Impact of a centralized tumour board on secondary intervention rate in patients with RAS mutant metastatic colorectal cancer after first-line treatment with FOLFOXIRI plus bevacizumab (FIRE-7)

Study code	FIRE-7
Short title	Centralized tumour board and secondary intervention rate in mCRC
Responsible institution	Klinikum der Universität München – LMU
AIO study number:	AIO KRK 0120
Version No and version date	Draft 0.14 of 15h January 2021
Amendment No.	

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Approval of the Observation Plan

Study title: Impact of a centralized tumour board on secondary intervention rate in patients with RAS mutant metastatic colorectal cancer after first-line treatment with FOLFOXIRI plus bevacizumab (FIRE-7)

Study code: FIRE-7

I have approved the observation plan version 0.14 of 25-January-2021 and confirm that the study will be conducted in accordance with this observation plan, the Declaration of Helsinki, the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) guidelines and the applicable regulatory requirements.

Representative of the Responsible Institution

Name of the representative of the responsible institution

Date

Signature

Principal Investigator

Name of principal investigator

Date

Signature

Approval of the Observation Plan

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Biometrician

Name of the biometrician

Date

Signature

Statement of Compliance

Study title: Impact of a centralized tumour board on secondary intervention rate in patients with RAS mutant metastatic colorectal cancer after first-line treatment with FOLFOXIRI plus bevacizumab (FIRE-7)

Study code: FIRE-7

I have read and understood this observation plan and agree to conduct the study in accordance with this observation plan, the Declaration of Helsinki, the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) guidelines and the applicable regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the study without the prior written consent of the responsible institution of the study.

Participating Physician

Name of the participating physician

Date

Signature

Participating physician's institution

Table of Content

Figures

Tables

Appendices

List of Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine amino transferase
AMG	German Medicinal Products Act (Arzneimittelgesetz)
AST	Aspartate amino transferase
BID	Twice a day (bis in die)
CR	Complete response
CRP	C-reactive protein
eCRF	Electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
5-FU	5-fluorouracil
FA	Folinic acid
FP	Fluoropyrimidine
FPFV	First patient first visit
GCP	Good clinical practice
GCP-V	GCP ordinance; German: *Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen*
GGT	Gamma glutamyl transferase
ICF	Informed consent form
IEC	Independent ethics committee
ITT	Intention-to-treat
iv	Intravenous
LLN	Lower limit of normal
LPLV	Last patient last visit
mCRC	Metastatic colorectal cancer
MWA	Microwave ablation
NED	No-evidence-of-disease
NCI	National Cancer Institute
OS	Overall survival
PD	Progression
PFS	Progression-free survival
PR	Partial response
RECIST	Response evaluation criteria in solid tumours
RR	Response rate
RFA	Radiofrequency ablation
SAE	Serious adverse event
SADR	Serious adverse drug reaction
SAP	Statistical analysis plan

SAS	Statistical analysis software
SDV	Source data verification
SmPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial master file
TNM	Classification of malignant tumours
ULN	Upper limit of normal

Synopsis

Study title	Impact of a centralized tumour board on secondary intervention rate in patients with RAS mutant metastatic colorectal cancer after first-line treatment with FOLFOXIRI plus bevacizumab (FIRE-7)
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Responsible institution and initiator of the study	Klinikum der Universität München – LMU München Marchioninistr. 15 81377 München Germany
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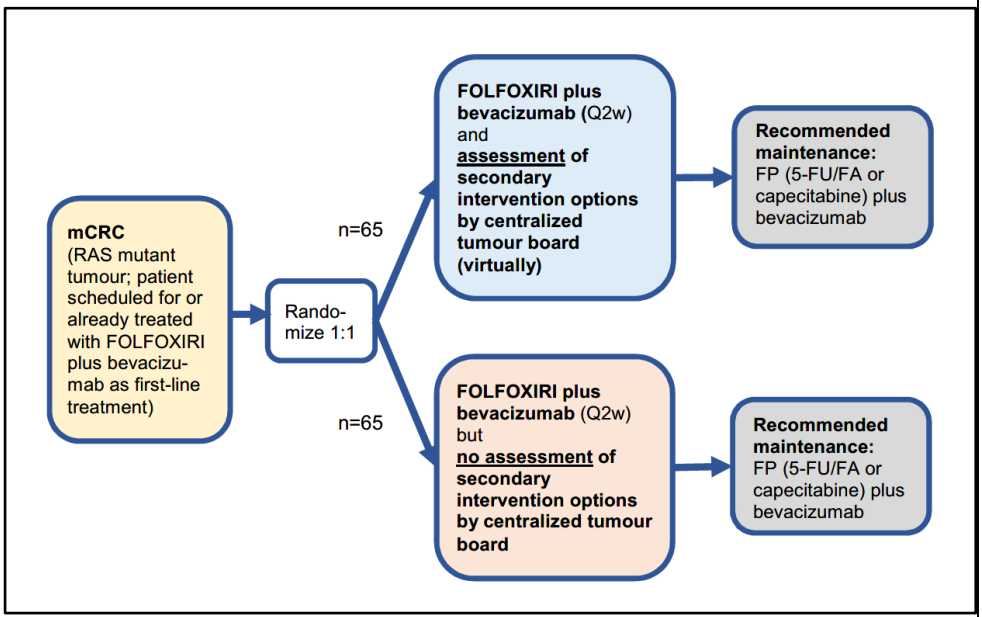
Scientific coordinator	Prof. Dr. med. Dominik Modest
Study coordinator	Dr. med. Arndt Stahler
Study code	FIRE-7
Observation plan version and version date	0.14 of 25th January 2021
Number of patients	130 patients (65 patients per arm)
Stratification factors	1. Synchronous vs. metachronous metastatic disease 2. Liver-limited disease vs. non-limited disease
Number of study sites	Up to 40 active centres
Background and rationale	The combination of a FOLFOXIRI and bevacizumab has been developed in phase 3 trials and is a valid treatment option - especially in patients with RAS mutant metastatic colorectal cancer (mCRC), who do not have the option to receive anti-EGFR therapy ((1), (2)). In particular, patients that might become candidates for secondary resection or ablation of metastases may benefit from FOLFOXIRI plus anti-VEGF therapy ((1), (2), (3)). Integration of surgery and ablative techniques into the treatment algorithm is associated with dramatically improved survival of patients with mCRC ((4), (5)). Central assessments for secondary resectability in mCRC suggest that more patients could undergo secondary interventions than actually is reported ((5), (6)). Central monitoring for interventional treatment options may help to improve the rate of patients with secondary operation and/or ablation. Thus, the study investigates in a randomized fashion whether the rate of patients in whom secondary interventions are performed in generally curative intent is improved when secondary intervention options are assessed virtually by a centralized tumour board. Only patients, who are planned to be treated with FOLFOXIRI plus bevacizumab or who have already received treatment with FOLFOXIRI plus bevacizumab are to be included to avoid bias as result of different treatment regimens. The number of treatment cycles with FOLFOXIRI plus bevacizumab will be according to local clinical routine and medical guidelines, recommended are 8 to 12 cycles FOLFOXIRI in combination with bevacizumab, followed by a maintenance therapy with a fluoropyrimidine (5-fluorouracil/folinic acid [5-FU/FA] or capecitabine) plus bevacizumab until progression.

Objectives	**Primary objective** • To compare the proportion of patients with secondary interventions performed in a generally curative context in patients with RAS mutant mCRC treated with FOLFOXIRI and bevacizumab when options for secondary interventions are either assessed by a centralized tumour board **versus** no centralized tumour board. **Secondary objectives** • to evaluate treatment efficacy in both study arms • to evaluate safety of treatment with FOLFOXIRI and bevacizumab (including maintenance treatment with fluoropyrimidine (FP) plus bevacizumab)
Endpoints	**Primary endpoint** • Rate of patients in whom secondary interventions (e.g. resection, ablation treatment or combination of both) are performed in curative intent **Secondary endpoints** **Efficacy** • Objective response rate (ORR) according to RECIST 1.1 • Progression-free survival (PFS) rate at 6, 12 and 16 months • Overall survival (OS) rate at 6, 12 and 16 months **Safety** • Type, incidence, relatedness, and severity of adverse events with severity ≥ Grad 3 (severity according to NCI CTCAE version 5.0)
Study design	This is a randomised, multicentre observational study in patients suffering from RAS mutant mCRC with primarily unresectable metastases, who are planned to be treated with FOLFOXIRI and bevacizumab or who have already received ≤ four cycles FOLFOXIRI and bevacizumab as first-line treatment of metastatic disease. The patients are randomised in a 1:1 ratio to compare the rate of patients in whom secondary interventions (e.g. resection, ablation) are performed in curative intent when secondary intervention options are assessed by a multidisciplinary centralized tumour board (Arm A) versus when secondary intervention options are not assessed by a multidisciplinary centralized tumour board (Arm B). All patients evaluated in the study will receive chemotherapy with FOLFOXIRI plus bevacizumab. After this induction/conversion therapy, imaging (CT or MRI) will be performed to evaluate resectability. In Arm A, a multidisciplinary, centralized tumour board will assess options of secondary intervention to be performed in the context of a generally curative treatment approach. If there are secondary intervention options according to the judgement of the centralized tumour board, they will be listed in their respective sequence and the assessment will be communicated to the participating physician or his/her deputy at the study center. The decision, whether or not any secondary intervention is performed as recommended by the centralized tumour board as well as the kind of interventional procedures is up to the discretion of the treating physicians and surgeons of each patient. Any secondary intervention is recorded. Evaluating the primary endpoint, the first interventions performed in one organ (e.g. liver) are rated when performed in a generally curative context (e.g. even in the presence of lung metastases that need to be approached in a further intervention).

	In Arm B, no centralized tumour board will be integrated in to clinical decision making and patients will be treated according to institutional guidelines. The number of treatment cycles with FOLFOXIRI and bevacizumab will be according to local clinical routine and medical guidelines, recommended are 8 to 12 cycles FOLFOXIRI in combination with bevacizumab, followed by a maintenance therapy with fluoropyrimidine (FP) plus bevacizumab until progression. The study design is displayed in the following figure:  **Note:** Inclusion of patients already treated with FOLFOXIRI and bevacizumab is permitted if ≤ 4 cycles FOLFOXIRI plus bevacizumab have been administered, treatment is ongoing and the first restaging has not been conducted prior to inclusion. **Abbreviations:** mCRC = metastatic colorectal carcinoma; FOLFOXIRI = 5-fluorouracil, folinic acid, oxaliplatin, irinotecan; FP = fluoropyrimidine; 5-FU = 5-fluorouracil; FA = folinic acid
Inclusion criteria	1. Written informed consent to participate in the study 2. Patients ≥ 18 years at the time of signing the informed consent 3. Histologically confirmed (in primary tumour or metastasis) UICC stage IV metastatic adenocarcinoma of the colon or rectum (mCRC) with primarily unresectable metastases 4. RAS mutant CRC (as determined by local pathology in tissue of primary tumour or metastasis) 5. At least one measurable lesion according to RECIST version 1.1 in a CT/MRI scan performed within 28 days prior to start of systemic treatment (first cycle of induction treatment) 6. ECOG performance status 0-1 7. Patients planned to receive chemotherapy with FOLFOXIRI plus bevacizumab as first-line treatment of metastatic disease. De-escalation of FOLFOXIRI to FOLFIRI or FOLFOX is allowed in case of toxicity. Patients can also be included if they had already received ≤ 4 cycles of induction/conversion therapy with FOLFOXIRI plus bevacizumab (including those patients in whom FOLFOXIRI has been de-escalated to FOLFIRI or FOLFOX due to toxicity) and the first restaging has not been conducted prior to randomization.

