.90	.	.	30.5
MR-DE-01-01	A	Cycle 2	Yes		08JUL21	140	3.92	.	.	25.6
MR-DE-01-01	A	Cycle 3	Yes		23JUL21	142	4.02	.	.	23.4
MR-DE-01-01	A	Cycle 4	Yes		06AUG21	140	4.03	.	.	18.2
MR-DE-01-01	A	Cycle 5	Yes		20AUG21	142	3.54	.	.	19.9
MR-DE-01-01	A	Cycle 6	Yes		03SEP21	138	3.48	.	2.14	19.0

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory blood chemistry done</i>	<i>Reason if no</i>	<i>Date of chemistry sampling</i>	<i>Sodium [mval/L]</i>	<i>Potassium [mmol/L]</i>	<i>Magnesium [mmol/L]</i>	<i>Calcium [mmol/L]</i>	<i>ASAT [U/L]</i>
MR-DE-01-01	A	Cycle 7	Yes		17SEP21	142	4.11	.	.	31.7
MR-DE-01-01	A	Cycle 8	Yes		04OCT21	137	3.71	.	.	17.1
MR-DE-01-01	A	Cycle 9	Yes		25OCT21	140	4.27	1.70	2.17	18.5
MR-DE-01-01	A	Cycle 10	Yes		02NOV21	140	3.27	.	2.21	14.8
MR-DE-01-01	A	EOT	Yes		25OCT21	140	4.27	1.70	2.17	18.5
MR-DE-02-01	B	Baseline	Yes		20APR21	140	4.80	0.82	2.34	29.0
MR-DE-02-01	B	Pre-cycle 1	Yes		26APR21	138	4.60	0.83	2.29	40.0
MR-DE-02-01	B	Pre-cycle 2	Yes		10MAY21	139	5.40	0.82	2.40	26.0
MR-DE-02-01	B	Pre-cycle 3	Yes		26MAY21	135	4.50	0.79	2.24	25.0
MR-DE-02-01	B	Pre-cycle 4	Yes		09JUN21	135	4.00	0.78	2.20	27.0
MR-DE-02-01	B	Cycle 1	Yes		29JUN21	137	4.30	0.77	2.24	20.0
MR-DE-02-01	B	Cycle 2	Yes		13JUL21	140	4.40	0.79	2.18	23.0
MR-DE-02-01	B	Cycle 3	Yes		02AUG21	138	4.30	0.78	2.21	18.0
MR-DE-02-01	B	Cycle 4	Yes		16AUG21	139	4.30	0.79	2.17	17.0
MR-DE-02-01	B	Cycle 5	Yes		13SEP21	140	4.30	0.73	2.22	18.0
MR-DE-02-01	B	Cycle 6	Yes		27SEP21	139	4.30	0.77	2.15	20.0
MR-DE-02-01	B	Cycle 7	Yes		11OCT21	142	4.50	0.80	2.18	16.0
MR-DE-02-01	B	EOT	Yes		13DEC21	142	4.50	0.82	2.32	24.0
MR-DE-02-02	A	Baseline	Yes		11MAY21	140	4.50	0.81	2.18	25.0
MR-DE-02-02	A	Pre-cycle 1	Yes		18MAY21	137	4.70	0.83	2.25	21.0
MR-DE-02-02	A	Pre-cycle 2	Yes		01JUN21	138	4.40	0.75	2.20	21.0
MR-DE-02-02	A	Pre-cycle 3	Yes		15JUN21	140	4.50	0.84	2.23	26.0
MR-DE-02-02	A	Pre-cycle 4	Yes		29JUN21	144	4.30	0.84	2.17	23.0
MR-DE-02-02	A	Cycle 1	Yes		20JUL21	142	4.40	0.83	2.36	28.0

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory blood chemistry done</i>	<i>Reason if no</i>	<i>Date of chemistry sampling</i>	<i>Sodium [mval/L]</i>	<i>Potassium [mmol/L]</i>	<i>Magnesium [mmol/L]</i>	<i>Calcium [mmol/L]</i>	<i>ASAT [U/L]</i>
MR-DE-02-02	A	Cycle 2	Yes		03AUG21	139	4.60	0.79	2.16	33.0
MR-DE-02-02	A	Cycle 3	Yes		17AUG21	138	4.20	0.78	2.21	32.0
MR-DE-02-02	A	Cycle 4	Yes		31AUG21	138	4.20	0.80	2.13	44.0
MR-DE-02-02	A	Cycle 5	Yes		14SEP21	138	4.60	0.78	2.14	40.0
MR-DE-02-02	A	Cycle 6	Yes		28SEP21	137	4.40	0.78	2.15	26.0
MR-DE-02-02	A	Cycle 7	Yes		12OCT21	141	.	0.74	2.20	.
MR-DE-02-02	A	Cycle 8	Yes		26OCT21	142	4.60	0.71	2.19	.
MR-DE-02-02	A	Cycle 9	Yes		09NOV21	140	4.40	0.69	2.14	35.0
MR-DE-02-02	A	Cycle 10	Yes		23NOV21	140	4.20	0.69	2.25	38.0
MR-DE-02-02	A	EOT	Yes		29DEC21	141	5.30	0.80	2.34	.
MR-DE-02-03	B	Baseline	Yes		12MAY21	139	5.10	0.94	2.27	186.0
MR-DE-02-03	B	Pre-cycle 1	Yes		19MAY21	133	4.30	0.85	2.36	109.0
MR-DE-02-03	B	Pre-cycle 2	Yes		02JUN21	134	4.10	0.79	2.35	73.0
MR-DE-02-03	B	Pre-cycle 3	Yes		16JUN21	139	4.20	0.89	2.22	72.0
MR-DE-02-03	B	Pre-cycle 4	Yes		29JUN21	140	3.90	0.88	2.26	66.0
MR-DE-02-03	B	Cycle 1	Yes		14JUL21	139	4.00	0.83	2.23	60.0
MR-DE-02-03	B	Cycle 2	Yes		04AUG21	139	4.30	.	2.28	56.0
MR-DE-02-03	B	Cycle 3	Yes		18AUG21	137	4.10	0.82	2.28	45.0
MR-DE-02-03	B	Cycle 4	Yes		30AUG21	140	3.80	0.84	2.31	49.0
MR-DE-02-03	B	Cycle 5	Yes		15SEP21	138	4.30	0.89	2.31	47.0
MR-DE-02-03	B	Cycle 6	Yes		29SEP21	138	3.80	0.84	2.24	52.0
MR-DE-02-03	B	EOT	Yes		08NOV21	139	4.70	82.00	2.31	71.0
MR-DE-14-01	A	Baseline	Yes		29DEC20	140	3.90	0.85	2.46	38.0
MR-DE-14-01	A	Pre-cycle 1	Yes		29DEC20	140	3.90	0.85	2.46	38.0

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory blood chemistry done</i>	<i>Reason if no</i>	<i>Date of chemistry sampling</i>	<i>Sodium [mval/L]</i>	<i>Potassium [mmol/L]</i>	<i>Magnesium [mmol/L]</i>	<i>Calcium [mmol/L]</i>	<i>ASAT [U/L]</i>
MR-DE-14-01	A	Pre-cycle 2	Yes		12JAN21	138	3.60	.	2.33	23.0
MR-DE-14-01	A	Pre-cycle 3	Yes		26JAN21	138	3.60	.	2.21	21.0
MR-DE-14-01	A	Pre-cycle 4	Yes		09FEB21	139	3.90	.	2.34	21.0
MR-DE-14-01	A	Pre-cycle 5	Yes		23FEB21	136	3.40	0.84	2.25	18.0
MR-DE-14-01	A	Cycle 1	Yes		09MAR21	139	3.70	2.43	2.28	20.0
MR-DE-14-01	A	Cycle 2	Yes		23MAR21	139	3.10	.	2.33	20.0
MR-DE-14-01	A	Cycle 3	Yes		07APR21	142	3.00	1.88	2.30	25.0
MR-DE-14-01	A	Cycle 4	Yes		20APR21	136	3.00	.	2.36	29.0
MR-DE-14-01	A	Cycle 5	Yes		04MAY21	139	3.20	.	2.26	28.0
MR-DE-14-01	A	Cycle 6	Yes		18MAY21	139	3.00	0.76	2.27	21.0
MR-DE-14-01	A	Cycle 7	Yes		01JUN21	141	2.90	0.93	2.31	20.0
MR-DE-14-01	A	Cycle 8	Yes		15JUN21	139	3.30	.	2.30	20.0
MR-DE-14-01	A	Cycle 9	Yes		29JUN21	142	3.50	.	2.31	20.0
MR-DE-14-01	A	Cycle 10	Yes		13JUL21	139	3.80	.	2.30	20.0
MR-DE-14-01	A	Cycle 12	No	Other: therapy paused as per clinical routine	.	.	.	.	.	.
MR-DE-14-01	A	Cycle 16	No	Other: medication paused as per local routine	.	.	.	.	.	.
MR-DE-14-01	A	Cycle 18	Yes		03NOV21	139	3.60	.	2.35	28.0
MR-DE-14-01	A	Cycle 19	Yes		17NOV21	140	3.60	.	2.23	24.0
MR-DE-14-01	A	Cycle 20	Yes		01DEC21	142	3.70	.	2.41	25.0
MR-DE-14-01	A	EOT	Yes		15DEC21	138	3.70	0.78	2.21	25.0
MR-DE-24-01	A	Baseline	Yes		13JUL21	140	4.19	0.90	2.26	47.0
MR-DE-24-01	A	Pre-cycle 1	Yes		22JUL21	142	4.15	.	2.31	.
MR-DE-24-01	A	Pre-cycle 2	Yes		05AUG21	142	4.16	.	2.24	.
MR-DE-24-01	A	Pre-cycle 3	Yes		18AUG21	142	3.71	.	2.32	.