<table>
<tr><td></td><td>8. Completion of adjuvant therapy for colorectal cancer > 3 months prior to start of systemic treatment (first cycle of induction treatment).
9. Patient’s ability for treatment with FOLFOXIRI and bevacizumab according to participating physician’s judgement.</td></tr>
<tr><td>Exclusion criteria</td><td>1. Pregnant or breast-feeding women. Females of childbearing potential (FCBPs) who do not practice adequate contraceptive measures as required according to SmPCs of the administered medicinal products.
2. Contraindication to intensive chemotherapy with FOLFOXIRI plus bevacizumab
3. Contraindications to treatment with 5-FU, oxaliplatin, folinic acid, irinotecan (FOLFOXIRI) and/or bevacizumab according to SmPCs of the administered medicinal products.
4. Patients with confirmed cerebral metastasis. In case of clinical suspicion of brain metastasis, a cranial CT or MRI must be performed to rule out brain metastasis before study inclusion.
5. Documentation of > 5 lung metastases (however, no limitation for the number of metastases in the liver)
6. Isolated distant nodal metastasis, isolated peritoneal metastasis or isolated bone metastasis
7. Limited legal capacity</td></tr>
<tr><td>Treatment recommendations</td><td>Treatment in both study arms is this same clinical standard treatment with FOLFOXIRI plus bevacizumab according to local practice and medical guidelines. Standardized procedures for this treatment to avoid bias between the study arms are recommended.

All the medicinal products recommended as part of the FIRE-7 study are used within the scope of their respective marketing authorisations.

Treatment with at least 8 cycles FOLFOXIRI plus bevacizumab or until either progression or unacceptable toxicity of this treatment regimen (if occurring before completion of 8 cycles FOLFOXIRI) according to the following schedule followed by maintenance therapy (see schedules for maintenance treatment below) is recommended, if applicable.
Duration of each treatment cycle with FOLFOXIRI plus bevacizumab is 2 weeks.
Treatment with FOLFORIXI plus bevacizumab may be extended to more than 8 cycles at the treating physician's discretion. However, we recommend that not more than 12 cycles should be given.

FOLFOXIRI plus Bevacizumab, every two weeks
<table>
<tr><th>Medicinal product</th><th>Dose</th><th>Route and duration of administration</th><th></th></tr>
<tr><td>Irinotecan</td><td>165 mg/m² BSA</td><td>iv, 30 - 90 min</td><td>Day 1</td></tr>
<tr><td>Oxaliplatin</td><td>85 mg/m² BSA</td><td>iv, 30 - 90 min</td><td>Day 1</td></tr>
<tr><td>Folinic acid</td><td>200 mg/m² BSA</td><td>iv, 120 min</td><td>Day 1</td></tr>
<tr><td>5-FU</td><td>3200 mg/m² BSA</td><td>iv infusion over 46 h</td><td>Days 1-2</td></tr>
<tr><td>Bevacizumab</td><td>5.0 mg/kg BW</td><td>iv, over 30 to 90 minutes*</td><td>Day 1</td></tr>
</table>
* 1st administration 90 min.; in case of good tolerability second administration 60 min., further administrations 30 min.

Continuous treatment with a maintenance therapy is recommended, if no progression has occurred after at least 8 cycles FOLFOXIRI plus bevacizumab, e.g. with the combination of a fluoropyrimidine plus bevacizumab according to local standards until progression to one of the following schedules:</td></tr>
</table>

Maintenance Treatment 5-FU/FA plus bevacizumab, every two weeks

Medicinal product	Dose	Route and duration of administration	
Folinic acid	400 mg/m² BSA	iv, 120 min	Day 1
5-FU	2400 mg/m² BSA	iv infusion over 46 h	Days 1-2
Bevacizumab	5.0 mg/kg BW	iv, over 30 to 90 minutes*	Day 1

*Infusion duration for bevacizumab utilized prior to start of maintenance treatment.

Or

Maintenance Treatment capecitabine plus bevacizumab, every three weeks

Medicinal product	Dose	Route and duration of administration	
Capecitabine	1250 mg/m² BSA	p.o. BID	Day 1-14
Bevacizumab	7.5 mg/kg BW	iv, over 30 to 90 minutes*	Day 1

* Infusion duration for bevacizumab utilized prior to start of maintenance treatment.

Statistical Considerations

Primary objective of the study is to compare the proportion of patients with secondary interventions performed in a generally curative context in patients with RAS mutant mCRC treated with FOLFOXIRI and bevacizumab when secondary intervention options are assessed by a centralized tumour board **versus** no centralized tumour board.

Primary endpoint is the rate of patients in whom secondary interventions (e.g. resection, ablation treatment or combination of both) are performed in curative intent. Evaluating the primary endpoint, the first interventions performed in one organ (e.g. liver) are rated when performed in a generally curative context with the objective to achieve a no-evidence-of-disease situation in the respective organ (e.g. even in the presence of lung metastases that need to be approached in a further intervention).

Secondary intervention with objective to achieve a no-evidence-of-disease situation in the respective organ is defined as any (combination of) procedure/procedures that eliminates/eliminate all tumour lesions in the respective organ with radiologically documented success about 8-12 weeks (time interval of radiological restaging according to local routine) after the intervention. In addition, patients who underwent resection must have a R0/R1 resection for a no-evidence-of-disease status.

A rate of patients in whom secondary interventions are performed in curative intent of about 15% is expected in study Arm B without assessment of secondary intervention options based on the resection rate of metastases in molecularly unselected patients of the FIRE-3 study (5) by a multidisciplinary centralized tumour board, whereas a rate of ≥ 35% would be considered as successful (7) in the study Arm A with assessment of secondary intervention options by a centralized tumour board.

Hence the hypotheses to be tested are:

H_0: Rate of patients in whom secondary interventions are performed in curative intent (with assessment by a centralized tumour board) ≤ Rate of patients in whom secondary interventions are performed in curative intent (without assessment by a centralized tumour board)

	H_1: Rate of patients in whom secondary interventions are performed in curative intent (with assessment by a centralized tumour board) >R ate of patients in whom secondary interventions are performed in curative intent (without assessment by a centralized tumour board) The primary endpoint will be evaluated by a one-sided Chi-square test. In order to reject the null hypothesis at a one-sided significance level of 5% with a power of at least 80% in total 114 patients are required, 57 patients per arm. The primary analysis of the rate of patients in whom secondary interventions are performed in curative intent will be performed in the following population: - Randomized patient in whom the planned treatment with FOLFOXIRI and bevacizumab has been initiated and who have received at least four cycles FOLFOXIRI and bevacizumab. - CT- and/or MRI images from baseline (before the effective start of treatment with FOLFOXIRI plus bevacizumab) and at least one restaging examination after baseline (during treatment phase or during follow-up) are available It is expected that 12% of the randomized patients will not be evaluable for the primary analysis. Hence, 130 patients (65 patients per arm) have to be randomized.
Duration and end of study	Estimated duration of the study: 4 years, estimated Q1 2021 to Q1 2025 Planned first patient first visit: Q1 2021 Planned recruitment period: 24 months; estimated Q1 2021 to Q1 2023 Individual treatment duration: Estimated treatment duration with FOLFOXIRI and bevacizumab and subsequent maintenance therapy will be 6-8 months. Individual documentation duration: Documentation until date of death or for 16 months after last administration of FOLFOXIRI in combination with bevacizumab including maintenance therapy, whichever date is earlier. Planned end of the study: Q1 2025
GCP statement	The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the applicable regulatory requirements.

Table 2-1: Schedule of study assessments

Procedures and Assessments to be documented	Screening	Treatment phase	Restaging	End of first-line treatment	Follow-up[12]
	Within 28 days prior to randomi-sation unless otherwise specified	Before start of every treatment cycle [13]	According to local clinical practice, recommen-ded interval: about every 8-12 weeks[17] and about 8-12-weeks after secondary interventions [17]	Within 3 weeks after progression or prior to start of next treatment line[14]	Every three months ± 1 months after the end of first-line treatment
Signed Informed Consent Form	X				
Verification of eligibility criteria	X				
Documentation of RAS mutational status [1]	X				
Medical history, including medical history of mCRC [2] and demographic information [3]	X				
Height (only at screening, body weight	X	X		X	
Documentation of vital signs (pulse, blood pressure, body temperature)	X [16]	X		X	
ECOG performance status	X [16]	X [4]		X	
Documentation of applied treatment with FOLFOXIRI and bevacizumab (including maintenance/modified treatment regimen, e.g. de-escalation)		Continuously during first-line treatment until end of first line treatment visit (medicinal products, duration, cycle delays etc.) including treatment cycles prior to study inclusion if applicable.			
Documentation of any secondary intervention (resection surgery, ablation treatment, radiotherapy) [5]		At any time point during first-line treatment until end of first-line treatment			
Record results from abdominal CT/MRI [6]	X [16]		X	(X) [8]	(X) [6]
Record results from chest X-ray in two planes or alternatively chest CT [6]	X [16]		(X) [7]	(X) [7, 8]	(X) [6, 7,
Record results from other imaging procedures if appropriate in case of known or suspected metastasis/metastases [6]	(X) [16]		(X)	(X) [8]	(X) [6]
Tumour assessment according RECIST 1.1 by means of the CT/MRI images at the local study center	X [16]		X	(X) [8]	(X) [6]

Procedures and Assessments to be documented	**Screening**	**Treatment phase**	**Restaging**	**End of first-line treatment**	**Follow-up[12]**
	Within 28 days prior to randomi-sation unless otherwise specified	Before start of every treatment cycle [13]	According to local clinical practice, recommen-ded interval: about every 8-12 weeks[17] and about 8-12-weeks after secondary interventions [17]	Within 3 weeks after progression or prior to start of next treatment line[14]	Every three months ± 1 months after the end of first-line treatment
Evaluation of secondary intervention options by the centralized tumour board ***–only in patients of study Arm A and obligatory after the 1st restaging, optional after the 2nd restaging.***			X [9]		
Documentation of haemogram [10]	(X) [16]	(X)		(X)	
Documentation of serum chemistry [11]	(X) [16]	(X)		(X)	
Documentation of urinalysis [18]	(X) [16]	(X)		(X)	
Documentation of pregnancy testing (in blood or urine) as and if performed	(X)	(X)		(X)	
Documentation of phenotype and/or genotype testing for DPD deficiency as and if performed	(X)				
Documentation of adverse events[15]	continuously				
Survival and subsequent anti-cancer therapies [12]					X

1 As determined by local pathology in tissue of primary tumour or metastasis; testing earlier than 28 days prior to randomisation permitted.

2 Date of first diagnosis of CRC; TNM stage and grading at first diagnosis; current TNM stage; primary tumour site and sidedness of the primary tumour (right-sided/left-sided); date of diagnosis of metastasis, site/sites of metastasis; type of metastasis (synchronous metastases or metachronous metastases); date of histological confirmation; surgery of primary tumour and/or metastases; adjuvant chemotherapy (yes/no, duration and administered anti-tumour medicinal products); in case of rectal cancer: prior radiotherapy or radiochemotherapy (if any).

3 Demographic information includes age and self-reported race/ethnicity.

4 ECOG performance status may be obtained ≤ 96 hours before Day 1 of each cycle. In patients, in whom treatment with FOLFOXIRI and bevacizumab had already been initiated before study inclusion, retrospective documentation as and if determined.

5 Kind of secondary intervention procedure/procedures (resection surgery, ablation treatment [RFA, MWA], radiotherapy), site/sites and date/dates of intervention, evaluation of residual tumour status (R0, R1, R2) if applicable

6 Imaging procedures are performed as part of the clinical routine at the study centers according to the present standards in oncology and the results of imaging procedures will be recorded. CT/MRI scans should be performed at baseline (before the effective start of treatment with FOLFOXIRI plus bevacizumab), during treatment as restaging according to local clinical practice with a recommended interval of about every 8-12 weeks after the effective start of treatment with FOLFOXIRI plus bevacizumab before or after randomisation

and about 8-12 weeks after first secondary intervention in one organ, at the end of first-line treatment (only if required in addition to those of the last restaging imaging up to the treating physician's discretion) and at any time if clinically indicated. Recording of results from CT/MRI scans during follow-up is only required until first progression after first line treatment during follow-up and only if treatment with medicinal products of first line was permanently discontinued without progression.
Note: Restaging about 8 -12 weeks after first secondary intervention in one organ must record whether a no-evidence-of-disease situation was obtained in the respective organ.

[7] Only in case of known or suspected pulmonary metastasis/metastases

[8] Only if any imaging procedures and respective tumour assessment in addition to those performed at the last restaging have been performed up to the treating physician's discretion.

[9] Evaluation of secondary intervention options by the centralized tumour board by means of CT/MRI scans after the first restaging (obligatory) and the second restaging (optional). Although the evaluation of second intervention options by the centralized tumour board after the second restaging is optional, re-evaluation after the second restaging is recommended in cases of delayed/improved treatment response at the second restaging. Pseudonymized copies of the respective restaging CT/MRI scans from the first restaging (obligatory), the second restaging (optional) and the baseline CT/MRI scans (baseline scan only for evaluation after the first restaging) have to be sent to the study office at the university hospital of the LMU att. Mr. M. Wolff/Prof. V. Heinemann for later presentation to the centralized tumour board members as soon as possible after the respective imaging diagnostics for restaging. In case that the option for evaluation of secondary intervention options by the centralized tumour board after the second restaging will not be utilized, the reason therefor should be laid down in the eCRF.

[10] Only documentation of haemogram and differential blood count **as and if determined according to local standard** (e.g. leukocytes, neutrophils, thrombocytes, and haemoglobin). In addition, no strict time window applies.

[11] Only documentation of the following serum chemistry values **as and if determined according to local standard:** creatinine, estimated glomerular filtration rate (GFR), C-reactive protein (CRP), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), In addition, no strict time window applies.

[12] Follow-up information has to be collected approximately every 3 months (± 28 days) after the end of first-line treatment until patient's death or for 16 months after last administration of FOLFOXIRI in combination with bevacizumab including maintenance therapy, whichever date is earlier. Follow-up information may be collected via telephone calls and/or clinic visits. Follow-up information about survival and further anti-tumour treatments may be as well requested from the treating physician via telephone or as copy of the medical report, if the patient gives his consent to this procedure.

[13] Before start of each treatment cycle is defined as the week before Day 1 of any treatment cycle as well as Day 1 of this treatment cycle. In patients, who have received treatment with FOLFOXIRI and bevacizumab prior to study inclusion, respective data should be documented retrospectively as and if determined according to local standard for the respective treatment cycles.

[14] The procedures at the end of first line treatment should be performed within three weeks after progression **or** before first administration of any medicinal product of the next treatment line (defined as a treatment line containing any anti-tumour medicinal product that is not part of the first line treatment with FOLFOXIRI and bevacizumab and maintenance).

[15] Documentation of non-serious and serious adverse events with severity ≥ Grade 3 (severity according the NCI CTCAE version 5.0). These adverse events and serious adverse events have to be reported continuously from the date of informed consent to take part in this observation study until 30 days after administration of the last dose of any medicinal product of the FOLFOXIRI (or de-escalated treatment schedule if applicable) plus bevacizumab regimen including recommended maintenance with FP plus bevacizumab or start of the next treatment line, whichever date is earlier. The next treatment line is defined as treatment line containing any anti-tumour medicinal product that is not part of the first line treatment with FOLFOXIRI and bevacizumab and maintenance.

[16] The time interval "within 28 days before randomisation" is only applicable for patients in whom treatment with FOLFOXIRI and bevacizumab has not yet been initiated. In patients, in whom treatment with FOLFOXIRI and bevacizumab has already been initiated, retrospective documentation of baseline values for a time interval of "within 28 days before start of the treatment".

[17] Recommended restaging intervals after the effective start of treatment with FOLFOXIRI plus bevacizumab before or after randomization. Recommended restaging interval after secondary interventions.

Urinalysis by urine dipstick. Only documentation urinalysis **as and if determined according to local standard**. In addition, no strict time window applies.

1.1 Background

1.1.1 Colorectal Cancer

Colorectal cancer (CRC) is one of the most common cancers worldwide. Over 1.8 million new colorectal cancer cases and 881,000 deaths were estimated to occur in 2018, accounting for about 1 in 10 cancer cases and deaths. Overall, in 2018 CRC ranked third in terms of incidence but second in terms of mortality (8).

In Germany, about 70,000 patients are diagnosed with colorectal cancer every year with roughly 30-35,000 deaths per year (9).

The individual lifetime prevalence is around 4-6%, with the average age of onset for men being 70 years and in women 75 years. In more than 90% of colorectal cancers, adenocarcinoma is involved (10) and 75% of all cases involve so-called sporadic, i.e. non-familial or hereditary disease. Approximately 25% of newly diagnosed patients have already developed metastases and a further 25% of CRC metastasize during the further course of the disease (mCRC). At the metastatic stage, it has been possible to increase the median overall survival from 6 months to approximately 30 months with the improvement of systemic treatment options.

In about 50% of metastatic colorectal cancer RAS mutations (KRAS and NRAS, exons 2-4) are found. Typically, RAS mutated tumours are associated with a more unfavourable outcome compared to RAS wild-type tumour.

1.1.2 Systemic Treatment in RAS Mutant Colorectal Cancer

Chemotherapy is the backbone of treatment in metastatic CRC (mCRC) regardless of RAS status, using either the doublet FOLFIRI (5-fluorouracil (5-FU) combined with folinic acid (FA) and irinotecan) or FOLFOX (5-FU combined with FA, and oxaliplatin) or the triplet FOLFOXIRI (5-FU combined with FA, irinotecan and oxaliplatin).

In untreated patients diagnosed with RAS mutant mCRC, chemotherapy in combination with bevacizumab as anti-VEGF antibody is standard of care (2), whereas EGFR antibodies are only indicated for treatment of RAS wild-type tumours and even contraindicated in RAS mutated tumours if administered in combination any oxaliplatin based chemotherapy.

A way to further improve the outcome of metastatic colorectal cancer patients is to administer FOLFOXIRI as first-line regimen containing all the three active cytostatic agents (5-FU, oxaliplatin and irinotecan) plus bevacizumab. This strategy has been developed in several phase III trials (one without bevacizumab) (1, 11-13).

The Italian GONO group protocol of FOLFOXIRI (irinotecan 165 mg/m² D1, oxaliplatin 85 mg/m² D1, folinic acid 200 mg/m² D1, fluorouracil 3200 mg/m² as 48-hour infusion starting on D1, every two weeks) was found to be effective and safe at the cost of increased but manageable side effects (1, 11-13).

The FOLFOXIRI regimen should be applied only in patients of ECOG performance status 0-1 according to the German S3 guideline for colorectal cancer (14).

1.1.3 The Role of Secondary Intervention (Resection, Ablation) in mCRC

In patients with primarily resectable metastases to the liver only, surgical removal of the lesions has become the standard of care, with additional neoadjuvant and/or adjuvant therapy further improving the results (15, 16). However, the advent of a variety of potent drugs for colorectal cancer has opened up the option of combined modality approaches, leading to the possibility of cure even in initially unresectable disease (17, 18). In fact, when looking at the 10-year

survival results of primarily resectable vs. primarily unresectable metastases downstaged by chemotherapy, the latter option seems to achieve cure rates in almost the same range (19).

The optimal pre-operative systemic therapy, for which the term “conversion therapy” has been coined, in patients with unresectable or “borderline” hepatic lesions is up to discussion, with an urgent requirement for additional study data (18). In general, three-drug combinations seem to yield higher response rates, and the high response rates correlate with high resection rates.

Until recently, the actual “conversion rate” after aggressive chemotherapy was unclear. In the first prospective study on this topic, the CELIM trial (20), patients were randomised to receive either FOLFOX or FOLFIRI combined with the EGFR antibody cetuximab, achieving an overall R0 resection rate in 34%, while “conversion” from unresectability to resectability was confirmed by a blinded expert panel in 25% of the patients.

The R0 secondary resection in the Italian phase III trial on FOLFOXIRI amounted to 15% among all patients (36% among patients with liver metastases only) compared to 6% (12%) in the FOLFIRI arm (12). The preliminary rate in the FOLFOXIRI + bevacizumab phase II was of similar magnitude (21).

Pathological complete or major response seems to be a valid predictor for long-term survival (22). Concerning the duration of pre-operative chemotherapy, the rate of complications due to hepatic insufficiency increases, if > 8 cycles are administered before surgery. Thus, in general, the therapy should not exceed 4 months (23).

The best outcome is achieved by a sequential therapeutic concept, which aims to achieve a stage of resectability. Secondary intervention options should be analysed in regular assessments by a multi-disciplinary tumour board. The decision of a resection of the metastases is of crucial importance for the overall survival (2).

1.2 Rationale

The combination of a FOLFOXIRI and bevacizumab has been developed in phase 3 trials and is a valid treatment option- especially in RAS mutant mCRC patients who do not have the option to undergo EGFR-targeted therapy (1), (2). In particular, patients that might become candidates for secondary resection or ablation of metastases may benefit from FOLFOXIRI plus anti-VEGF therapy (1), (2), (3).

Integration of surgery and ablative techniques into the treatment algorithm is associated with dramatically improved survival of patients with mCRC (4), (5). Retrospective central assessments for secondary resectability in mCRC suggest that more patients could undergo interventions than actually is reported (5), (6). Central monitoring for interventional treatment options may help to improve the rate of patients with secondary operation and/or ablation.

Thus, the study is designed to investigate in a randomised fashion whether the proportion of patients in whom secondary interventions are performed in generally curative intent is improved when secondary intervention options are assessed virtually by a centralized tumour board.

Only patients planned to be treated with FOLFOXIRI plus bevacizumab as well as patients in whom treatment with FOLFOXIRI plus bevacizumab has already been started are to be included to avoid bias as result of different treatment regimens. The number of treatment cycles with FOLFOXIRI plus bevacizumab will be according to local clinical routine and medical guidelines, recommended are at least 8 cycles FOLFOXIRI in combination with bevacizumab, followed by a maintenance therapy with fluoropyrimidine (5-FU/FA or capecitabine) plus bevacizumab until progression.

1.3 Risk/Benefit Assessment

As laid down in Section 1.2, only patients already planned to be treated with FOLFOXIRI plus bevacizumab prior to enrolment as well as patients in whom treatment with FOLFOXIRI plus bevacizumab has already been started will be included in this observational study. The FOLFOXIRI and bevacizumab regimen including the number of treatment cycles as well as any dose modifications and maintenance therapy are administered according to local clinical routine and medical guidelines and are up to the treating physician's discretion. The treatment administered is only documented. All the medicinal products administered as part of the FOLFOXIRI and bevacizumab regimen have a marketing authorization for treatment of mCRC. Thus, there are no additional risks imposed by the treatment regimen if patients participate in this study.

Imaging procedures for tumour measurement(s) that are needed for the pre-planned assessments of secondary interventional treatment options will be performed in clinical standard intervals as necessary for response control of any first-line treatment in RAS mutant mCRC patients in both study arms. In addition, imaging procedures for monitoring of success after secondary intervention are performed as part of the clinical routine at the study centers according to the present standards in oncology.

Resulting risks of the study participation are confined to risks of data protection. We ensure that all the conditions of the General Data Protection Regulation (GDPR) will be strictly observed. Only pseudonymized copies of CTs/ MRIs are sent to the study office at the university hospital of the LMU for the pre-planned assessments by the centralized tumour board members.

On the other hand, central assessment of secondary intervention options during anti-tumour treatment might improve the rate of secondary interventions in generally curative intent and consecutively improve PFS and OS. PFS- and OS-rates at 6, 12 and 16 months are analysed in both study arms as secondary endpoints.

The possible benefits to achieve a prolongation of disease control and survival as consequence of an improved secondary intervention rate outweigh the identified risks of data protection and we consider the risk-benefit ratio to be favourable.

2 Objectives and Endpoints

2.1 Primary Objective

The primary objective of this study is to compare the proportion of patients with secondary interventions performed in a generally curative context in patients with RAS mutant mCRC treated with FOLFOXIRI and bevacizumab when options for secondary interventions are either assessed by a centralized tumour board versus no centralized tumour board.

Corresponding primary endpoint:

- Rate of patients in whom secondary interventions (e.g. resection, ablation treatment or combination of both) are performed in curative intent

2.2 Secondary Objectives

The secondary study objectives are:

- to evaluate treatment efficacy in both study arms
- to evaluate safety of treatment with FOLFOXIRI and bevacizumab (including maintenance treatment with fluoropyrimidine plus bevacizumab)

Corresponding secondary endpoints:

Efficacy

- Objective response rate (ORR) according to RECIST 1.1
- Progression-free survival (PFS) rate at 6, 12 and 16 months
- Overall survival (OS) rate at 6, 12 and 16 months

Safety

- Type, incidence, relatedness, and severity of adverse events with severity ≥ Grade 3 (severity according to NCI CTCAE version 5.0)

3 Study Design

3.1 General Study Design

This is a randomised, multicentre observational study in patients suffering from RAS mutant mCRC with primarily unresectable metastases, who are planned to be treated with FOLFOXIRI plus bevacizumab or who have already received ≤ four cycles FOLFOXIRI and bevacizumab as first-line treatment of metastatic disease. The patients are randomised in a 1:1 ratio to compare the rate of patients in whom secondary interventions (e.g. resection, ablation treatment) are performed in a generally curative context if secondary intervention options are assessed by a multidisciplinary centralized tumour board (Arm A) versus no assessment of secondary intervention options by a multidisciplinary centralized tumour board (Arm B).