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory blood chemistry done</i>	<i>Reason if no</i>	<i>Date of chemistry sampling</i>	<i>Sodium [mval/L]</i>	<i>Potassium [mmol/L]</i>	<i>Magnesium [mmol/L]</i>	<i>Calcium [mmol/L]</i>	<i>ASAT [U/L]</i>
MR-DE-24-01	A	Pre-cycle 4	Yes		31AUG21	144	3.54	.	2.38	.
MR-DE-24-01	A	Pre-cycle 5	Yes		14SEP21	145	3.98	.	2.31	.
MR-DE-24-01	A	Pre-cycle 6	Yes		28SEP21	141	3.77	.	2.36	.
MR-DE-24-01	A	Cycle 1	Yes		21OCT21	144	4.57	0.86	2.35	22.0
MR-DE-24-01	A	Cycle 2	Yes		02NOV21	143	4.69	0.86	2.38	23.0
MR-DE-24-01	A	Cycle 3	Yes		16NOV21	145	3.75	.	2.37	.
MR-DE-24-01	A	Cycle 4	Yes		30NOV21	146	3.70	.	2.33	.
MR-DE-24-01	A	Cycle 5	Yes		14DEC21	142	3.33	.	2.12	.
MR-DE-24-01	A	Cycle 6	Yes		28DEC21	144	3.42	.	2.17	.
MR-DE-24-01	A	Cycle 7	Yes		11JAN22	142	3.82	0.62	2.25	31.0
MR-DE-24-01	A	Cycle 8	Yes		28JAN22	143	4.35	.	2.22	.
MR-DE-24-01	A	Cycle 9	Yes		11FEB22	147	4.35	.	2.26	.
MR-DE-24-01	A	Cycle 10	Yes		25FEB22	143	3.72	.	2.23	.
MR-DE-24-01	A	Cycle 11	Yes		11MAR22	142	3.46	.	2.20	.
MR-DE-24-01	A	Cycle 12	Yes		25MAR22	141	3.99	0.66	2.23	29.0
MR-DE-24-01	A	Cycle 13	Yes		08APR22	141	4.05	0.76	2.25	26.0
MR-DE-24-01	A	Cycle 14	Yes		22APR22	143	3.86	0.81	2.32	28.0
MR-DE-24-01	A	Cycle 15	Yes		06MAY22	144	4.15	0.83	2.26	27.0
MR-DE-24-01	A	Cycle 16	Yes		20MAY22	141	3.66	0.81	2.24	22.0
MR-DE-24-01	A	Cycle 17	Yes		07JUN22	141	3.61	.	2.27	25.0
MR-DE-24-01	A	EOT	No	Other: The last blood collection was 10.06.2022 control to AE.Next collection will be planed for 21.06.2022.	.	.	.	.	.	.

(Data source: Listing 17.1. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

MoLiMoR

Clinical Study Report

EudraCT-No. 2019-003714-14

<i>Patient No.</i>	<i>Arm</i>	<i>Date of chemistry sampling</i>	<i>ALAT [U/L]</i>	<i>Alkaline phosphatase [U/L]</i>	<i>Bilirubin (total)</i>	<i>GGT [U/L]</i>	<i>Urea [mg/dL]</i>	<i>Creatinine [mg/dL]</i>	<i>Creatinine-clearance [mL/s]</i>	<i>CRP [mg/dL]</i>
MR-DE-01-01	A	30APR21	45.6	97	0.42	19	12.30	0.71	.	0.425
MR-DE-01-01	A	.	.	.	.	.	.	.	.	.
MR-DE-01-01	A	14MAY21	43.3	87	0.29	25	8.20	0.64	.	0.425
MR-DE-01-01	A	31MAY21	50.4	96	0.28	31	12.60	0.69	.	0.425
MR-DE-01-01	A	14JUN21	36.2	.	0.32	30	12.60	0.74	.	0.425
MR-DE-01-01	A	28JUN21	56.3	94	0.26	40	13.60	0.70	.	0.470
MR-DE-01-01	A	08JUL21	38.4	92	0.42	36	13.10	0.74	.	0.425
MR-DE-01-01	A	23JUL21	23.8	103	0.20	38	11.70	0.68	.	0.600
MR-DE-01-01	A	06AUG21	21.9	110	0.29	28	9.20	0.70	.	2.100
MR-DE-01-01	A	20AUG21	24.2	126	0.26	29	8.80	0.70	.	2.200
MR-DE-01-01	A	03SEP21	23.0	132	0.27	28	8.90	0.64	.	1.370
MR-DE-01-01	A	17SEP21	41.9	132	0.20	39	10.50	0.68	.	1.020
MR-DE-01-01	A	04OCT21	25.8	115	0.32	35	12.10	0.63	.	0.560
MR-DE-01-01	A	25OCT21	17.4	119	0.59	15	13.70	0.68	.	0.425
MR-DE-01-01	A	02NOV21	30.4	138	0.36	49	8.80	0.54	.	1.780
MR-DE-01-01	A	25OCT21	17.4	119	0.59	15	13.70	0.68	.	0.425
MR-DE-02-01	B	20APR21	32.0	69	0.50	64	36.00	1.09	84.000	0.100
MR-DE-02-01	B	26APR21	49.0	66	0.40	66	33.00	1.06	87.000	0.100
MR-DE-02-01	B	10MAY21	48.0	69	0.20	154	27.00	1.09	84.000	0.100
MR-DE-02-01	B	26MAY21	48.0	66	0.20	110	28.00	0.95	99.000	0.100
MR-DE-02-01	B	09JUN21	129.0	71	0.40	403	32.00	1.10	83.000	0.100
MR-DE-02-01	B	29JUN21	30.0	68	0.30	207	29.00	0.99	94.000	0.100
MR-DE-02-01	B	13JUL21	46.0	67	0.20	213	24.00	0.91	104.000	0.200
MR-DE-02-01	B	02AUG21	25.0	68	0.20	117	34.00	1.14	79.000	0.100



<i>Patient No.</i>	<i>Arm</i>	<i>Date of chemistry sampling</i>	<i>ALAT [U/L]</i>	<i>Alkaline phosphatase [U/L]</i>	<i>Bilirubin (total)</i>	<i>GGT [U/L]</i>	<i>Urea [mg/dL]</i>	<i>Creatinine [mg/dL]</i>	<i>Creatinine-clearance [mL/s]</i>	<i>CRP [mg/dL]</i>
MR-DE-02-01	B	16AUG21	30.0	57	0.20	125	23.00	0.95	99.000	0.100
MR-DE-02-01	B	13SEP21	25.0	65	0.30	92	32.00	1.09	84.000	0.100
MR-DE-02-01	B	27SEP21	32.0	59	0.20	82	34.00	0.98	95.000	0.100
MR-DE-02-01	B	11OCT21	29.0	57	0.20	78	30.00	0.91	104.000	0.100
MR-DE-02-01	B	13DEC21	31.0	81	0.60	61	30.00	1.12	81.000	0.100
MR-DE-02-02	A	11MAY21	23.0	73	0.50	23	32.00	0.95	82.000	0.500
MR-DE-02-02	A	18MAY21	20.0	70	0.50	20	26.00	0.96	81.000	0.500
MR-DE-02-02	A	01JUN21	27.0	60	0.70	22	28.00	0.99	78.000	0.100
MR-DE-02-02	A	15JUN21	32.0	60	0.50	23	30.00	1.05	73.000	0.100
MR-DE-02-02	A	29JUN21	31.0	61	0.60	23	28.00	1.02	76.000	0.200
MR-DE-02-02	A	20JUL21	30.0	68	0.70	24	34.00	1.19	63.000	0.500
MR-DE-02-02	A	03AUG21	38.0	60	0.40	26	21.00	0.92	86.000	0.200
MR-DE-02-02	A	17AUG21	48.0	67	0.50	30	21.00	0.94	84.000	0.400
MR-DE-02-02	A	31AUG21	72.0	72	0.50	33	24.00	0.92	86.000	0.700
MR-DE-02-02	A	14SEP21	67.0	78	0.60	32	25.00	1.02	76.000	0.400
MR-DE-02-02	A	28SEP21	36.0	78	0.70	30	18.00	0.95	82.000	0.700
MR-DE-02-02	A	12OCT21	59.0	91	0.40	38	22.00	0.91	87.000	0.500
MR-DE-02-02	A	26OCT21	57.0	83	0.60	30	16.00	0.93	85.000	0.400
MR-DE-02-02	A	09NOV21	63.0	85	0.40	30	16.00	0.81	92.000	0.300
MR-DE-02-02	A	23NOV21	65.0	85	0.50	33	20.00	0.85	90.000	0.300
MR-DE-02-02	A	29DEC21	54.0	97	0.40	24	27.00	0.95	82.000	0.300
MR-DE-02-03	B	12MAY21	361.0	393	0.70	623	36.00	0.77	106.000	0.700
MR-DE-02-03	B	19MAY21	231.0	448	2.30	513	25.00	0.80	104.000	1.400
MR-DE-02-03	B	02JUN21	148.0	467	1.90	502	24.00	0.79	105.000	1.000

<i>Patient No.</i>	<i>Arm</i>	<i>Date of chemistry sampling</i>	<i>ALAT [U/L]</i>	<i>Alkaline phosphatase [U/L]</i>	<i>Bilirubin (total)</i>	<i>GGT [U/L]</i>	<i>Urea [mg/dL]</i>	<i>Creatinine [mg/dL]</i>	<i>Creatinine-clearance [mL/s]</i>	<i>CRP [mg/dL]</i>
MR-DE-02-03	B	16JUN21	142.0	540	1.70	651	22.00	0.82	102.000	1.000
MR-DE-02-03	B	29JUN21	126.0	482	1.40	614	24.00	0.90	99.000	0.600
MR-DE-02-03	B	14JUL21	110.0	446	1.70	636	23.00	0.76	106.000	0.500
MR-DE-02-03	B	04AUG21	73.0	474	1.50	484	21.00	0.85	101.000	1.000
MR-DE-02-03	B	18AUG21	77.0	430	1.60	508	27.00	0.78	105.000	0.500
MR-DE-02-03	B	30AUG21	94.0	453	1.80	669	25.00	0.82	102.000	0.800
MR-DE-02-03	B	15SEP21	81.0	482	2.00	735	17.00	0.77	105.000	0.800
MR-DE-02-03	B	29SEP21	82.0	498	1.90	676	16.00	0.71	109.000	1.400
MR-DE-02-03	B	08NOV21	104.0	535	5.20	549	22.00	0.64	113.000	2.100
MR-DE-14-01	A	29DEC20	36.0	125	0.80	141	40.00	0.89	109.720	9.200
MR-DE-14-01	A	29DEC20	36.0	125	0.80	141	40.00	0.89	109.720	9.200
MR-DE-14-01	A	12JAN21	25.0	127	0.50	112	35.00	0.87	111.690	5.700
MR-DE-14-01	A	26JAN21	27.0	92	0.70	113	39.00	1.05	91.491	9.000
MR-DE-14-01	A	09FEB21	21.0	91	0.80	92	42.00	0.98	97.600	5.980
MR-DE-14-01	A	23FEB21	21.0	81	0.90	77	43.00	0.88	108.200	7.500
MR-DE-14-01	A	09MAR21	19.0	82	1.20	60	45.00	1.01	94.800	6.800
MR-DE-14-01	A	23MAR21	23.0	78	1.10	61	40.00	0.83	115.010	3.840
MR-DE-14-01	A	07APR21	25.0	78	1.20	54	35.00	0.93	104.180	7.100
MR-DE-14-01	A	20APR21	29.0	78	1.20	49	34.00	0.90	108.500	13.400
MR-DE-14-01	A	04MAY21	24.0	82	0.70	43	33.00	0.85	113.590	7.970
MR-DE-14-01	A	18MAY21	26.0	80	0.60	43	29.00	0.94	103.890	3.700
MR-DE-14-01	A	01JUN21	23.0	74	0.60	43	32.00	0.90	107.890	5.600
MR-DE-14-01	A	15JUN21	19.0	82	0.90	44	31.00	0.94	105.050	5.960
MR-DE-14-01	A	29JUN21	22.0	79	0.70	44	32.00	0.90	113.380	1.500

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Clinical Study Report

EudraCT-No. 2019-003714-14

<i>Patient No.</i>	<i>Arm</i>	<i>Date of chemistry sampling</i>	<i>ALAT [U/L]</i>	<i>Alkaline phosphatase [U/L]</i>	<i>Bilirubin (total)</i>	<i>GGT [U/L]</i>	<i>Urea [mg/dL]</i>	<i>Creatinine [mg/dL]</i>	<i>Creatinine-clearance [mL/s]</i>	<i>CRP [mg/dL]</i>
MR-DE-14-01	A	13JUL21	20.0	79	0.50	45	41.00	0.96	107.440	2.800
MR-DE-14-01	A	.	.	.	.	.	.	.	.	.
MR-DE-14-01	A	.	.	.	.	.	.	.	.	.
MR-DE-14-01	A	03NOV21	22.0	149	0.90	164	33.00	0.90	111.940	16.800
MR-DE-14-01	A	17NOV21	25.0	171	0.50	171	32.00	1.00	98.580	15.500
MR-DE-14-01	A	01DEC21	27.0	161	0.40	162	38.00	1.03	95.710	10.900
MR-DE-14-01	A	15DEC21	26.0	140	0.60	192	40.00	1.10	87.650	3.800
MR-DE-24-01	A	13JUL21	28.0	167	0.45	260	.	.	105.000	2.700
MR-DE-24-01	A	22JUL21	18.0	177	0.47	.	.	0.95	81.100	3.000
MR-DE-24-01	A	05AUG21	13.0	109	0.23	.	.	1.02	74.700	1.000
MR-DE-24-01	A	18AUG21	12.0	86	0.38	.	.	1.17	67.700	0.900
MR-DE-24-01	A	31AUG21	15.0	78	0.48	.	.	1.22	60.700	0.300
MR-DE-24-01	A	14SEP21	11.0	66	0.49	.	.	0.98	78.200	0.100
MR-DE-24-01	A	28SEP21	12.0	63	0.53	.	.	0.97	79.200	0.100
MR-DE-24-01	A	21OCT21	19.0	62	0.30	28	28.40	0.99	.	0.300
MR-DE-24-01	A	02NOV21	20.0	66	0.42	29	31.70	0.94	82.100	0.100
MR-DE-24-01	A	16NOV21	22.0	63	0.46	.	4.35	0.86	90.900	0.000
MR-DE-24-01	A	30NOV21	27.0	62	0.49	.	.	0.80	98.900	0.100
MR-DE-24-01	A	14DEC21	26.0	56	0.30	20	.	0.74	106.000	0.100
MR-DE-24-01	A	28DEC21	28.0	64	0.25	27	.	0.94	125.000	0.000
MR-DE-24-01	A	11JAN22	30.0	72	0.36	27	38.70	0.96	155.000	0.000
MR-DE-24-01	A	28JAN22	29.0	68	0.43	25	.	0.87	146.000	0.000
MR-DE-24-01	A	11FEB22	29.0	77	0.33	24	.	0.95	192.000	0.000
MR-DE-24-01	A	25FEB22	27.0	81	0.25	22	.	0.92	219.000	0.100

<i>Patient No.</i>	<i>Arm</i>	<i>Date of chemistry sampling</i>	<i>ALAT [U/L]</i>	<i>Alkaline phosphatase [U/L]</i>	<i>Bilirubin (total)</i>	<i>GGT [U/L]</i>	<i>Urea [mg/dL]</i>	<i>Creatinine [mg/dL]</i>	<i>Creatinine-clearance [mL/s]</i>	<i>CRP [mg/dL]</i>
MR-DE-24-01	A	11MAR22	28.0	90	0.32	24	25.30	0.78	.	0.100
MR-DE-24-01	A	25MAR22	24.0	94	0.28	26	28.80	0.85	173.000	0.000
MR-DE-24-01	A	08APR22	23.0	95	0.24	29	35.50	0.95	.	0.200
MR-DE-24-01	A	22APR22	23.0	104	0.28	42	33.80	0.99	77.100	0.000
MR-DE-24-01	A	06MAY22	21.0	135	0.21	49	43.20	1.15	64.900	1.400
MR-DE-24-01	A	20MAY22	15.0	102	0.23	44	.	1.12	66.900	0.700
MR-DE-24-01	A	07JUN22	17.0	117	0.41	40	.	1.10	91.000	9.900
MR-DE-24-01	A	.	.	.	.	.	.	.	.	.

(Data source: Listing 17.2. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory tumor markers done</i>	<i>Reason if no</i>	<i>Date of tumor markers sampling</i>	<i>CEA [µg/L]</i>	<i>CA 19-9 [U/L]</i>
MR-DE-01-01	A	Baseline	Yes		30APR21	190.40	872.10
MR-DE-01-01	A	Pre-cycle 1	No	Other: same like baseline	.	.	.
MR-DE-01-01	A	Pre-cycle 2	No	Missed by site	.	.	.
MR-DE-01-01	A	Pre-cycle 3	Yes		31MAY21	24.46	157.00
MR-DE-01-01	A	Pre-cycle 4	No	Other: done at 11.06.2021	.	.	.
MR-DE-01-01	A	Cycle 1	Yes		05JUL21	2.75	24.51
MR-DE-01-01	A	Cycle 2	No	Missed by site	.	.	.
MR-DE-01-01	A	Cycle 3	Yes		23JUL21	1.90	11.41
MR-DE-01-01	A	Cycle 4	Yes		06AUG21	1.75	8.50
MR-DE-01-01	A	Cycle 5	Yes		20AUG21	2.36	7.50
MR-DE-01-01	A	Cycle 6	Yes		03SEP21	2.33	6.31

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory tumor markers done</i>	<i>Reason if no</i>	<i>Date of tumor markers sampling</i>	<i>CEA [µg/L]</i>	<i>CA 19-9 [U/L]</i>
MR-DE-01-01	A	Cycle 7	Yes		17SEP21	2.60	7.47
MR-DE-01-01	A	Cycle 8	Yes		04OCT21	.	6.86
MR-DE-01-01	A	Cycle 9	Yes		25OCT21	1.94	7.49
MR-DE-01-01	A	Cycle 10	No	Other: operation	.	.	.
MR-DE-01-01	A	EOT	Yes		25OCT21	1.94	7.49
MR-DE-02-01	B	Baseline	Yes		20APR21	2.20	16.40
MR-DE-02-01	B	Pre-cycle 1	Yes		26APR21	1.80	14.10
MR-DE-02-01	B	Pre-cycle 2	Yes		10MAY21	2.60	18.50
MR-DE-02-01	B	Pre-cycle 3	Yes		26MAY21	2.20	20.00
MR-DE-02-01	B	Pre-cycle 4	Yes		09JUN21	2.30	24.60
MR-DE-02-01	B	Cycle 1	Yes		29JUN21	3.00	20.50
MR-DE-02-01	B	Cycle 2	Yes		13JUL21	2.80	22.10
MR-DE-02-01	B	Cycle 3	Yes		02AUG21	2.30	19.30
MR-DE-02-01	B	Cycle 4	Yes		16AUG21	21.40	2.60
MR-DE-02-01	B	Cycle 5	Yes		13SEP21	2.20	19.50
MR-DE-02-01	B	Cycle 6	Yes		27SEP21	3.00	20.60
MR-DE-02-01	B	Cycle 7	Yes		11OCT21	2.30	19.60
MR-DE-02-01	B	EOT	Yes		13DEC21	1.60	20.70
MR-DE-02-02	A	Baseline	Yes		11MAY21	1.90	21.70
MR-DE-02-02	A	Pre-cycle 1	Yes		18MAY21	2.30	27.00
MR-DE-02-02	A	Pre-cycle 2	Yes		01JUN21	1.10	25.90
MR-DE-02-02	A	Pre-cycle 3	Yes		15JUN21	1.00	21.80
MR-DE-02-02	A	Pre-cycle 4	Yes		29JUN21	1.20	25.40
MR-DE-02-02	A	Cycle 1	Yes		20JUL21	1.30	.