All patients evaluated in the study will receive chemotherapy with FOLFOXIRI plus bevacizumab. After this induction/conversion therapy, imaging (CT or MRI) will be performed to evaluate resectability. In Arm A, a multidisciplinary, centralized tumour board will assess options of secondary interventions to be performed in the context of a generally curative treatment approach.

If there are secondary intervention options according to the judgement of the centralized tumour review board, they will be listed in their respective sequence and the assessment will be communicated to the participating physician or his/her deputy at the study center. The decision, whether or not any secondary intervention is performed as recommended by the centralized review board as well as the kind of interventional procedures is up to the discretion of the treating physicians and surgeons of each patient. Any secondary intervention is recorded.

Primary endpoint is rate of patients in whom secondary interventions (e.g. resection, ablation treatment or combination of both) are performed in curative intent.

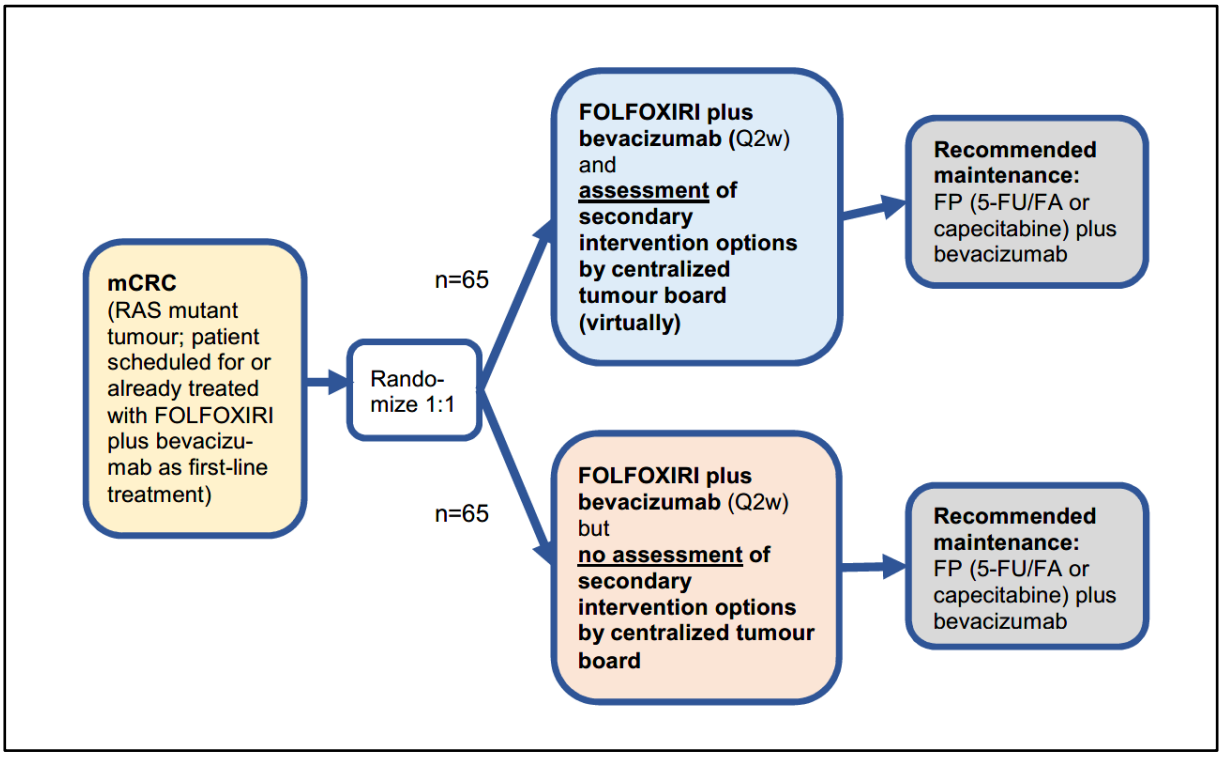
Evaluating the primary endpoint, the first interventions performed in one organ (e.g. liver) are rated when performed in a generally curative context with the objective to achieve a no-evidence-of-disease situation in the respective organ (e.g. even in the presence of lung metastases that need to be approached in a further intervention).

Secondary intervention with objective to achieve a no-evidence-of-disease situation in the respective organ is defined as any (combination of) procedure/procedures that eliminates/eliminate all tumour lesions in the respective organ with radiologically documented success about 8-12 weeks (time interval of radiological restaging according to local routine) after the intervention. In addition, patients who underwent resection must have a R0/R1 resection for a no-evidence-of-disease status.

The number of treatment cycles with FOLFOXIRI and bevacizumab will be according to local clinical routine and medical guidelines, recommended are at least 8 cycles FOLFOXIRI in combination with bevacizumab, followed by a maintenance therapy with fluoropyrimidine (5-FU/FA or capecitabine) plus bevacizumab until progression.

The study design is displayed in the following figure:

Figure 3.1: Study design of the study FIRE-7



Note:
Inclusion of patients already treated with FOLFOXIRI and bevacizumab is permitted if ≤ 4 cycles FOLFOXIRI and bevacizumab have been administered, treatment is ongoing and the first restaging has not been conducted prior to inclusion.

Abbreviations:
mCRC = metastatic colorectal carcinoma; FOLFOXIRI = 5-fluorouracil, folinic acid, oxaliplatin, irinotecan; FP = fluoropyrimidine; 5-FU = 5-fluorouracil; FA = folinic acid

3.2 Duration and End of the Study

Estimated duration of the study	4 years, estimated Q1 2021 to Q1 2025
Planned first patient first visit	Q1 2021
Planned recruitment period	24 months; estimated Q1 2021 to Q1 2023
Individual treatment duration	Estimated median treatment duration with FOLFOXIRI and bevacizumab and subsequent maintenance treatment will be 6-8 months.
Individual documentation duration	Documentation until date of death or for 16 months after last administration of FOLFOXIRI in combination with bevacizumab including maintenance therapy, whichever date is earlier.
Planned end of the study	Q1 2025

4 Study Population

Adult patients with primarily unresectable mCRC who meet all the following inclusion criteria and none of the exclusion criteria are eligible for the study.

4.1 Inclusion Criteria

1. Written informed consent to participate in the study
2. Patients ≥ 18 years at the time of signing the informed consent
3. Histologically confirmed (in primary tumour or metastasis) UICC stage IV metastatic adenocarcinoma of the colon or rectum (mCRC) with primarily unresectable metastases
4. RAS mutant CRC (as determined by local pathology in tissue of primary tumour or metastasis)
5. At least one measurable lesion according to RECIST version 1.1 in a CT/MRI scan performed within 28 days prior to start of systemic treatment (first cycle of induction treatment)
6. ECOG performance status 0-1
7. Patients planned to receive chemotherapy with FOLFOXIRI plus bevacizumab as first-line treatment of metastatic disease. In these patients de-escalation of FOLFOXIRI to FOLFIRI or FOLFOX is allowed in case of toxicity.
   Patients can also be included if they had already received ≤ 4 cycles of induction/conversion therapy with FOLFOXIRI plus bevacizumab (including those patients in whom FOLFOXIRI has been de-escalated to FOLFIRI or FOLFOX due to toxicity) and the first restaging has not been conducted prior to randomization.
8. Completion of adjuvant therapy for colorectal cancer > 3 months prior to start of systemic treatment (first cycle of induction treatment)
9. Patient's ability for treatment with FOLFOXIRI and bevacizumab according to participating physician's judgement.

4.2 Exclusion Criteria

1. Pregnant or breast-feeding women. Females of childbearing potential (FCBPs) who do not practice adequate contraceptive measures as required according to SmPCs of the administered medicinal products.
2. Contraindication to intensive chemotherapy with FOLFOXIRI plus bevacizumab.
3. Contraindications to treatment with 5-FU, oxaliplatin, folinic acid, irinotecan (FOLFOXIRI) and/or bevacizumab according to SmPCs of the administered medicinal products.
4. Patients with confirmed cerebral metastasis. In case of clinical suspicion of brain metastasis, a cranial CT or MRI must be performed to rule out brain metastasis before study inclusion.
5. Documentation of > 5 lung metastases (however, no limitation for the number of metastases in the liver)
6. Isolated distant nodal metastasis, isolated peritoneal metastasis or isolated bone metastasis
7. Limited legal capacity

4.3 Justification of Gender and Age Selection

Female and male patients will be enrolled into the study, as CRC may occur in both genders. It is expected that the gender ratio of enrolled patients will reflect the higher prevalence of CRC in men.

Only adult patients ≥ 18 years of age will be included as the safety and efficacy of bevacizumab as well as oxaliplatin, 5-fluorouracil and irinotecan in children and adolescents aged below 18 years have not been established according to the SmPCs of these medicinal products.

4.4 Patient Recruitment

Patients will be recruited by the participating physicians at the local study sites. Patients, after being informed about the study and having signed the informed consent form, will be screened with regard to the observation plan's selection criteria.

Enrolled patients will be allocated a patient identification number in the registration process**.**

4.5 Randomization and Stratification

Patients will be randomized after verification of eligibility criteria according to a randomization plan generated prior to the study by ClinAssess Biometrics Department.

Patients are randomized at a 1:1 ratio to the following treatment arms:

Arm A: Assessment of secondary intervention options by a multidisciplinary centralized tumour review board

Arm B: No assessment of secondary intervention options by a multidisciplinary centralized tumour review board

During the randomisation process, stratification will be performed, according to the parameters below, details concerning the following stratification parameters must be available prior to the randomisation:

1. Synchronous vs. metachronous metastatic disease
2. Liver-limited disease vs. non-limited disease.

For the stratification, synchronous disease is defined as metastasis/metastases, detected at the time of initial diagnosis of the CRC or within 6 months after the initial diagnosis of the CRC whereas metachronous disease is defined as metastasis/metastases, first detected later than 6 months after the initial diagnosis of the CRC.

The randomisation list (separately for each strata) follows a permuted block design with number of patients equally for both arms in each block.

5 Treatment

5.1 Treatment Regimen

Treatment in both study arms is the same clinical standard treatment with FOLFOXIRI and bevacizumab followed by maintenance treatment with fluoropyrimidine (5-FU/FA or capecitabine) plus bevacizumab if no progression has occurred according to local practice and medical guidelines. We recommend standardized procedures for this treatment to avoid bias between the study arms.

All the medicinal products recommended as part of the FIRE-7 study are used within the scope of their respective marketing authorisations. Please refer to their respective Summary of Product Characteristics (SmPCs) for further information (SmPC Irinotecan Kabi 20 mg/mL concentrate exemplary for irinotecan; SmPC ELOXATIN® 5mg/mL concentrate exemplary for oxaliplatin; SmPC Leucovorin 10 mg/mL solution for folinic acid; SmPC 5-FU medac 50 mg/mL exemplary for 5-FU; SmPC MVASI® 25 mg/mL concentrate exemplary for bevacizumab. The respective SmPCs can be downloaded on the following website: www.fachinfo.de.

5.1.1 FOLFOXIRI plus bevacizumab

We recommend treatment with at least 8 cycles FOLFOXIRI plus bevacizumab or until either progression or unacceptable toxicity of this treatment regimen (if occurring before completion of 8 cycles FOLFOXIRI) according to the following schedule (Table 5-1) followed by maintenance therapy if applicable (see Section 5.1.2). Duration of each treatment cycle with FOLFOXIRI plus bevacizumab is 2 weeks.

Treatment with FOLFORIXI plus bevacizumab may be extended to more than 8 cycles at the treating physician's discretion. However, we recommend that not more than 12 cycles should be given.