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory tumor markers done</i>	<i>Reason if no</i>	<i>Date of tumor markers sampling</i>	<i>CEA [µg/L]</i>	<i>CA 19-9 [U/L]</i>
MR-DE-02-02	A	Cycle 2	Yes		03AUG21	1.30	26.70
MR-DE-02-02	A	Cycle 3	Yes		17AUG21	1.30	32.20
MR-DE-02-02	A	Cycle 4	Yes		31AUG21	1.30	26.30
MR-DE-02-02	A	Cycle 5	Yes		14SEP21	1.40	28.90
MR-DE-02-02	A	Cycle 6	Yes		28SEP21	1.50	24.40
MR-DE-02-02	A	Cycle 7	Yes		12OCT21	1.40	27.30
MR-DE-02-02	A	Cycle 8	Yes		26OCT21	1.80	33.10
MR-DE-02-02	A	Cycle 9	Yes		09NOV21	1.60	35.30
MR-DE-02-02	A	Cycle 10	Yes		23NOV21	1.60	29.10
MR-DE-02-02	A	EOT	Yes		28DEC21	1.60	23.60
MR-DE-02-03	B	Baseline	Yes		12MAY21	20.10	1934.00
MR-DE-02-03	B	Pre-cycle 1	Yes		19MAY21	26.20	2236.00
MR-DE-02-03	B	Pre-cycle 2	Yes		02JUN21	22.10	1648.00
MR-DE-02-03	B	Pre-cycle 3	Yes		16JUN21	20.30	998.00
MR-DE-02-03	B	Pre-cycle 4	Yes		29JUN21	15.10	755.00
MR-DE-02-03	B	Cycle 1	Yes		14JUL21	14.90	593.00
MR-DE-02-03	B	Cycle 2	Yes		04AUG21	11.70	521.00
MR-DE-02-03	B	Cycle 3	Yes		18AUG21	14.10	671.00
MR-DE-02-03	B	Cycle 4	Yes		30AUG21	14.10	623.00
MR-DE-02-03	B	Cycle 5	Yes		15SEP21	15.70	655.00
MR-DE-02-03	B	Cycle 6	Yes		29SEP21	16.20	578.00
MR-DE-02-03	B	EOT	Yes		08NOV21	36.70	2764.00
MR-DE-14-01	A	Baseline	Yes		08DEC20	268.00	1055.00
MR-DE-14-01	A	Pre-cycle 1	Yes		08DEC20	268.00	1055.00

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory tumor markers done</i>	<i>Reason if no</i>	<i>Date of tumor markers sampling</i>	<i>CEA [µg/L]</i>	<i>CA 19-9 [U/L]</i>
MR-DE-14-01	A	Pre-cycle 2	Yes		12JAN21	264.00	1180.00
MR-DE-14-01	A	Pre-cycle 3	Yes		26JAN21	242.00	1100.00
MR-DE-14-01	A	Pre-cycle 4	Yes		09FEB21	162.00	747.00
MR-DE-14-01	A	Pre-cycle 5	Yes		23FEB21	118.00	543.00
MR-DE-14-01	A	Cycle 1	Yes		09MAR21	85.70	334.00
MR-DE-14-01	A	Cycle 2	Yes		23MAR21	64.10	226.00
MR-DE-14-01	A	Cycle 3	Yes		07APR21	41.00	134.00
MR-DE-14-01	A	Cycle 4	Yes		20APR21	34.20	98.00
MR-DE-14-01	A	Cycle 5	No	Missed by site	.	.	.
MR-DE-14-01	A	Cycle 6	Yes		18MAY21	26.80	60.00
MR-DE-14-01	A	Cycle 7	Yes		01JUN21	31.50	67.00
MR-DE-14-01	A	Cycle 8	No	Missed by site	.	.	.
MR-DE-14-01	A	Cycle 9	No	Missed by site	.	.	.
MR-DE-14-01	A	Cycle 10	Yes		13JUL21	62.00	22.20
MR-DE-14-01	A	Cycle 12	No	Other: therapy paused as per clinical routine	.	.	.
MR-DE-14-01	A	Cycle 16	No	Other: medication paused as per local routine	.	.	.
MR-DE-14-01	A	Cycle 18	Yes		03NOV21	120.00	2137.00
MR-DE-14-01	A	Cycle 19	No	Missed by site	.	.	.
MR-DE-14-01	A	Cycle 20	No	Medical reason	.	.	.
MR-DE-14-01	A	EOT	Yes		15DEC21	55.50	695.00
MR-DE-24-01	A	Baseline	Yes		13JUL21	57.10	165.00
MR-DE-24-01	A	Pre-cycle 1	No	Missed by site	.	.	.
MR-DE-24-01	A	Pre-cycle 2	No	Missed by site	.	.	.
MR-DE-24-01	A	Pre-cycle 3	No	Missed by site	.	.	.

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Laboratory tumor markers done</i>	<i>Reason if no</i>	<i>Date of tumor markers sampling</i>	<i>CEA [µg/L]</i>	<i>CA 19-9 [U/L]</i>
MR-DE-24-01	A	Pre-cycle 4	Yes		01SEP21	37.20	79.10
MR-DE-24-01	A	Pre-cycle 5	Yes		15SEP21	32.20	58.40
MR-DE-24-01	A	Pre-cycle 6	Yes		28SEP21	31.80	53.90
MR-DE-24-01	A	Cycle 1	Yes		21OCT21	29.00	44.20
MR-DE-24-01	A	Cycle 2	No	Missed by site	.	.	.
MR-DE-24-01	A	Cycle 3	No	Missed by site	.	.	.
MR-DE-24-01	A	Cycle 4	Yes		30NOV21	32.60	30.40
MR-DE-24-01	A	Cycle 5	Yes		14DEC21	28.70	25.90
MR-DE-24-01	A	Cycle 6	Yes		29DEC21	29.90	25.00
MR-DE-24-01	A	Cycle 7	Yes		12JAN22	26.40	23.70
MR-DE-24-01	A	Cycle 8	Yes		31JAN22	24.30	21.30
MR-DE-24-01	A	Cycle 9	Yes		14FEB22	22.60	21.40
MR-DE-24-01	A	Cycle 10	Yes		28FEB22	19.00	18.80
MR-DE-24-01	A	Cycle 11	Yes		11MAR22	20.70	21.80
MR-DE-24-01	A	Cycle 12	No	Missed by site	.	.	.
MR-DE-24-01	A	Cycle 13	Yes		08APR22	15.60	13.10
MR-DE-24-01	A	Cycle 14	No	Other: according to the Protocol	.	.	.
MR-DE-24-01	A	Cycle 15	Yes		06MAY22	12.10	24.50
MR-DE-24-01	A	Cycle 16	Yes		20MAY22	12.60	24.90
MR-DE-24-01	A	Cycle 17	Yes		07JUN22	88.40	50.50
MR-DE-24-01	A	EOT	No	Medical reason	.	.	.

(Data source: Listing 18. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)



## 14.4 Other data

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Examinations and/or treatments performed</i>	<i>Reason if no</i>	<i>First day of cycle</i>	<i>Study treatment administered</i>	<i>Resection of metastases since last visit</i>	<i>Date of surgery</i>	<i>Resected metastases</i>
MR-DE-01-01	A	Pre-cycle 1	Yes		30APR21	Yes		.	
MR-DE-01-01	A	Pre-cycle 2	Yes		17MAY21	Yes		.	
MR-DE-01-01	A	Pre-cycle 3	Yes		31MAY21	Yes		.	
MR-DE-01-01	A	Pre-cycle 4	Yes		14JUN21	Yes		.	
MR-DE-01-01	A	Cycle 1	Yes		28JUN21	Yes	No	.	
MR-DE-01-01	A	Cycle 2	Yes		12JUL21	Yes	No	.	
MR-DE-01-01	A	Cycle 3	Yes		26JUL21	Yes	No	.	
MR-DE-01-01	A	Cycle 4	Yes		09AUG21	Yes	No	.	
MR-DE-01-01	A	Cycle 5	Yes		23AUG21	Yes	No	.	
MR-DE-01-01	A	Cycle 6	Yes		06SEP21	Yes	No	.	
MR-DE-01-01	A	Cycle 7	Yes		20SEP21	Yes	No	.	
MR-DE-01-01	A	Cycle 8	Yes		.	No	No	.	
MR-DE-01-01	A	Cycle 9	Yes		.	No	No	.	
MR-DE-01-01	A	Cycle 10	Yes		.	No	Yes	26OCT21	liver
MR-DE-02-01	B	Pre-cycle 1	Yes		26APR21	Yes		.	
MR-DE-02-01	B	Pre-cycle 2	Yes		10MAY21	Yes		.	
MR-DE-02-01	B	Pre-cycle 3	Yes		26MAY21	Yes		.	
MR-DE-02-01	B	Pre-cycle 4	Yes		09JUN21	Yes		.	
MR-DE-02-01	B	Cycle 1	Yes		29JUN21	Yes	No	.	
MR-DE-02-01	B	Cycle 2	Yes		13JUL21	Yes	No	.	
MR-DE-02-01	B	Cycle 3	Yes		02AUG21	Yes	No	.	
MR-DE-02-01	B	Cycle 4	Yes		16AUG21	Yes	No	.	