Please note, that dose modifications and dose delays of any medicinal product/products including the requirement to omit one or more than one medicinal product in case of adverse reactions are up to the treating physician’s discretion and should be performed in line with the SmPC of the respective medicinal product/ products.

Table 5-1 FOLFOXIRI plus bevacizumab, every 2 weeks

Medicinal product	Dose	Route and duration of administration	
Irinotecan	165 mg/m² BSA	iv, 30 - 90 min	Day 1
Oxaliplatin	85 mg/m² BSA	iv, 30 - 90 min	Day 1
Folinic acid	200 mg/m² BSA	iv, 120 min	Day 1
5-FU	3200 mg/m² BSA	iv infusion over 46 h	Days 1-2
Bevacizumab	5.0 mg/kg BW	iv, over 30 to 90 minutes*	Day 1

* 1st administration 90 min.; in case of good tolerability second administration 60 min., further administrations 30 min.

If any patient undergoes secondary intervention (e.g. ablation treatment, surgery) and has not been administered at least 8 cycles FOLFOXIRI plus bevacizumab before this secondary intervention, we recommend to continue treatment with FOLFOXIRI plus bevacizumab after this intervention, so that the patient will be administered at least 8 cycles.

However, treatment with bevacizumab should be discontinued for at least 28 days prior to major secondary surgical interventions and treatment with FOLFOXIRI and bevacizumab

should be reinitiated not earlier than 28 days following major surgery and only if the surgical wound is fully healed. In patients who experienced wound healing complications, treatment should be withheld until the wound is fully healed.

We recommend that the treatment should not be reinitiated later than 8-10 weeks after surgery.

5.1.2 Maintenance therapy

Continuous treatment with a maintenance therapy with a fluoropyrimidine (5-FU/FA or capecitabine) plus bevacizumab until progression is recommended, if no progression has occurred after at least 8 cycles FOLFOXIRI plus bevacizumab.

Maintenance treatment with a fluoropyrimidine plus bevacizumab is recommended according to local standards until progression to one of the following schedules (Table 5-2or Table 5-3).

Table 5-2: Maintenance treatment with 5-FU/FA plus bevacizumab, every two weeks

Maintenance Treatment 5-FU/FA plus bevacizumab, every two weeks

Medicinal product	Dose	Route and duration of administration	
Folinic acid	400 mg/m² BSA	iv, 120 min	Day 1
5-FU	2400 mg/m² BSA	iv infusion over 46 h	Days 1-2
Bevacizumab	5.0 mg/kg BW	iv, over 30 to 90 minutes*	Day 1

*Infusion duration for bevacizumab utilized prior to start of maintenance.

Table 5-3: Maintenance treatment with capecitabine plus bevacizumab, every three weeks

Maintenance Treatment capecitabine plus bevacizumab, every three weeks

Medicinal product	Dose	Route and duration of administration	
Capecitabine	1250 mg/m² BSA	p.o. BID	Day 1-14
Bevacizumab	7.5 mg/kg BW	iv, over 30 to 90 minutes*	Day 1

* Infusion duration for bevacizumab utilized prior to start of maintenance treatment.

Please note, that dose modifications and dose delays of medicinal products including the requirement to omit one or more than one medicinal product in case of adverse reactions are up to the treating physician's discretion but should be performed in line with the SmPC of the respective medicinal product/medicinal products.

5.1.3 Secondary interventions

Surgery or any suitable intervention (e.g. MWA, RFA, RTx) is permitted to treat tumour lesions. The secondary intervention will be performed according to the standards of the respective institution, but should follow the published S3 guidelines of the German Cancer Society.

Furthermore, all assessments and procedures necessary to prepare for surgery or other suitable interventions, as well as those during surgery and after surgery will follow local institutional practice for standard of care procedures.

Evaluating the primary endpoint, the first interventions performed in one organ (e.g. liver) are rated when performed in a generally curative context with the objective to achieve a no-evidence-of-disease situation in the respective organ (e.g. even in the presence of lung metastases that need to be approached in a further intervention).

It must be documented in the eCRF:

- Secondary interventions of all documented tumour sites (i.e. all tumour lesions found by means of CT/MRI imaging) in their respective sequence including kind of secondary intervention procedure/procedures (resection surgery; ablation treatment: [RFA, MWA]; radiotherapy), site/sites and date/dates of interventional procedure, evaluation of residual tumour status (R0, R1, R2) if applicable.
- Success of the first secondary intervention performed in one organ evaluated by means of CT/MRI imaging of the respective organ about 8-12 weeks after the intervention (time interval of radiological restaging according to local routine).

6 Patient Withdrawal and Study Discontinuation

6.1 Patient Withdrawal

As treatment with FOLFOXIRI and bevacizumab follows local clinical routine and medical guidelines, patient's withdrawal from treatment with FOLFOXIRI plus bevacizumab (or maintenance treatment with fluoropyrimidine (FP) plus bevacizumab) is up to participating physician's discretion and not subject of this study observation plan. However, reason for permanent treatment withdrawal will be documented in the eCRF as follows:

- Disease progression
- Suspected pregnancy or inadequate contraception (only for FCBPs)
- Adverse event(s) whether or not suspected related to any of the medicinal products of FOLFOXIRI plus bevacizumab (or maintenance treatment with FP plus bevacizumab) or any medical condition that, according to the participating physician's discretion, may cause severe or permanent harm to the patient if he/she continues study treatment
- Patient non-compliance that could place the patient at an unacceptable risk in the participating physician's and/or responsible institution's judgment
- Patient's will not to continue treatment with FOLFOXIRI plus bevacizumab (or maintenance treatment with FP plus bevacizumab)
- Withdrawal of patient's consent to further participation in the observational study
- Death
- Lost to follow-up

The primary reason for discontinuation of treatment will be recorded on the eCRF.

Patients have the right to withdraw consent at any time and without giving any reasons without prejudice to their future medical care by the participating physician or other medical health care personnel at the institution.

6.2 Discontinuation of a Study Centre

An individual study site will be stopped from participation in the study if any of the following criteria applies:

- Unsatisfactory enrolment with respect to quantity or quality at the study centre
- Changes at the study centre (personnel, technical facilities) that prevent conducting the study in accordance with the observation plan
- Falsification of data or records at the respective study centre
- Withdrawal of favourable opinion by the respective ethics committee

6.3 Discontinuation of the Entire Study

New safety findings that may constitute an unacceptable safety risk for the patients will cause discontinuation of the entire study.

The ethics committee may stop the study or participation of a study site in the study for medical, safety, regulatory, administrative or other reasons consistent with ICH-GCP.

7 Schedule of Study Assessments and Procedures

Refer to Table 2-1 for an outline of procedures and assessments to be documented.

As treatment with FOLFOXIRI and bevacizumab (or maintenance treatment with fluoropyrimidine plus bevacizumab) follows local clinical routine and medical guidelines, laboratory testing (haematology and serum chemistry) as well as any radiological imaging procedures are performed as part of the clinical routine at the study centers according to the present standards in oncology. Accordingly, all laboratory parameters evaluated including the frequency of their evaluation are part of clinical routine and are only documented as and if determined according to local standard in the eCRF. No strict time windows for these assessments apply in addition to standard of care requirements.

7.1 Screening Procedures and Baseline Examinations

In general, screening procedures will have to be completed within 28 days before randomisation. Other time intervals may be applicable if indicated below. In patients, in whom treatment with FOLFOXIRI plus bevacizumab has already been initiated prior to study inclusion, retrospective documentation of baseline values for a time interval of within 28 days before start of the treatment instead of within 28 days before randomisation.

- Signed patient informed consent
- Verification of selection criteria
- Documentation of RAS mutational status as determined by local pathology in tissue of primary tumour or metastasis; testing earlier than 28 days prior to randomisation permitted.
- Record medical history including medical history of mCRC (date of first diagnosis of CRC; TNM stage and grading at first diagnosis; current TNM stage; primary tumour site and sidedness of the primary tumour (right-sided/left-sided); site/sites of metastasis; date of diagnosis of metastasis, type of metastasis (synchronous metastases or metachronous metastases); date of histological confirmation; surgery of primary tumour and/or metastases; adjuvant chemotherapy (yes/no, duration and administered anti-tumour medicinal products); in case of rectal cancer: prior radiotherapy or radiochemotherapy (if any)
- Record demographic information including age and self-reported race/ethnicity
- Body weight, height
- Documentation of vital signs (pulse, blood pressure, body temperature)
- ECOG performance status
- Record results of imaging procedures
  - Abdominal CT/MRI
  - Chest X-ray in two planes or alternatively chest CT
  - Other imagine procedures if appropriate in case of known or suspected metastasis
- Tumour assessment according RECIST 1.1 by means of the CT/MRI images at the local study center
- Documentation of haemogram and differential blood count **as and if determined according to local standard** (e.g. leukocytes, neutrophils, thrombocytes and haemoglobin)

- Documentation of the following serum chemistry values **as and if determined according to local standard:** creatinine, estimated GFR, C-reactive protein (CRP), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT))
- Documentation of urinalysis by urine dipstick **as and if determined according to local standard**.
- Documentation of pregnancy testing (in blood or urine) **as and if determined**
- Documentation of phenotype and/or genotype testing for DPD deficiency as and if performed
- Continuous documentation of non-serious and serious adverse events with severity ≥ Grade 3 (severity according the NCI CTCAE version 5.0), starting with the date of informed consent

7.2 Assessments during the Treatment Phase

7.2.1 Assessments before Start of Each Treatment Cycle

The following procedures have to be performed in the week before Day 1 of each treatment cycle or on Day 1 of each treatment cycle if not otherwise specified below.

In patients, who have received treatment with FOLFOXIRI plus bevacizumab prior to study inclusion, respective data should be documented retrospectively as and if determined according to local standard for the respective treatment cycles.

- ECOG performance status
- Body weight
- Documentation of vital signs (pulse, blood pressure, body temperature
- Documentation of haemogram and differential blood count **as and if determined according to local standard** (e.g. leukocytes, neutrophils, thrombocytes and haemoglobin). In addition, no strict time window applies.
- Documentation of the following serum chemistry values **as and if determined according to local standard**: creatinine, GFR, CRP, total bilirubin, AST, ALT). In addition, no strict time windows applies.
- Documentation of urinalysis by urine dipstick **as and if determined according to local standard.**
- Documentation of pregnancy testing (in blood or urine) **as and if determined**
- Documentation of applied treatment with FOLFOXIRI and bevacizumab (or modified treatment schedule/maintenance treatment schedule) – continuous documentation during the treatment phase
- Documentation of any secondary intervention procedure/procedures including kind of interventional procedure/procedures (resection surgery; ablation treatment: [RFA, MWA]; radiotherapy), site/sites and date/dates of intervention, evaluation of residual tumour status (R0, R1, R2)
- Continuous documentation of non-serious and serious adverse events with severity ≥ Grade 3 (severity according the NCI CTCAE version 5.0)

7.2.2 Restaging

Restaging procedures have to be performed in those intervals that are the local clinical standard interval for response control of first-line treatment in RAS mutant mCRC patients.

We recommend to perform restaging procedures about every 8-12 weeks after the effective start of treatment with FOLFOXIRI plus bevacizumab before or after randomisation **and about 8-12 weeks after secondary intervention/interventions in one organ.**

In addition, imaging procedures may be performed at any time if clinically indicated.

- Record results of the following imaging procedures
  - Abdominal CT/MRI
  - Chest X-ray in two planes or alternatively chest CT (only in case of known or suspected pulmonary metastasis/metastases)
  - Other imagine procedures if appropriate in case of known or suspected metastasis/metastases

  Note: Restaging about 8 -12 weeks after first secondary intervention in one organ must record whether a no-evidence-of-disease situation was obtained in the respective organ.
- Tumour assessment according RECIST 1.1 by means of the CT/MRI images at the local study center
- **Only in patients of study Arm A:** Evaluation of secondary intervention options by the centralized tumour board by means of CT/MRI scan after the first restaging (obligatory) and second restaging (optional).
  Although the evaluation of second intervention options by the centralized tumour board after the second restaging is optional, re-evaluation after the second restaging is recommended in cases of delayed/improved treatment response at the second restaging.
  Pseudonymized copies of the CT/MRI scans from the first restaging (obligatory), the second restaging (optional) and the baseline CT/MRI scans (baseline scan applicable only for the evaluation after the first restaging) have to be sent to the study office at the university hospital of the LMU, att. Mr. M.Wolff/Prof. V. Heinemann for presentation to the centralized tumour board members as soon as possible after the respective imaging diagnostics for restaging.
  In case that the option for evaluation of secondary intervention options by the centralized tumour board after the second restaging will not be utilized, the reason therefor should be laid down in the eCRF (e.g. progressive disease, contraindication against secondary intervention, patient's wish).
- Documentation of applied treatment with FOLFOXIRI and bevacizumab (or modified treatment schedule/maintenance treatment schedule) – continuous documentation during the treatment phase
- Documentation of any secondary intervention procedure/procedures including kind of interventional procedure (resection surgery; ablation treatment: [RFA, MWA]; radiotherapy), site/sites and date/dates of intervention, evaluation of residual tumour status (R0, R1, R2) if applicable
- Continuous documentation of non-serious and serious adverse events with severity ≥ Grade 3 (severity according the NCI CTCAE version 5.0)

7.3 Assessments at the End of First-line Treatment

The following procedures have to be performed within 3 weeks after progression under first-line treatment **or** prior to first administration of any medicinal product of the next treatment line, whichever date is earlier.

The next treatment line is defined as a treatment line containing any anti-tumour medicinal product that is not part of the first line treatment with FOLFOXIRI and bevacizumab and maintenance.

- Body weight
- ECOG-performance status
- Documentation of vital signs (pulse, blood pressure, body temperature
- Documentation of haemogram and differential blood count **as and if determined according to local standard** (e.g. leukocytes, neutrophils, thrombocytes and haemoglobin)
- Documentation of the following serum chemistry values **as and if determined according to local standard:** creatinine, estimated creatinine clearance, CRP, total bilirubin, AST, ALT
- Documentation of urinalysis by urine dipstick **as and if determined according to local standard**
- Documentation of pregnancy testing (in blood or urine) **as and if determined**
- Documentation of applied treatment with FOLFOXIRI and bevacizumab (or modified treatment schedule/maintenance treatment schedule) – continuous documentation during the treatment phase
- Documentation of any secondary intervention procedure/procedures including kind of interventional procedure/procedures (resection surgery; ablation treatment: [RFA, MWA]; radiotherapy), site/sites and date/dates of intervention, evaluation of residual tumour status (R0, R1, R2) if applicable
- Record results of imaging procedures **(only if any imaging procedures in addition to those performed as the last restaging have been performed up to the treating physician's discretion)**
  - Abdominal CT/MRI
  - Chest X-ray in two planes or alternatively chest CT (only in case of known or suspected pulmonary metastasis/metastases
  - Other imagine procedures if appropriate in case of known or suspected metastasis/metastases
- Tumour assessment according RECIST 1.1 by means of the CT/MRI images at the local study center (only if any imaging procedures in addition to those performed as the last restaging have been performed up to the treating physician's discretion)
- Continuous documentation of non-serious and serious adverse events with severity ≥ Grade 3 (severity according the NCI CTCAE version 5.0) until 30 days after administration of the last dose of any medicinal product of the FOLFOXIRI (or de-escalated treatment schedule if applicable) plus bevacizumab regimen including recommended maintenance with FP plus bevacizumab or start of the next treatment line, whichever date is earlier.
  The next treatment line is defined as treatment line containing any anti-tumour medicinal product that is not part of the first line treatment with FOLFOXIRI and bevacizumab and maintenance.

7.4 Assessments during Follow-up

Follow-up assessments have be performed every three months ± 4 weeks after the end of first-line treatment until death or for 16 months after last administration of FOLFOXIRI in combination with bevacizumab including maintenance therapy, whichever date is earlier.

Follow-up information about survival and further anti-tumour treatments may be collected via telephone calls and/or clinic visits.

Follow-up information about survival and further anti-tumour treatments may be as well requested from the treating physician via telephone or as copy of the medical report, if the patient gives his consent to this procedure.

- Record results of imaging procedures **- only required until first progression after first line treatment during follow-up and only if treatment with medicinal products of first line was permanently discontinued without progression.**
  - Abdominal CT/MRI
  - Chest X-ray in two planes or alternatively chest CT (only in case of known or suspected pulmonary metastasis/metastases
  - Other imagine procedures if appropriate in case of known or suspected metastasis/metastases
  - Tumour assessment according RECIST 1.1 by means of the CT/MRI images at the local study center
- Record survival data
- Record subsequent anti-cancer therapies

8 Study Assessments

8.1 Efficacy Assessments

8.1.1 Rate of Patients in Whom Secondary Interventions are Performed in Curative Intent (Primary Endpoint)

Rate of patients in whom secondary interventions are performed in curative intent is the percentage of patients in whom secondary interventions in curative intent (e.g. resection, ablation treatment or combination of both) were performed after treatment with FOLFOXIRI and bevacizumab had been initiated and prior to start of the next treatment line. The next treatment line is defined as treatment line containing any anti-tumour medicinal product that is not part of the first line treatment with FOLFOXIRI and bevacizumab and maintenance.

Evaluating the primary endpoint, the first interventions performed in one organ (e.g. liver) are rated when performed in a generally curative context with the objective to achieve a no-evidence-of-disease situation in the respective organ (e.g. even in the presence of lung metastases that need to be approached in a further intervention).

Secondary intervention with objective to achieve a no-evidence-of-disease situation in the respective organ is defined as any (combination of) procedure/procedures that eliminates/eliminate all tumour lesions in the respective organ with radiologically documented success about 8-12 weeks (time interval of radiological restaging according to local routine) after the intervention. In addition, patients who underwent resection must have a R0/R1 resection for a no-evidence-of-disease status.Generally, only the first and second restaging (recommended to be performed 8-12 and 16-24 weeks after the effective start of treatment with FOLFOXIRI plus bevacizumab before or after randomisation) will be taken into account for assessment of secondary intervention options. To avoid a bias due to shorter or longer time between restagings, further restagings can be taken into account if not performed more than 6 months after effective start of treatment. Furthermore, restagings more than 6 months after effective start of treatment as well as any restagings after start of maintenance treatment irrespective of the time elapsed until start of maintenance treatment will **not** be taken into account. Patients not fulfilling these criteria will be discussed in a data review meeting.

8.1.2 Response Evaluation

Tumour response will be evaluated according to the response evaluation criteria in solid tumours (RECIST) criteria version 1.1 (24) locally at the study center.

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

Measurable

A tumour lesion is categorized measurable if the lesion can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT/MRI scan. CT layer thickness must not be greater than 5 mm.

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan. The CT scan slice thickness must not be greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-Measurable

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: blastic bone leasons, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Target and Non-Target Lesions

When more than one measurable lesion is present at baseline (i.e. prior to start of induction treatment) all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all in involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline as “present”.

Tumour Measurements

Imaging procedures for tumour measurement(s) will be performed within 28 days before randomisation for the baseline assessment and during treatment at every restaging (recommended to be performed about every 8-12 weeks after first administration of FOLFOXIRI and bevacizumab) and at the EoT visit with additional imaging procedures at any time point if clinically indicated. This interval is the clinical standard interval for response control of first-line treatment in RAS mutant mCRC patients.

If the treatment with medicinal products of the first line treatment is permanently discontinued without progression, imaging procedures during follow-up will be continued until first progression to first line treatment (including treatment with FOLFOXIRI and bevacizumab as well as any secondary intervention) during follow-up.

Imaging procedures performed within 6 weeks prior to the EoT visit do not need to be repeated.

Imaging has to be performed with MRI or CT. The method used is up to the treating physician’s decision.

However, participating physicians must adhere to the same imaging method during the study. Ultrasound and positron emission tomography (PET) scans as methods of tumour measurement must not be used. All measurable tumour manifestations identified as target lesions must be measured at each evaluation. Non-target lesions do not need to be measured but should be assessed qualitatively instead.

Table 8-1: Definitions of criteria to determine objective tumour response

Complete response (CR)	Disappearance of all target lesions and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have

	reduction in short axis to < 10 mm. No appearance of one or more new lesions.
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters **and** no unequivocal progression of existing non-target lesions **and** no appearance of one or more new lesion.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study **and** no unequivocal progression of existing non-target lesions **and** no appearance of one or more new lesion.
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. **Or** unequivocal progression of existing non-target lesions. **Or** appearance of one or more new lesion.

Table 8-2: Assessment of overall tumour response

Overall response	Target lesion	Non-target lesion	New lesion
CR	CR	CR	No
PR	CR	Not CR, not PD	No
PR	CR	Not assessed	No
PR	PR	Not PD or not all assessed	No
SD	SD	Not PD or not all assessed	No
PD	PD	Indifferent	No or yes
PD	Indifferent	PD	No or yes
PD	Indifferent	Indifferent	Yes
Not assessable	Not all assessed	Not PD	No

8.1.3 Objective Response Rate (ORR)

The ORR is defined as the proportion of patients in whom a CR or PR was observed.

8.1.4 Time-to-Event Measures

Progression-free survival (PFS) is defined as time from the effective date of the first administration of FOLFOXIRI plus bevacizumab before or after randomisation (as administration of up to four cycles FOLFOXIRI and bevacizumab permitted before study inclusion) to objective tumour progression or death from any cause. Patients without an event will be censored at the last date known to be progression-free.

Progression-free survival rate at 6, 12 and 16 months is the percentage of patients who are alive and without progression after 6, 12 and 16 months.

Overall survival (OS) is defined as time from the effective date of the first administration of FOLFOXIRI plus bevacizumab either before or after randomisation (as administration of up to four cycles FOLFOXIRI and bevacizumab permitted before study inclusion) to the date of death of any cause. Patients who are alive will be censored at the date of the last patient contact with the respective study site or treating physician.

Overall survival rate at 6, 12 and 16 months is the percentage of patients who are alive after 6, 12 and 16 months.

8.2 Safety Assessments

8.2.1 Definition, Assessment and Follow-up of Adverse Events

An **adverse event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. (ICH E6(R2), ICH E2A).

The definition of an AE includes any worsening of a pre-existing condition or underlying disease and events associated with the discontinuation of the use of medicinal product/products. Elective or previously scheduled (prior to enrolment) procedures or treatments for a pre-existing condition, that had not worsened from the baseline assessment, are not considered AEs. However, untoward medical events occurring during these procedures or treatments should be considered AEs.

All the medicinal products of the FOLFOXIRI combination chemotherapy (5-fluorouracil, folinic acid, oxaliplatin, irinotecan), the recommended maintenance therapy (capecitabine, 5-fluorouracil, folinic acid, irinotecan) as well as the VEGF-antibody bevacizumab under the trade name Avastin® have a marketing authorization since more than 10 years and have been used widely in treatment of tumour patients. Thus, their safety profile is well known. Bevacizumab biosimilars have a marketing authorisation since about 1 to 2 years. It is very unlikely that bevacizumab biosimilars will produce different event rates than AVASTIN and AEs of grade 2 or less are very unlikely to drive clinical decisions and even more unlikely to be clearly related to any bevacizumab biosimilar. Therefore only clinical relevant AEs and SAEs with a severity ≥ Grade 3 are addressed that are of interest for clinical decision making and also in terms of treatment exposition. As all these medicinal products (5-fluorouracil, folinic acid, oxaliplatin, irinotecan, capecitabine, bevacizumab) are used within their marketing authorization, only adverse events and serious adverse events with a severity ≥ Grade 3 (severity according to NCI CTCAE version 5.0) will be recorded in this observation study.

Participating physicians are responsible for continuously documenting non-serious AEs and SAEs with a severity ≥ Grade 3 from the date of informed consent to take part in this observation study until 30 days after administration of the last dose of any medicinal product of the FOLFOXIRI (or de-escalated treatment schedule if applicable) plus bevacizumab regimen including recommended maintenance with FP plus bevacizumab or start of the next treatment line, whichever date is earlier. The next treatment line is defined as treatment line containing any anti-tumour medicinal product that is not part of the first line treatment with FOLFOXIRI and bevacizumab and maintenance.