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Examinations and/or treatments performed</i>	<i>Reason if no</i>	<i>First day of cycle</i>	<i>Study treatment administered</i>	<i>Resection of metastases since last visit</i>	<i>Date of surgery</i>	<i>Resected metastases</i>
MR-DE-02-01	B	Cycle 5	Yes		13SEP21	Yes	No	.	
MR-DE-02-01	B	Cycle 6	Yes		27SEP21	Yes	No	.	
MR-DE-02-01	B	Cycle 7	Yes		11OCT21	Yes	No	.	
MR-DE-02-02	A	Pre-cycle 1	Yes		18MAY21	Yes		.	
MR-DE-02-02	A	Pre-cycle 2	Yes		01JUN21	Yes		.	
MR-DE-02-02	A	Pre-cycle 3	Yes		15JUN21	Yes		.	
MR-DE-02-02	A	Pre-cycle 4	Yes		29JUN21	Yes		.	
MR-DE-02-02	A	Cycle 1	Yes		20JUL21	Yes	No	.	
MR-DE-02-02	A	Cycle 2	Yes		03AUG21	Yes	No	.	
MR-DE-02-02	A	Cycle 3	Yes		17AUG21	Yes	No	.	
MR-DE-02-02	A	Cycle 4	Yes		31AUG21	Yes	No	.	
MR-DE-02-02	A	Cycle 5	Yes		14SEP21	Yes	No	.	
MR-DE-02-02	A	Cycle 6	Yes		28SEP21	Yes	No	.	
MR-DE-02-02	A	Cycle 7	Yes		12OCT21	Yes	No	.	
MR-DE-02-02	A	Cycle 8	Yes		26OCT21	Yes	No	.	
MR-DE-02-02	A	Cycle 9	Yes		09NOV21	Yes	No	.	
MR-DE-02-02	A	Cycle 10	Yes		23NOV21	Yes	No	.	
MR-DE-02-03	B	Pre-cycle 1	Yes		19MAY21	Yes		.	
MR-DE-02-03	B	Pre-cycle 2	Yes		02JUN21	Yes		.	
MR-DE-02-03	B	Pre-cycle 3	Yes		16JUN21	Yes		.	
MR-DE-02-03	B	Pre-cycle 4	Yes		30JUN21	Yes		.	
MR-DE-02-03	B	Cycle 1	Yes		14JUL21	Yes	No	.	
MR-DE-02-03	B	Cycle 2	Yes		04AUG21	Yes	No	.	
MR-DE-02-03	B	Cycle 3	Yes		18AUG21	Yes	No	.	

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<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Examinations and/or treatments performed</i>	<i>Reason if no</i>	<i>First day of cycle</i>	<i>Study treatment administered</i>	<i>Resection of metastases since last visit</i>	<i>Date of surgery</i>	<i>Resected metastases</i>
MR-DE-02-03	B	Cycle 4	Yes		01SEP21	Yes	No	.	
MR-DE-02-03	B	Cycle 5	Yes		15SEP21	Yes	No	.	
MR-DE-02-03	B	Cycle 6	Yes		29SEP21	Yes	No	.	
MR-DE-14-01	A	Pre-cycle 1	Yes		29DEC20	Yes		.	
MR-DE-14-01	A	Pre-cycle 2	Yes		12JAN21	Yes		.	
MR-DE-14-01	A	Pre-cycle 3	Yes		26JAN21	Yes		.	
MR-DE-14-01	A	Pre-cycle 4	Yes		09FEB21	Yes		.	
MR-DE-14-01	A	Pre-cycle 5	Yes		23FEB21	Yes		.	
MR-DE-14-01	A	Cycle 1	Yes		09MAR21	Yes	No	.	
MR-DE-14-01	A	Cycle 2	Yes		23MAR21	Yes	No	.	
MR-DE-14-01	A	Cycle 3	Yes		07APR21	Yes	No	.	
MR-DE-14-01	A	Cycle 4	Yes		20APR21	Yes	No	.	
MR-DE-14-01	A	Cycle 5	Yes		04MAY21	Yes	No	.	
MR-DE-14-01	A	Cycle 6	Yes		18MAY21	Yes	No	.	
MR-DE-14-01	A	Cycle 7	Yes		01JUN21	Yes	No	.	
MR-DE-14-01	A	Cycle 8	Yes		15JUN21	Yes	No	.	
MR-DE-14-01	A	Cycle 9	Yes		29JUN21	Yes	No	.	
MR-DE-14-01	A	Cycle 10	Yes		13JUL21	Yes	No	.	
MR-DE-14-01	A	Cycle 11	No	Other: therapy paused as per site routine	.		No	.	
MR-DE-14-01	A	Cycle 12	Yes		.	No	No	.	
MR-DE-14-01	A	Cycle 13	No	Other: therapy paused as per clinical routine	.		No	.	

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Examinations and/or treatments performed</i>	<i>Reason if no</i>	<i>First day of cycle</i>	<i>Study treatment administered</i>	<i>Resection of metastases since last visit</i>	<i>Date of surgery</i>	<i>Resected metastases</i>
MR-DE-14-01	A	Cycle 14	No	Other: medication paused as per local routine	.	.	No	.	.
MR-DE-14-01	A	Cycle 15	No	Other: medication paused as per local routine	.	.	No	.	.
MR-DE-14-01	A	Cycle 16	Yes		.	No	No	.	.
MR-DE-14-01	A	Cycle 17	No	Other: medication paused as per local routine	.	.	No	.	.
MR-DE-14-01	A	Cycle 18	Yes		03NOV21	Yes	No	.	.
MR-DE-14-01	A	Cycle 19	Yes		17NOV21	Yes	No	.	.
MR-DE-14-01	A	Cycle 20	Yes		01DEC21	Yes	No	.	.
MR-DE-24-01	A	Pre-cycle 1	Yes		22JUL21	Yes		.	.
MR-DE-24-01	A	Pre-cycle 2	Yes		05AUG21	Yes		.	.
MR-DE-24-01	A	Pre-cycle 3	Yes		18AUG21	Yes		.	.
MR-DE-24-01	A	Pre-cycle 4	Yes		01SEP21	Yes		.	.
MR-DE-24-01	A	Pre-cycle 5	Yes		15SEP21	Yes		.	.
MR-DE-24-01	A	Pre-cycle 6	Yes		29SEP21	Yes		.	.
MR-DE-24-01	A	Cycle 1	Yes		22OCT21	Yes	No	.	.
MR-DE-24-01	A	Cycle 2	Yes		03NOV21	Yes	No	.	.
MR-DE-24-01	A	Cycle 3	Yes		17NOV21	Yes	No	.	.
MR-DE-24-01	A	Cycle 4	Yes		01DEC21	Yes	No	.	.
MR-DE-24-01	A	Cycle 5	Yes		15DEC21	Yes	No	.	.
MR-DE-24-01	A	Cycle 6	Yes		29DEC21	Yes	No	.	.
MR-DE-24-01	A	Cycle 7	Yes		12JAN22	Yes	No	.	.

<i>Patient No.</i>	<i>Arm</i>	<i>Point in time</i>	<i>Examinations and/or treatments performed</i>	<i>Reason if no</i>	<i>First day of cycle</i>	<i>Study treatment administered</i>	<i>Resection of metastases since last visit</i>	<i>Date of surgery</i>	<i>Resected metastases</i>
MR-DE-24-01	A	Cycle 8	Yes		31JAN22	Yes	No	.	
MR-DE-24-01	A	Cycle 9	Yes		14FEB22	Yes	No	.	
MR-DE-24-01	A	Cycle 10	Yes		28FEB22	Yes	No	.	
MR-DE-24-01	A	Cycle 11	Yes		14MAR22	Yes	No	.	
MR-DE-24-01	A	Cycle 12	Yes		28MAR22	Yes	No	.	
MR-DE-24-01	A	Cycle 13	Yes		11APR22	Yes	No	.	
MR-DE-24-01	A	Cycle 14	Yes		25APR22	Yes	No	.	
MR-DE-24-01	A	Cycle 15	Yes		09MAY22	Yes	No	.	
MR-DE-24-01	A	Cycle 16	Yes		23MAY22	Yes	No	.	
MR-DE-24-01	A	Cycle 17	Yes		08JUN22	Yes	No	.	

(Data source: Listing 22.1. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

<i>Patient No.</i>	<i>Arm</i>	<i>EOT evaluation date</i>	<i>Reason for EOT</i>	<i>Resection date if resection performed</i>	<i>Resection status if resection performed</i>	<i>New tumor therapy since last study treatment</i>	<i>New therapy</i>	<i>Start date of new therapy</i>	<i>End date of new therapy</i>
MR-DE-01-01	A	26OCT21	Patient became eligible for resection	26OCT21	R0	No		.	.
MR-DE-02-01	B	13DEC21	Investigator's decision	.		No		.	.
MR-DE-02-02	A	29DEC21	Investigator's decision	.		No	Folfiri schema	14JUN22	22NOV22
MR-DE-02-02	A	29DEC21	Investigator's decision	.		No	Trifluridin/Tipiracil	16JAN23	.
MR-DE-02-03	B	08NOV21	Other: Disease Progression , clinical progression, and physicians decision	.		Yes	Folfox6 modified q2w	08NOV21	10DEC21
MR-DE-02-03	B	08NOV21	Other: Disease Progression , clinical progression, and physicians decision	.		Yes	Bevacizumab	10DEC21	10DEC21

<i>Patient No.</i>	<i>Arm</i>	<i>EOT evaluation date</i>	<i>Reason for EOT</i>	<i>Resection date if resection performed</i>	<i>Resection status if resection performed</i>	<i>New tumor therapy since last study treatment</i>	<i>New therapy</i>	<i>Start date of new therapy</i>	<i>End date of new therapy</i>
MR-DE-02-03	B	08NOV21	Other: Disease Progression , clinical progression, and physicians decision	.		Yes	Trifluridine/Tipiracil	21JAN22	18FEB22
MR-DE-02-03	B	08NOV21	Other: Disease Progression , clinical progression, and physicians decision	.		Yes	Panitumumab	04MAR22	06MAY22
MR-DE-02-03	B	08NOV21	Other: Disease Progression , clinical progression, and physicians decision	.		Yes	Sotorasib	04MAR22	06MAY22
MR-DE-14-01	A	15DEC21	Other: PD	.		No	Folfiri	29DEC21	18JAN22
MR-DE-14-01	A	15DEC21	Other: PD	.		No	Bevacizumab /FOLFOX	05JUL22	08DEC22
MR-DE-24-01	A	14JUN22	Other: Progressive Disease	.		Yes	Bevacizumab-/FOLFOX-Protokoll	22JUN22	.
MR-DE-24-01	A	14JUN22	Other: Progressive Disease	.		Yes	Lonsurf in combination with Bevacizumab analog to Sunlight Studie	25SEP23	.
MR-DE-24-01	A	14JUN22	Other: Progressive Disease	.		Yes	Bevacizumab in combintion with Longsurf analog to Sunlight Studie	28SEP23	.

(Data source: Listing 25.1. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

<i>Patient No.</i>	<i>Arm</i>	<i>Follow-up No.</i>	<i>Follow-up visit date</i>	<i>Contact with patient</i>	<i>Changes in new therapy since last visit</i>	<i>New therapy</i>	<i>Start date of new therapy</i>	<i>End date of new therapy</i>
MR-DE-01-01	A	1	03MAR22	In-house visit	No		.	.
MR-DE-01-01	A	2	17MAY22	Telephone call	No		.	.
MR-DE-02-01	B	1	16MAR22	In-house visit	No		.	.
MR-DE-02-01	B	2	04JUL22	In-house visit	No		.	.
MR-DE-02-01	B	3	18OCT22	In-house visit	No		.	.
MR-DE-02-01	B	4	10FEB23	In-house visit	No		.	.

<i>Patient No.</i>	<i>Arm</i>	<i>Follow-up No.</i>	<i>Follow-up visit date</i>	<i>Contact with patient</i>	<i>Changes in new therapy since last visit</i>	<i>New therapy</i>	<i>Start date of new therapy</i>	<i>End date of new therapy</i>
MR-DE-02-01	B	5	08MAY23	Telephone call	No		.	.
MR-DE-02-01	B	6	20JUL23	In-house visit	No		.	.
MR-DE-02-01	B	7	27OCT23	In-house visit	No		.	.
MR-DE-02-02	A	1	22MAR22	In-house visit	No		.	.
MR-DE-02-02	A	2	04MAY22	In-house visit	No		.	.
MR-DE-02-02	A	3	10AUG22	In-house visit	Yes	Folfiri schema	14JUN22	22NOV22
MR-DE-02-02	A	4	08NOV22	In-house visit	No		.	.
MR-DE-02-02	A	5	10FEB23	In-house visit	Yes	Trifluridin/Tipiracil	16JAN23	.
MR-DE-02-02	A	6	05MAY23	In-house visit	No		.	.
MR-DE-02-02	A	7	29AUG23	In-house visit	No		.	.
MR-DE-02-02	A	8	07NOV23	In-house visit	No		.	.
MR-DE-02-02	A	9	01FEB24	Telephone call	No		.	.
MR-DE-02-02	A	10	30APR24	In-house visit	No		.	.
MR-DE-02-02	A	11	11JUN24	In-house visit	No		.	.
MR-DE-02-03	B	1	31JAN22	Telephone call	Yes	Bevacizumab	10DEC21	10DEC21
MR-DE-02-03	B	1	31JAN22	Telephone call	Yes	Folfox6 modified q2w	08NOV21	10DEC21
MR-DE-02-03	B	1	31JAN22	Telephone call	Yes	Trifluridine/Tipiracil	21JAN22	18FEB22
MR-DE-02-03	B	2	21MAR22	In-house visit	Yes	Panitumumab	04MAR22	06MAY22
MR-DE-02-03	B	2	21MAR22	In-house visit	Yes	Sotorasib	04MAR22	06MAY22
MR-DE-02-03	B	3	03MAY22	In-house visit	No		.	.
MR-DE-14-01	A	1	18JAN22	In-house visit	No	Folfiri	29DEC21	18JAN22
MR-DE-14-01	A	2	28MAR22	In-house visit	Yes		.	.
MR-DE-14-01	A	3	05JUL22	In-house visit	Yes	Bevacizumab /FOLFOX	05JUL22	08DEC22

Patient No.	Arm	Follow-up No.	Follow-up visit date	Contact with patient	Changes in new therapy since last visit		New therapy	Start date of new therapy	End date of new therapy
MR-DE-14-01	A	4	27SEP22	In-house visit	No			.	.
MR-DE-14-01	A	5	09JAN23	In-house visit	Yes			.	.
MR-DE-14-01	A	6	28APR23	Telephone call	No			.	.
MR-DE-24-01	A	1	15SEP22	In-house visit	Yes	Bevacizumab-/FOLFOX-Protokoll		22JUN22	.
MR-DE-24-01	A	2	13DEC22	In-house visit	No			.	.
MR-DE-24-01	A	3	07MAR23	In-house visit	No			.	.
MR-DE-24-01	A	4	23MAY23	In-house visit	No			.	.
MR-DE-24-01	A	5	25AUG23	In-house visit	No	Bevacizumab in combintion with Longsurf analog to Sunlight Studie		28SEP23	.
MR-DE-24-01	A	5	25AUG23	In-house visit	No	Lonsurf in combination with Bevacizumab analog to Sunlight Studie		25SEP23	.

(Data source: Listing 26.1. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

Death related AE if applicable											
Patient No.	Arm	Date of last contact	Reason for end of study	Date of death if applicable	Reason of death if applicable	Grade	Term	Other	Death related disease if applicable	Date of withdrawal if applicable	Reason for withdrawal if applicable
MR-DE-01-01	A	17MAY22	Patient died	17MAY22	Adverse event related	5	Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	mutated metastatic colorectal cancer		.	
MR-DE-02-01	B	27OCT23	Patient died	27OCT23	Carcinoma related	.				.	
MR-DE-02-02	A	11JUN24	Study closed / terminated	.	.	.				.	
MR-DE-02-03	B	15MAY22	Patient died	15MAY22	Other: disease progression	.				.	



Death related AE if applicable											
Patient No.	Arm	Date of last contact	Reason for end of study	Date of death if applicable	Reason of death if applicable	Grade	Term	Other	Death related disease if applicable	Date of withdrawal if applicable	Reason for withdrawal if applicable
MR-DE-14-01	A	28APR23	Patient died	28APR23	Other: unknown reason, no letter available	.					.
MR-DE-24-01	A	23OCT23	Patient died	27OCT23	Adverse event related	5	Gastric ulcer				.

(Data source: Listing 27. MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06)

## 15 LIST OF REFERENCES

- Aljehani MA, Morgan JW, Guthrie LA, Jabo B, Ramadan M, Bahjri K, Lum SS, Selleck M, et al. Association of Primary Tumor Site With Mortality in Patients Receiving Bevacizumab and Cetuximab for Metastatic Colorectal Cancer. *JAMA Surg.* 2018 Jan 1;153(1):60-67  
American Cancer Society. Cancer facts and figures 2018.
- Basu AS. Digital Assays Part I: Partitioning Statistics and Digital PCR. *SLAS Technology* 2017, Vol. 22(4) 369–386
- Bettgowda C, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, Bartlett BR, Wang H, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci Transl Med.* 2014 Feb 19; 6(224):224ra24. doi: 10.1126/scitranslmed.3007094.
- Ciombor KK, Bekaii-Saab T. A Comprehensive Review of Sequencing and Combination Strategies of Targeted Agents in Metastatic Colorectal Cancer. *Oncologist.* 2018 Jan; 23(1):25-34. doi: 10.1634/theoncologist.2017-0203. Epub 2017 Oct 11.  
colorectal-cancer-statistics (last accessed on 17.12.2024)
- Cremolini C, Rossini D, Dell'Aquila E, Lonardi S, Conca E, Del Re M, et al. Rechallenge for Patients With RAS and BRAF Wild-Type Metastatic Colorectal Cancer With Acquired Resistance to First-line Cetuximab and Irinotecan: A Phase 2 Single-Arm Clinical Trial. *JAMA Oncol.* 2018.
- De Roock W, Claes B, Bernasconi D, De Schutter J, Biesmans B, Fountzilas G, Kalogeras KT, 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.
- Diaz LA Jr, Williams RT, Wu J, Kinde I, Hecht JR, Berlin J, Allen B, et al. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. *Nature.* 2012 Jun 28; 486(7404):537-40. doi: 10.1038/nature11219.
- Garrigou S, Perkins G, Garlan F, Normand C, Didelot A, Le Corre D, Peyvandi S, et al. A Study of Hypermethylated Circulating Tumor DNA as a Universal Colorectal Cancer Biomarker. *Clin Chem.* 2016 Aug;62(8):1129-39. doi:10.1373/clinchem.2015.253609.
- Grasselli J, Elez E, Caratù G, Matito J, Santos C, Macarulla T, Vidal J, et al. Concordance of blood- and tumor-based detection of RAS mutations to guide anti-EGFR therapy in metastatic colorectal cancer. *Ann Oncol.* 2017 Jun 1;28(6):1294-1301. doi: 10.1093/annonc/mdx112.
- Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2014 Sep;15(10):1065-75. doi:10.1016/S1470-2045(14)70330-4. Epub 2014 Jul 31.
- <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-andstatistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf>. (last accessed on 17.12.2024)
- Investigator's Brochure Cetuximab version 23 -release-17-april-2018
- Khan KH, Cunningham D, Werner B, Vlachogiannis G, Spiteri I, Heide T, et al. Longitudinal Liquid Biopsy and Mathematical Modeling of Clonal Evolution Forecast Time to Treatment Failure in the PROSPECT-C Phase II Colorectal Cancer Clinical Trial. *Cancer discovery.* 2018;8(10):1270-85.

Klein-Scory S, Maslova M, Pohl M, Eilert-Micus C, Schroers R, Schmiegel W, et al. Significance of Liquid Biopsy for Monitoring and Therapy Decision of Colorectal Cancer. *Transl Oncol*. 2018; 11(2):213-20.

Klein-Scory S, Wahner I, Maslova M, Al-Sewaidi Y, Pohl M, Mika T, Ladigan S, et al. SO-33 Clonal selection of RAS mutant metastatic colorectal cancer into RAS wild-type during first-line therapy. *Ann.Oncol*. 2020; 31(3): 229. doi: 10.1016/j.annonc.2020.04.049

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Kolorektales Karzinom, Langversion 2.1, 2019, AWMF Registrierungsnummer: 021/007OL, <http://www.leitlinienprogramm.onkologie.de/leitlinien/kolorektales-karzinom/> last accessed on: 18.12.2024

Masuishi, T., Tsuji, A., Kotaka, M. et al. Phase 2 study of irinotecan plus cetuximab rechallenging as third-line treatment in KRAS wild-type metastatic colorectal cancer: JACCRO CC-08. *Br J Cancer* **123**, 1490–1495 (2020). <https://doi.org/10.1038/s41416-020-01042-w>

Morelli MP, Overman MJ, Dasari A, Kazmi SM, Mazard T, Vilar E, et al. Characterizing the patterns of clonal selection in circulating tumor DNA from patients with colorectal cancer refractory to anti-EGFR treatment. *Ann Oncol*. 2015;26(4):731-6.