The participating physician is responsible for ensuring that all adverse events are documented in the patients' source documents and the AE page of the eCRF with the following information:

- Description of AE (medical term or preferably a diagnosis)
- Date of onset and date of resolution
- Severity (Section 8.2.1.1)
- Seriousness and if serious event, seriousness criterion (Section 8.2.1.2)

- Causal relationship to any medicinal product of the FOLFOXIRI regimen and bevacizumab as well as to any medicinal product of the recommended maintenance with FP and bevacizumab if applicable (Section 8.2.1.3)
- Exposure to medicinal product of the FOLFOXIRI regimen and/or bevacizumab including brand name of the administered drug for bevacizumab and dose
- Actions taken to treat the event
- Outcome

8.2.1.1 Assessment of Severity/Intensity

For the grading of the severity/intensity of an AE, the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 5.0 must be used. Site staff must have access to a copy of NCI-CTCAE version 5.0.

AEs not defined in the NCI-CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activity of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

8.2.1.2 Assessment of Seriousness

A **serious adverse event (SAE)** is any untoward medical occurrence that at any dose

- Results in death,
- Is life-threatening,

  Note: The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions; it does not refer to experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions, but that do not constitute a substantial disruption),,Is a congenital anomaly/birth defect. (ICH E6(R2), ICH E2A)
- Any suspected transmission via a medicinal product of an infectious agent
- Is a medically significant event (i.e., an event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions

in a person who has never before had seizure activity, but that do not result in hospitalization, or the development of drug dependency or drug abuse).

Each adverse event has to be assessed by the participating physician of the trial center if this adverse event is serious or not. If any adverse event is assessed as serious, the applicable seriousness criterion has to be reported.

Hospitalisation due to procedures and treatment that have to be documented according to the observation plan including hospitalisations for secondary interventions as treatment of the underlying tumour diseases as well as hospitalisation for any treatment of pre-existing conditions planned prior to start of the study are not considered SAEs.

8.2.1.3 Assessment of Causal Relationship

All noxious and unintended responses to a medicinal product related to any dose should be considered **adverse drug reactions (ADR)**. The phrase 'responses to a medicinal product' means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. (ICH E2A)

- AE occurs in a plausible time relationship to drug administration.
- AE cannot be explained by concurrent disease or other drugs or chemicals.
- The response to withdrawal of the drug (de-challenge) should be clinically plausible.

In consideration of these guidelines, the causal relationship of each adverse event to any medicinal product of the FOLFOXIRI regimen and bevacizumab as well as to any medicinal product of the recommended maintenance with FP and bevacizumab has be assessed by the participating physician of the trial center as "related" or "not related".

8.2.1.4 Follow-up of Adverse Drug Reactions

ADRs should be followed until resolution or stabilisation. Patients with ongoing ADRs at the last scheduled visit should be further followed until resolution or stabilisation for at least three months.

8.2.2 Reporting of Serious Adverse Events, Serious Adverse Drug Reactions, Other Safety-Related Events and Non-serious Adverse Drug Reactions

SAEs with a severity ≥ Grade 3 (see Section 8.2.1 for the rationale) including death of patients for whom no further details of the death circumstances are provided or available so that a causal relationship with medicinal products cannot be ruled out must be reported from the date of informed consent to take part in this observation study until 30 days after the last dose of any medicinal product of the FOLFOXIRI (or de-escalated treatment schedule if applicable) plus bevacizumab regimen including recommended maintenance with FP plus bevacizumab or start of the next treatment line, whichever date is earlier. The next treatment line is defined as treatment line containing any anti-tumour medicinal product that is not part of the first line treatment with FOLFOXIRI and bevacizumab and maintenance.

Beyond this date only those Serious Adverse Drug Reactions (SADRs) must be reported for which a causal relationship to bevacizumab is suspected including death of patients for whom no further details of the death circumstances are provided or available so that a causal relationship to bevacizumab cannot be excluded

SAEs should be reported immediately, preferably not later than 24 hours to Clin*Assess* GmbH (contact details below).

Clin*Assess* GmbH
Werkstättenstraße 39b
51379 Leverkusen
Germany
Tel.: +49 (0)2171 36336 -0
Fax: +49 (0)2171 36336 -55

Any report of a SADR related to MVASI® or the administration of bevacizumab of unknown brand name or other Amgen product including any report of death of patients for whom no further details of the death circumstances are provided to the drug safety department of Amgen GmbH within 1 business day after the responsible institution (as sponsor) becomes aware of the event.

In addition, non-serious adverse drug reactions related to MVASI® or the administration of bevacizumab of unknown brand name or other Amgen product are provided to the drug safety department of Amgen GmbH in form of AR listings every 14 calendar days on the basis of the eCRF (i.e. within 15 calendar days after the responsible institution (as sponsor) becomes aware of the event).

If an SAE has resolved, if no further improvement is expected or if new information concerning the SAE is available, the participating physician has to send a SAE follow-up form, which will be distributed as described above.

The responsible institution (as sponsor) will also provide individual reports of other safety findings relating to MVASI® or the administration of bevacizumab of unknown brand name or other Amgen product to the drug safety department of Amgen GmbH within 15 calendar days after the responsible institution (as sponsor) becomes aware of the event.

Other safety findings include:

- Pregnancy of female patients and female partners of male patients (refer to Section 8.2.3 for further information)
- Breast-feeding of female patients
- Medication errors
- Overdose, underdose
- Misuse, abuse, addiction
- Accidental exposure, occupational exposure

Off-label useListings for safety data reconciliation (containing ADRs, SADRs, Other safety findings) related to MVASI® or the administration of bevacizumab of unknown brand name or other Amgen product will be provided to the drug safety department of Amgen GmbH annually and at the end of the study.

Other aggregate analysis will be provided to Amgen at the time of submission to any body governing research conduct by the responsible institution.

An abbreviated Annual Safety Report providing a listing of SAE events, SAR events, observed other safety findings relating to MVASI® or the administration of bevacizumab of unknown brand name or other Amgen product und containing information about general study update, number of patients and centers will be provided to Amgen annually.

This study is a non-interventional study according to German Medicinal Products Act. The responsible institution Klinikum der Universität München -LMU München is not the marketing authorisation holder of any medicinal product administered in this study.

All participating physicians are kindly requested to report adverse drug reactions, including suspected cases, either to the Drug Commission of the German Medical Association or to BfArM/PEI via the spontaneous reporting system in accordance with their professional code of conduct in order to identify new risks associated with medicinal products as quickly as possible.

8.2.3 Reporting of Pregnancies

Pregnancies or suspected pregnancies (including a positive pregnancy test) of a female patient occurring while the patient is being treated with any medicinal product of the FOLFOXIRI (or de-escalated treatment schedule if applicable) plus bevacizumab regimen including recommended maintenance with FP plus bevacizumab or in the 6 months after the last administration of these medicinal products are considered medically important safety findings. These events have to be reported as soon as possible, preferably **within 24 hours** of knowledge of the event by fax to Clin*Assess* GmbH (contact details below).

Clin*Assess* GmbH
Werkstättenstraße 39b
51379 Leverkusen
Germany
Tel.: +49 (0)2171 36336 -0
Fax: +49 (0)2171 36336 -55

A follow-up on the pregnancy, the fetus and the child is important. All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death occurring after 28 days that the participating physician suspects to be related to the in utero exposure to the medicinal product/medicinal products should also be reported as SAEs within 24 hours of the participating physician's knowledge.

Any report of a pregnancy or suspected pregnancy (including a positive pregnancy test) of a female patient who has received MVASI® or bevacizumab of unknown brand name or another Amgen product are provided to the drug safety department of Amgen GmbH within 15 calendar days after the responsible institution (as sponsor) becomes aware of the event.

Female partners of a male patient being treated with any medicinal product of the FOLFOXIRI (or de-escalated treatment schedule if applicable) plus bevacizumab regimen including recommended maintenance with FP plus bevacizumab or in the 6 months after the last administration of these medicinal products should be advised to call their health care provider immediately if they get pregnant. Male patients are requested to notify the participating physician of their partner's pregnancy if their partner has consented to share the information about her pregnancy with the participating physician.

If a pregnancy-related event occurs in a female partner of a male patient, the participating physician should make an effort to obtain the female partner's consent to share information about the pregnancy including the outcome of the pregnancy with the responsible institution and Amgen and allow the pregnancy-related event to be followed up to completion. Pregnancies of the female partner including the outcome of this pregnancy occurring while the patient is treated with any medicinal product of the FOLFOXIRI (or de-escalated treatment

schedule if applicable) plus bevacizumab regimen including recommended maintenance with FP plus bevacizumab or in the 6 months after the last administration of these medicinal products should be reported and forwarded as described above.

Any report of a pregnancy or suspected pregnancy (including a positive pregnancy test) of a female partner of a male study participant who has received or still receives MVASI® or bevacizumab of unknown brand name or another Amgen product are provided to the drug safety department of Amgen GmbH within 15 calendar days after the responsible institution (as sponsor) becomes aware of the event.

8.2.4 Reporting of Product Complaints to Amgen Products

Product complaints to Amgen products are defined as any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either: (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging, drug containers, delivery system, labelling, and inserts.

Examples include:

- Device that is damaged or broken
- Bent or blunt needles
- Missing or illegible labeling
- Inability of customer to administer the product
- Product with an unexpected color, appearance, or particles
- Use error (i.e, an act or omission of an act that results in a different combination product or medical device response than intended by the manufacturer or expected by the user, where the user attempted to use the combination product or medical device in good faith and experienced difficulty or deficiency administering the product).

Reports of misuse of a combination product or medical device (i.e, the intentional and improper use of a combination product or medical device not in accordance with the authorized product information) are not considered Product Complaints.

The responsible institution (as sponsor) will notify Amgen of all product complaints to Amgen products as defined above in connection with a drug or medical device immediately or not later than one business day after awareness regardless of whether they are related to an ADR or not.

9 Statistical Considerations

9.1 Overview

This is a randomised, multicentre study with two arms.

Primary objective of the study is to compare the proportion of patients with secondary interventions performed in a generally curative context in patients with RAS mutant mCRC treated with FOLFOXIRI and bevacizumab when secondary intervention options are either assessed by a centralized tumour board **versus** no centralized tumour board.

The statistical evaluation will be performed at the CRO ClinAssess GmbH, Leverkusen. Details of the analysis will be described in the statistical analysis plan (SAP) to this study. The SAP will be finalized and signed before database closure.

9.2 Statistical Hypotheses

A rate of patients in whom secondary interventions are performed in curative intent of about 15% is expected in study Arm B without assessment of secondary intervention options by a multidisciplinary centralized tumour board based on the resection rate of metastases in molecularly unselected patients of the FIRE-3 study (5), whereas a rate of ≥ 35% would be considered as successful (7) in the study Arm A with assessment of secondary intervention options by a multidisciplinary centralized tumour board.

Hence the hypotheses to be tested are:

H_0: Rate of patients in whom secondary interventions are performed in curative intent (with assessment by a centralized tumour board) ≤ Rate of patients in whom secondary interventions are performed in curative intent (without assessment by a centralized tumour board)

H_1: Rate of patients in whom secondary interventions are performed in curative intent (with assessment by a centralized tumour board) > Rate of patients in whom secondary interventions are performed in curative intent (without assessment by a centralized tumour board)

9.3 Sample Size Calculation

The primary endpoint will be evaluated by a one-sided Chi-square test.

In order to reject the null hypothesis at a one-sided significance level of 5% with a power of at least 80% in total 114 patients are required, 57 patients per arm.

It is expected that 12% of the randomized patients will not be evaluable for the primary analysis of the rate of patients in whom secondary interventions are performed in curative intent (as defined in Section 9.4). Hence, 130 patients (65 patients per arm) have to be randomized.

9.4 Patient Populations for Analysis

The **full analysis set (FAS)** includes all randomised patients and is used to perform the intent-to-treat (ITT) analysis. The full analysis set will be used for all baseline and efficacy parameters, except for primary endpoint.

The **safety set (SAF)** consists of all randomised patients who were treated within the study and is used to perform the safety analysis. The safety set will be used for all safety parameters.

The primary analysis of the rate of patients in whom secondary interventions are performed in curative intent will be performed in a subset of the FAS with the following conditions:

- Randomized patient in whom the planned treatment with FOLFOXIRI and bevacizumab has been initiated and who have received at least four cycles FOLFOXIRI and bevacizumab (either before and/or after randomisation).
- CT- and/or MRI images from baseline (before the effective start of treatment with FOLFOXIRI plus bevacizumab) and at least one restaging examination after baseline (during treatment phase or during follow-up) are available.