Petrelli F, Ardito R, Ghidini A, Zaniboni A, Ghidini M, Barni S, Tomasello G. Different Toxicity of Cetuximab and Panitumumab in Metastatic Colorectal Cancer Treatment: A Systematic Review and Meta-Analysis. *Oncology*. 2018; 94(4):191-199. doi: 10.1159/000486338. Epub 2018 Jan 23.

Roperch JP, Incitti R, Forbin S, Bard F, Mansour H, Mesli F, Baumgaertner I, et al. Aberrant methylation of NPY, PENK, and WIF1 as a promising marker for blood-based diagnosis of colorectal cancer. *BMC Cancer*. 2013 Dec 1;13:566. doi:10.1186/1471-2407-13-566.

Schmiegel W, Scott RJ, Dooley S, Lewis W, Meldrum CJ, Pockney P, Draganic B, et al. Blood-based detection of RAS mutations to guide anti-EGFR therapy in colorectal cancer patients: concordance of results from circulating tumor DNA and tissue-based RAS testing. *Mol Oncol*. 2017 Feb;11(2):208-219. doi: 10.1002/1878-0261.12023. Epub 2017 Jan 20.

Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, Nordlinger B, van de Velde CJ, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. *Ann Oncol*. 2012 Oct;23(10):2479-516.

Schwarzenbach H, Hoon DS, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. *Nat Rev Cancer*. 2011 Jun; 11(6):426-37. doi: 10.1038/nrc3066. Epub 2011 May 12.  
Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. *CA Cancer J Clin*. 2014 Mar-Apr; 64(2):104-17. doi: 10.3322/caac.21220. Epub 2014 Mar 17.

Siravegna G, Mussolin B, Buscarino M, Corti G, Cassingena A, Crisafulli G, et al. Clonal evolution and resistance to EGFR blockade in the blood of colorectal cancer patients. *Nat Med*. 2015;21(7):795-801.

Stintzing S, Modest DP, Rossius L, Lerch MM, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Held S, Giessen-Jung C, Moehler M, Jagenburg A, Kirchner T, Jung A, Heinemann V; FIRE-3 investigators. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIREDocuSign 3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. *Lancet Oncol*. 2016 Oct;17(10):1426-1434. doi: 10.1016/S1470-2045(16)30269-8.

Stroun M, Anker P, Maurice P, Lyautey J, Lederrey C, Beljanski M. Neoplastic characteristics of the DNA found in the plasma of cancer patients. *Oncology*. 1989; 46(5):318-22.

Sunakawa Y, Usher J, Satake H, Jaimes Y, Miyamoto Y, Makamura M, Kataoka M, et al. Gene mutation status in circulating tumor DNA (ctDNA) and 1st-line FOLFOXIRI plus bevacizumab (bev) in metastatic colorectal cancer (mCRC) harboring RAS mutation. ESMO 2018 congress.

Tabernero J, Ciardiello F, Rivera F, et al. Cetuximab administered once every second week to patients with metastatic colorectal cancer: a two-part pharmacokinetic/pharmacodynamic phase I dose-escalation study. *Ann Oncol*. 2010;21(7):1537-1545. doi:10.1093/annonc/mdp549

Taylor SC, Laperriere G, Germain H. Droplet Digital PCR versus qPCR for gene expression analysis with low abundant targets: from variable nonsense to publication quality data. *Sci Rep*. 2017 May 25; 7(1):2409. doi: 10.1038/s41598-017-02217-x.

Tejpar S, Stintzing S, Ciardiello F, Tabernero J, Van Cutsem E, Beier F, Esser R, et al. Prognostic and Predictive Relevance of Primary Tumor Location in Patients With RAS Wild-Type Metastatic Colorectal Cancer: Retrospective Analyses of the CRYSTAL and FIRE-3 Trials. *JAMA Oncol*. 2017 Feb 1; 3(2):194-201. doi: 0.1001/jamaoncol.2016.3797.

The Blood Profiling Atlas in Cancer (BloodPAC). Available from: <https://www.bloodpac.org/>, last accessed on 18.12.2024.

Thierry AR, El Messaoudi S, Gahan PB, Anker P, Stroun M. Origins, structures, and functions of circulating DNA in oncology. *Cancer Metastasis Rev*. 2016; 35(3):347– 376. doi:10.1007/s10555-016-9629-x

Toledo RA, Cubillo A, Vega E, Garralda E, Alvarez R, de la Varga LU, et al. Clinical validation of prospective liquid biopsy monitoring in patients with wild-type RAS metastatic colorectal cancer treated with FOLFIRI-cetuximab. *Oncotarget*. 2017;8(21):35289-300.

Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009 Apr 2;360(14):1408-17. doi: 10.1056/NEJMoa0805019.

Van Cutsem E, Lenz HJ, Köhne CH, Heinemann V, Tejpar S, Melezínek I, Beier F, Stroh C, et al. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. *J Clin Oncol*. 2015 Mar 1;33(7):692-700. doi: 10.1200/JCO.2014.59.4812.

van der Geest LG, Lam-Boer J, Koopman M, Verhoef C, Elferink MA, de Wilt JH. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. *Clin Exp Metastasis*. 2015 Jun;32(5):457-65. doi:10.1007/s10585-015-9719-0. Epub 2015 Apr 22.

Venook A, Niedzwiecki D, Innocenti F, Fruth B, Greene C, O'Neil BH, Shaw J, et al. Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance). *J Clin Oncol*. 2016; 34(15) (suppl): 3504

Wang W, Kong P, Ma G, Li L, Zhu J, Xia T, Xie H, Zhou W, Wang S. Characterization of the release and biological significance of cell-free DNA from breast cancer cell lines. *Oncotarget*. 2017; 8 (26):43180–43191. doi:10.18632/oncotarget.17858.

Wong AHN, Ma B, Lui RN. New developments in targeted therapy for metastatic colorectal cancer. *Ther Adv Med Oncol*. 2023;15: doi:10.1177/17588359221148540

World Cancer research Fund, <https://www.wcrf.org/dietandcancer/cancertrends/>  
Yamada T, Iwai T, Takahashi G, Kan H, Koizumi M, Matsuda A, et al. Utility of KRAS mutation detection using circulating cell-free DNA from patients with colorectal cancer. Cancer science. 2016;107(7):936-43.

## 16 APPENDICES

### 16.1 Study Information

#### 16.1.1 Study Protocol and Amendments

Available as stand-alone documents (see Section 16.5)

#### 16.1.2 Sample CRF

Available as stand-alone document (see Section 16.5)

#### 16.1.3 List of Ethics Committees

<i>Ethic committee</i>	<i>Address</i>
Ethikkommission der med. Fakultät der Ruhr-Universität Bochum	Gesundheitscampus 33 44801 Bochum
Ethikkommission bei der Landesärztekammer Nordrhein	Tersteegenstraße 9 40474 Düsseldorf
Ethikkommission der Universität Tübingen	Gartenstraße 47 72074 Tübingen
Ethikkommission an der Medizinischen Fakultät der Universität Leipzig Karl-Sudhoff-Institut	Liebigstraße 18 04103 Leipzig
Ethikkommission bei der Landesärztekammer Bayern	Mühlbaurstr. 16 81677 München
Ethik-Kommission des Landes Sachsen-Anhalt c/o Verbraucherschutz	Kühnauer Straße 70 06846 Dessau-Roßlau
Ethikkommission des Landes Bremen Institut für Klinische Pharmakologie	Sankt-Jürgen-Straße 1 28177 Bremen
Ethik-Kommission an der Medizinischen Fakultät der Universität Rostock	St.-Georg-Straße 108 18055 Rostock
Ethikkommission bei der Ärztekammer Niedersachsen	Karl-Wichert-Allee 18-22 30625 Hannover
Medizinische Ethikkommission der Carl von Ossietzky Universität Oldenburg	Ammerländer Heerstraße 114-118 26129 Oldenburg
Ethikkommission der Ärztekammer Westfalen-Lippe und der Westf. Wilhelms-Universität Münster	Gartenstraße 210 – 214 48147 Münster
Ethikkommission bei der Landesärztekammer Hessen	Hanauer Landstraße 152 60314 Frankfurt am Main
Ethikkommission bei der Landesärztekammer Brandenburg	Dreifertstraße 12 03044 Cottbus

Ethikkommission bei der Landesärztekammer Schleswig-Holstein	Bismarckallee 8-12 23795 Bad Segeberg
Ethikkommission der Ärztekammer Westfalen-Lippe und der Westf. Wilhelms-Universität Münster	Gartenstraße 210-214 48147 Münster
Ethikkommission der Medizinischen Fakultät Heidelberg	Alte Glockengießerei 11/ 1 69115 Heidelberg
Landesamt für Gesundheit und Soziales	Turmstr. 21 10559 Berlin
Ethikkommission der Medizinischen Universität Wien	Borschkegasse 8b/E06 1090 Wien
Ethikkommission der Medizinischen Fakultät der JKU	Wagner-Jauregg Weg 15 2020 Linz
Ethikkommission des Landes Vorarlberg	Römerstraße 15 6901 Bregenz

#### 16.1.4 List of Investigators and Other Important Participants in the Trial

*By-centre list of Investigators should show linkage of centres to the number of subjects enrolled*