9.5 Statistical Analysis

In general, the recorded baseline, efficacy, and safety will be presented using standard descriptive methods. For continuous data, distribution parameters (mean, standard deviation, minimum, median, and maximum) will be computed. For categorical data, frequency counts will be given.

If requested, individual patient data listings will be generated for any study parameter.

With regard to response rates (or other rates), patients in whom the respective response criteria are not met will be evaluated as non-responders.

Time-to-event data (e.g. progression–free survival, overall survival) will be graphically presented according to Kaplan-Meier. Estimates for the median time to event as well as the proportion of patients not having reached the event after appropriate times will be presented. The starting point will be the day of first administration of treatment with FOLFOXIRI plus bevacizumab. Patients not having documented the respective event will be censored with the last date at which it is known that the respective event has not been reached.

Missing data will not be replaced. If necessary, incomplete dates will be imputed appropriately.

All secondary and exploratory parameters will be analysed in descriptive manner. In case of comparison between treatment arms/groups appropriate tests will be used (chi-square test or Fisher’s exact test for proportions, Wilcoxon rank-sum test for continuous parameters, log-rank test for time-to-event parameters).

Further details will be laid down in the statistical analysis plan (SAP).

10 Data Handling and Record Keeping

10.1 Participating Physician's Site Files

The participating physicians at each study site should keep a study master file containing, at all times, the essential documents relating to the study in the participating physician's study file (ISF). The essential documents allow for the verification of the conduct of the study and the quality of data generated; they include the observation plan and amendments, patient information and informed consent form, ethics committee approval, staff curriculum vitae and authorization forms and other documents/correspondence. The participating physician must also keep the original informed consent form signed by the patient (a signed copy is given to the patient). The ISF should be readily available and directly accessible upon request.

10.2 Source Data and Source Documents

Source data are defined as the information in original records and certified copies of original records of clinical findings, observations, or other activities in a study necessary for the evaluation of the study. Source data are contained in source documents (original records or certified copies). Source documents may be hospital records, patient files, clinical and office charts, laboratory notes, pharmacy dispensing records, recorded data from automated instruments or x-rays.

There are no data that are recorded directly on the eCRF and considered as source data.

10.3 Data Collection

Data collection is the responsibility of the site staff at the study centre under the supervision of the site's participating physician. The participating physician must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study patients. Source data must be attributable, legible, contemporaneous, original, accurate and complete. Changes to source data must be traceable, should not obscure the original entry and should be explained if necessary.

Data and information to be reported to the responsible institution according to the observation plan on each individual patient will be recorded in study-specific case report forms (CRF). The participating physician must ensure the accuracy, completeness, legibility and timeliness of the data in the CRFs.

Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained (Section 10.3.1).

10.3.1 Database/eCRF

CRF data will be collected with an electronic data capture (EDC) system provided by the CRO contracted with this task by the responsible institution. The EDC contents and functionalities regarding patient data will be proposed by the CRO and approved by the responsible institution.

The individual modules of the EDC system will be validated in a test environment and must be approved by the responsible institution prior to uploading to the production environment. Further changes will only be made according to change control process. Edit checks will be implemented in the EDC system according to the data validation plan (DVP), also approved by the responsible institution. Edit checks will be performed during data entry; further offline checks will be performed on an ongoing basis according to the agreement with the responsible institution.

User role specific access rights will be granted or revoked by the CRO or their EDC vendor upon authorized request from the sites participating in the study. Password-protected access ensures that changes and corrections are only made by authorised participating physician's site staff (21 CFR 11.10(c)). The eCRF will include an audit trail with all user activities recorded by user name, action and time. For any data change or correction, a reason is required.

The eCRF data are regularly reviewed. The EDC system enables the CRO data management and data reviewers to raise data queries for clarification of data inconsistencies.

To ensure accuracy and completeness of the eCRFs, the participating physician should review and electronically sign the completed eCRF for each patient. If changes are made in the eCRF after the participating physician has already signed, the changes should be reviewed and electronically signed again.

The data tables from the database will be transformed into SAS® data sets for final data analysis.

After data base closure, the EDC vendor provides all data collected with the eCRF system including the audit trail to the participating physicians (data of the respective site) and the responsible institution.

10.4 Record Retention

The responsible institution and the participating physicians should archive the content of the study master file/participating physician's site file for at least 10 years after the end of the study in a way that ensures that it is readily available and accessible, upon request, to the competent authorities. The medical files should be archived longer if legally required (e.g., x-ray). The contents have to remain complete and legible throughout the entire archiving period. No records will be destroyed without the written consent of the responsible institution.

If the participating physician cannot fulfil the archiving requirement at the participating physician site, archiving arrangements must be made between the participating physician and the responsible institution to store these in sealed containers outside of the site so that they can be returned sealed to the participating physician in the event of a regulatory audit.

11 Regulatory, Ethical, Legal and Study Oversight Considerations

11.1 General Provisions and Agreements

The observation plan was developed and the study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and ICH Good Clinical Practice guidelines.

11.2 Notification According to German Medicinal Products Act section 4 para 23

The study is a non-interventional study according to German Medicinal Products Act section 4 para 23, performed by the university hospital of the university Munich – LMU Munich.

As study which serves the purpose of gathering knowledge resulting from the use of authorised or registered medicinal products (“Anwendungsbeobachtung”), notification of the study will be sent to the competent higher federal authority, the Federal Association of Panel Physicians, the Central Federal Association of the Health Insurance Funds, as well as the Association of Private Health Insurance Funds in accordance with German Medicinal Products Act section 67 para 6. In this regard, the names of the participating physicians will be revealed to the Federal Panel Physicians' Association and the Central Federal Association of the Health Insurance Funds.

11.3 Approval by the Ethics Committees

Each participating physician is responsible to obtain a favourable opinion for the study by the ethics committee of his study center prior to the initiation of the study in his study center in accordance with the Declaration of Helsinki and the Medical Association's professional code of conduct for each study site. The responsible institution will obtain approval for the study by the ethics committee of each participating study center.

Any substantial amendment to the observation plan after receipt of the favourable opinion for the study by the respective ethics committees must again get approval by the respective ethics committees.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the ethics committees prior to use.

11.4 Informed Consent

Informed consent is the free and voluntary agreement of a patient to participate in a study after having been informed of all aspects of the study relevant to the patient’s decision to participate.

The participating physicians must obtain freely given informed consent from every patient prior any procedures related to the study including the documentation of results of clinical routine procedures for study purposes.

The information given to a patient has to be comprehensive, concise, clear, relevant and understandable to a layperson and enable the patient to understand

- the nature, objectives, benefits, implications, risks and inconveniences of the study
- the patient’s right and guarantees regarding the patient’s protection, in particular the right to refuse to participate and to withdraw from the study at any time without any resulting detriment and without having to provide any justification
- the conditions of study conduct including the expected duration of the patient’s participation in the study

The information will be given to the patient in writing as informed consent document(s) that must have been approved by the ethics committee prior to use; any written informed consent form and written information revised in the course of the study must receive the ECs approval prior use. If a patient is unable to read, the participating physician must provide an impartial witness to read the informed consent and to be present during the entire informed consent interview.

The information will furthermore be provided in an interview by an appropriately qualified member of the investigating team (i.e., a medical doctor according to the German Medicinal Products Act). The patient should have the opportunity to ask questions at any moment. Adequate time should be provided for the patient to consider his or her decision.

The informed consent process has to be documented and recorded in the patient's source documents. The original consent form, signed and dated by the patient and by the participating physician providing the patient information (i.e., a medical doctor according to the German Medicinal Products Act) prior to the patient's enrolment in the study, must be maintained in the participating physician's study files.

11.5 Quality Assurance and Quality Control

11.5.1 Direct Access to Source Data/Documents

Upon request, participating physicians must permit study-related monitoring (Section 11.5.2), audits (Section 11.5.3) and regulatory inspections providing direct access to source data/documents.

The responsible institution must verify that each patient has consented, in writing, to direct access to his/her original medical records for study-related monitoring, audit and regulatory inspection.

11.5.2 Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of patients are protected, the reported study data are accurate, complete and verifiable from source documents and that the conduct of the study is in compliance with the currently approved observation plan/amendment(s), with GCP and with the applicable regulatory requirement(s). Periodic monitoring of the study will be performed on-site in the study centres, i.e., in terms of visits by Clinical Research Associates (CRAs), using a risk-based monitoring approach.

Following written Standard Operating Procedures (SOP), monitors will verify that the study is conducted and data generated, collected, recorded and reported according to GCP and the applicable regulatory requirements. The activities the CRA should carry out when relevant and necessary to the study and the study site include the following:

- Availability of the patient's informed consent
- Verification that the participating physician is enrolling only eligible patients
- Verification that written informed consent was obtained before each patient's participation in the study
- Verifying that the participating physician and site staff are adhering to the observation plan and GCP
- Ensuring the completeness of the study documents in the study centre
- Source document verification by cross-checking the electronic CRFs against the participating physician's records

- Verifying that source documents and other study records are accurate, complete, kept up-to-date and maintained

11.5.3 Audits

The responsible institution may conduct or commission audits in the course of the study, which are independent of and separate from routine monitoring or quality control functions, to evaluate study conduct and compliance with the observation plan, SOPs, GCP and the applicable regulatory requirements. The appointed auditors should be independent of the study and qualified by training and experience to conduct audits properly. The audit will be conducted according to an audit plan that is guided by the importance of the study to submissions to regulatory authorities, the number of patients in the study, the type and complexity of the study, the level of risks to the study patients and any identified problem(s).

11.6 Confidentiality and Data Protection

The responsible institution affirms the patient's right to protection against invasion of privacy. All pertinent provisions of European and national data protection legislation in order to guarantee confidentiality and protection of privacy will be fully observed.

All records identifying the patients will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. The participating physician must assure that the patient's anonymity will be maintained and that the identities are protected from unauthorized parties. The participating physician should maintain documents not for submission to the responsible institution, e.g. patients' written consent forms, in strict confidence. On the eCRFs and other documents patients should not be identified by their names or birth dates. All clinical and scientific data are collected under a patient-identification code.

All data transfer with the study centres will be made without any exception via the patient-code. All participating study centres are obliged to keep a strictly confidential patient identification list at a safe locked place.

Persons who are authorized by the responsible institution or regulatory authorities (e.g. CRAs, auditors or representatives of regulatory authorities) may be permitted to patient-related data medical records relevant to the study for review or inspections respectively in accordance with local laws and the patient's statement in the informed consent.

12 Financing and Insurance

Responsible institution for this study is: Klinikum der Universität München – LMU, 81377 München.

The responsible institution will take care of the financing/funding of the study, according to written agreements between the responsible institution and participating physicians (or their institutions) of the study sites, the contract research organization (CRO) and the source(s) of funding.

AMGEN provides financial support for the study.

13 Study Results and Publication

13.1 Study Report

The final statistical analysis and a study report will be prepared within one year after the end of the study.

In accordance with section 67 para 6 of the German Medicinal Products Act the final report shall be transmitted to the competent higher federal authority within one year following completion of the data collection process for this observational study.

The final study report will be provided to Amgen at the time its submission to the competent authorities in Germany.

13.2 Publication

Regardless of the outcome of a study, the responsible institution is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals.

Once the biometrical analysis and study report are available, a publication will be drafted under primary authorship of the principal investigator as responsible institution's representative. Any other centres involved that have recruited at least 5 patients may, insofar as the publication medium allows, put forward one co-author respectively. Other individuals who played a key role in planning, conducting and analysing the study will be offered to appear as co-authors.

All co-authors will be given the opportunity to make a statement within an appropriate period before submission of the manuscript/abstract. The co-authors may recommend scientifically justifiable changes and corrections, but the ultimate decision concerning formulation of the publication will be at the responsibility of the principal investigator.

The study centres involved are entitled to publication of the data generated in their centres. In principle, the data obtained in an own centre may only be published after primary publication of the entire study. The principal investigator is to be informed of data to be presented during oral presentations and shall receive copies of manuscripts containing data derived from the study. This condition shall apply exclusively to information of the principal investigator and shall not involve any claim to editorial processing or restriction of the contents of publications and lectures.

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Appendix A ECOG Performance Status Scale

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

As published by (25)