<i>Organisation No.</i>	<i>Investigator</i>	<i>Organisation</i>	<i>Address</i>	<i>N Enrolled patients</i>
Sites reported to the relevant ethics committee but not further initiated				
	Dr. med. Martin Fuchs	Städtisches Klinikum München, München Klinik Bogenhausen	Englschalkinger Straße 77 81925 München	
	Dr. med. Jörg-Dietrich Neumann	Krankenhaus St. Joseph-Stift Bremen	Schwachhauser Heerstraße 54 28209 Bremen	
	Prof. Dr. med. Gerhard Heil	Märkische Kliniken GmbH Klinikum Lüdenscheid	Paulmannshöher Straße 14 585151 Lüdenscheid	
	Prof. Dr. med. Tom Michael Ganten	Fürst-Stirum-Klinik Bruchsal	Gutleutstraße 1-14 76646 Bruchsal	
	Dr. med. Gita Maher	Vivantes Klinikum im Friedrichshain	Landsberger Allee 49 10249 Berlin	
	Dr. Georg Schreil	OgG GmbH, Pyhrn-Eisenwurzen Klinikum Steyr	Sierninger Straße 170, 4400 Steyr.	
	Prof. Dr. Gerald Prager	Medizinische Universität Wien,	Währinger Gürtel 18-20, 1090 Wien.	
Sites reported to the relevant ethics committee and initiated				

MoLiMoR	Clinical Study Report			EduraCT-No. 2019-003714-14
AT-03	PD Dr. Thomas Winder	Landeskrankenhaus Feldkirch,	Carinagasse 47, 6800 Feldkirch.	
DE-01	Prof. Dr. med. Roland Schroers	Medizinische Universitätsklinik Bochum	In der Schornau 23-25 44892 Bochum	1
DE-02	Prof. Dr. med. Michael Stahl	Kliniken-Essen-Mitte Evang. Huyssens-Stiftung	Henrichstr. 92 45136 Essen	3
DE-03	PD Dr. med. Ulrich Hacker	Universitätsklinikum Leipzig	Liebigstraße 20 04103 Leipzig	
DE-04	Prof. Dr. med. Christoph Kahl	Klinikum Magdeburg	Birkenallee 34 39130 Magdeburg	
DE-06	Prof. Dr. med. Claudio Denzlinger	Marienhospital Stuttgart	Böheimstraße 37 70199 Stuttgart	
DE-07	Dr. med. Christian Constantin	Klinikum Lippe-Lemgo	Rintelner Str. 85 32657 Lemgo	
DE-08	Prof. Dr. med. Dirk Hempel	Onkologisches Zentrum Donauwörth	Neudegger Allee 10 86609 Donauwörth	
DE-09	PD Dr. med. Rüdiger Liersch	Gemeinschaftspraxis für Hämatologie und Onkologie	Steinfurter Straße 60 b 48149 Münster	
DE-10	Prof. Dr. med. Claus Henning Köhne	Klinikum Oldenburg AöR	Rahel-Straus-Str. 10 26133 Oldenburg	
DE-11	Dr. med. Beate Krammer-Steiner	Klinikum Südstadt Rostock	Südring 81 18059 Rostock	
DE-12	Dr. med. Wolfgang Blau	Helios Dr. Horst Schmidt Kliniken Wiesbaden	Ludwig-Erhard-Straße 100 65199 Wiesbaden	
DE-14	Dr. med. Filippo Rozzo	Onkologisches Zentrum Donauwörth Onkologisches Zentrum (Dachau II)	Hochstr. 27 85221 Dachau	1
DE-15	Inessa Paulenz	Städtisches Klinikum Dessau	Auenweg 38 06847 Dessau	
DE-16	Dr. med. Robert Radkowski	Klinikum Dortmund gGmbH	Beurhausstraße 40 44137 Dortmund	
DE-18	Dr. med. Kai Wille	Johannes Wesling Klinikum Minden	Hans-Nolte-Straße 1 32429 Minden	



MoLiMoR	Clinical Study Report			EduraCT-No. 2019-003714-14
DE-19	Prof. Dr. Dr. med. Jens Atzpodien	Niels-Stensen- Kliniken	Alte Rothenfelder Straße 23 49124 Georgsmarienhütte	
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		Gefos Dortmund mbH - Standort Brackel	Am Knappschafts Krankenhaus 1 44309 Dortmund	
DE-24	PD Dr. med. Alexander Baraniskin	Evangelisches Krankenhaus Hamm	Werler Str. 110 39063 Hamm	1


16.1.5 Signatures of the Principal or Coordinating Investigator(s), the Sponsor’s Responsible Medical Officer, and the Biostatistician, and, if applicable, of Other Authors

By signing this Clinical Study Report, the undersigned authors agree with the contents of this Clinical Study Report. The clinical trial reported here was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP), and applicable legislation.

Sponsor (Representative)

Dr. Bernhard Remes

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Gießen, 28.03.2025 | 11:3


Name, title

Place, date

Principal / Coordinating Investigator

Prof. Dr. Alexander Baraniskin

Signiert von:



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16:05

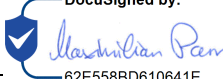
Name, title

Place, date

Biostatistician

Dr. Maximilian Parr

DocuSigned by:



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tzbach31.03.2025 | 08:01

Name, title

Place, date

16.1.6 List of Investigational Products(s) Batch Numbers

16.1.6.1 Cetuximab Batch Numbers

G00T4B  
G00SY1  
G00X1K  
G010XY  
G012F4  
G012F5  
G013DH  
G0157D  
G015RU  
G017AM  
G00XGL

16.1.6.2 Irinotecan Batch Numbers

Prerandomization phase	Randomization phase
M2006116	M2010732
M2010732	M2014001
AC0283S	AC0283S
M2014001	AC0284S
CF41	AC0292AS
CF45	AC0303S
CM94	AC291
	M2015432
	AC0921
	CF41
	M2100663
	CF33

CG22  
CM94

### 16.1.6.3 Folinic acid Batch Numbers

<i>Prerandomization phase</i>	<i>Randomization phase</i>
OH125HO	9N109N9
BK81U	0N138N0
BR90	BK81U
CB21	CB21
BL10U	CH89
CL13	BL10U
	CL13
	0N139C1
	CL10U
	10CL13
	CL24
	16QG1971
	OG124H0

### 16.1.6.4 5-FU Batch Numbers

<i>Prerandomization phase</i>	<i>Randomization phase</i>
PY06909	F200304A
E200264A	F200322AA
E200270A	F200306A
F200304A	F200307A
2004009S	F200328A
2004010S	P2001386
L190730AA	F200324A
C200111AA	F200333A
F200323AA	H210313A
G200389AA	P2000331
F200331AA	2004010S
	C200152AA
	AF0074S
	AF0077
	D200202AA
	AF0087F
	E200259AA
	AF0087S
	AF0101S
	F210313A
	H210305A
	H210307A
	H210309A
	H210312A
	K210463A

### 16.1.7 Randomization Scheme and Codes

Patients were randomized 1:1 into the experimental arm or the control arm. Randomization was performed by block randomization, with a block length of 4.

**16.1.8 Audit Certificates**

Not applicable.

**16.1.9 Documentation of Statistical Methods**

The MoLiMoR SAP v2.0 (dated September 12<sup>th</sup>, 2024) is available as stand-alone document (see Section **Fehler! Verweisquelle konnte nicht gefunden werden.**)

**16.1.10 Documentation of Inter-laboratory Standardization Methods and Quality Assurance Procedures**

For this study a DSMB was established. The dates for DSMB meetings defined in the stopping rules were not reached. Therefore, no meeting minutes were filed. Quarterly reports of the (S)AEs reported in the study were made available to the DSMB members and evaluated by the DSMB members.

**16.1.11 Publications Based on the Clinical Trial**

Not applicable.

**16.1.12 Important Publications Cited in This Report (Copies)**

Please refer to Section 15.

**16.1.13 Optional Appendix**

Not applicable.

**16.2 Patient Data Listings****16.2.1 Dropouts, Discontinued Patients**

Not applicable.

**16.2.2 Protocol Deviations**

All protocol deviations are presented in Section 10.3.

**16.2.3 Patients Excluded from the Efficacy Analysis**

Not applicable as none of the patients randomized was excluded from the efficacy analysis.

**16.2.4 Demographic Data**

All demographic data are presented in Section 11.2

**16.2.5 Compliance Data and / or Drug Concentration data (if available)**

Not applicable.

**16.2.6 Individual Efficacy and Response Data**

All individual efficacy and response data can be found as Table 3 and Listing 24 of the MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06

16.2.7 AE Listings (by patient)

A complete AE Listing by patient is available as Listing 28.1. of the MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06

16.2.8 Listing of Individual Laboratory Measurements (by patient), if required by regulatory authorities

A complete Listing of individual laboratory measurements by patient is available in Listings 16., 17.1., 17.2. of the MoLiMoR\_Final\_TLFs\_v1.0\_2024-12-06

16.3 Case Report Forms

16.3.1 CRFs of Deaths, Other SAEs, and Withdrawals for AEs

16.3.2 Other CRFs

16.4 Individual Data Listings (US archival listings)

Not applicable.

16.5 List of standalone documents

1	Protocol and Amendments	Version 3.0/March 9 <sup>th</sup> , 2021
2	Patient Information Sheet/Informed Consent Form	Germany: Version 3.0/June 1 <sup>st</sup> , 2021 Austria: Version 3.0/June 1 <sup>st</sup> , 2021
3	Data Management Plan	Version 1.0/August 26 <sup>th</sup> , 2020
4	Statistical analysis plan	Version 2.0/September 12 <sup>th</sup> , 2024
5	Statistical report	MoLiMoR_Final_TLFs_v1.0_2024-12-06 MoLiMoR_PFS_OS_TFTS_additional_tables_2024-12-09

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Status: Abgeschlossen

Betreff: Mit Docusign abschließen: MoLiMoR\_TheraOP\_ CSR\_v1.0\_2025\_03\_26.pdf

Quellumschlag:

Dokumentenseiten: 181

Signaturen: 3

Umschlagersteller:

Zertifikatsseiten: 5

Initialen: 0

Melina Schmitt

Signatur mit Anleitung: Aktiviert

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Umschlag-ID-Stempel: Aktiviert

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### Zeitstempel

Dr. Bernhard Remes

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alexander.baraniskin@ruhr-uni-bochum.de

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Abgeschlossen	Sicherheitsprüfung ausgeführt	01.04.2025 16:06:00
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