Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase II single-arm study to investigate tepotinib combined with cetuximab in *RAS*/*BRAF* wild-type left-sided metastatic colorectal cancer (mCRC) patients having acquired resistance to anti-EGFR antibody targeting therapy due to *MET* amplification (PERSPECTIVE)
Study Number:	MS202202-0002
Merck Compound:	MSB0010442D (cetuximab) MSC2156119J (tepotinib)
Merck Registered Compound Name in Japan:	Not Applicable
Study Phase:	II
Short Title:	Phase II single-arm study of tepotinib combined with cetuximab (PERSPECTIVE)
Acronym:	PERSPECTIVE
Coordinating Investigator:	PPD
Sponsor Name and Legal Registered Address:	Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 Darmstadt, Germany In the US and Canada: EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA

Regulatory Agency Identifying Numbers:	IND: CCI EudraCT: 2020-001776-15
Approval Date:	08 Mar 2021
Medical Monitor Name and Contact Information:	PPD Phone: PPD email: PPD

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	27 Apr 2020
1.1 USA	Local amendment for USA only	30 Jul 2020
1.2 FRA	Local amendment for France only	06 Oct 2020
2.0	Global Amendment	08 Mar 2021

Protocol Version 2.0 (08 Mar 2021)

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The purpose of this amendment is to provide a global protocol incorporating country-specific Health Authority requests from the USA and France in addition to administrative updates.

Section # and Name	Description of Change	Brief Rationale
Title Page, 1.1 Synopsis, Appendices 10, 11, 12, page headers	Added the study acronym "PERSPECTIVE" to study title and short title. Added row on title page indicating the study acronym "PERSPECTIVE".	Administrative change
1.1 Synopsis	Removed "if applicable" after Cohort B.	Updated because Cohort B will be initiated. Sites in North America will be included in this study. The language in the study administrative section has been changed to reflect this.
1.2 Schema	Removed "and might be initiated at a later time point" after Cohort B will include US participants only.	Updated as Cohort B will be initiated in parallel to Cohort A. Sites in North America will be included in this study. The language in the study administrative section has been changed to reflect this.
1.3 Schedules of Activities	End of treatment was changed from the last dose taken to the decision to withdraw IMP.	Safety measure to allow for decisions to withdraw from study if dosing of participant's study drug had been interrupted.

Section # and Name	Description of Change	Brief Rationale
	Note added that screening laboratory assessments should be performed within 7 days prior to Cycle 1 Day 1.	Added screening window to facilitate protocol adherence.
	For ECG assessments, allowed a 60-minute window (from the previous 20-minute window).	Updated to facilitate protocol adherence and reduce burden at sites due to logistical constraints in agreement with safety.
	For the AE and SAE assessments, removed "Screening" from the description of the ICF in the Notes.	Administrative change
2 Introduction	Added "The proposed administered dose of 500 mg tepotinib corresponds to 500 mg tepotinib hydrochloride hydrate and is equivalent to 450 mg tepotinib (free base form). The 250 mg tepotinib corresponds to 250 mg tepotinib hydrochloride hydrate and is equivalent to 225 mg tepotinib (free base form)".	Revised the protocol to clarify the amount of tepotinib free base administered.
2.1 Study Rationale	Removed "if Cohort B is initiated" and revised the description of countries to be included in Cohorts A and B.	Updated as Cohort B will be initiated. Sites in North America will be included in this study. The language in the study administrative section has been changed to reflect this.
2.3 Benefit/Risk Assessment	Updated the reporting period for the most current Cetuximab IB.	Administrative change
	Under Tepotinib – Risks, clarified edema and updated to nausea and vomiting as risks.	Updated to provide current guidance on tetopinib.
	Under Benefit/Risk Assessment: Combination of tepotinib with cetuximab, revised to include that participants with a history of or developing ILD would be excluded from the study. Minor restructuring change to place inclusion information for participants with adequate hepatic function with information more directly related.	Revised to reflect current exclusion criteria. Revision for clarification.
4.1 Overall Design	Removed "if Cohort B is initiated".	Updated as Cohort B will be initiated. Sites in North America will be included in this study.
	Revised sentence beginning "After the safety run-in period…" in Cohort expansion at RP2D subsection with "Safety run-in period can include participants from Cohorts A and/or B".	
4.2 Scientific Rationale for Study Design	Corrected hazard ratios for OS in the first-line FOLFIRI plus cetuximab therapy.	Administrative change

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	To criterion #2, clarified left-sided CRC tumors, "from splenic flexure to rectum." Included reference to current National Comprehensive Cancer Network (NCCN) CRC v1.2021 guidelines.	Added additional description for left-sided tumors.
	To criterion #2, clarified that advanced tumors are also unresectable.	Updated to clarify tumors are unresectable to better reflect the requirements of the patient population.
	To criterion #7b, added "First-line treatment must include a fluoropyrimidine and oxaliplatin or irinotecan and second-line treatment must include a fluoropyrimidine, oxaliplatin, or irinotecan".	Added at the request of a Health Authority to clarify that first-line treatment must include a fluoropyrimidine and oxaliplatin or irinotecan and second-line treatment must include a fluoropyrimidine, oxaliplatin, or irinotecan.
	To criterion #11, corrected to add the superscripted numbers to the estimated glomerular filtration rate formula.	Administrative change
5.2 Exclusion Criteria	Added to criterion #8 as point "g. Corrected QT interval by Fridericia (QTcF > 480 ms)".	Safety measure clarification to exclude patients with QTc intervals >480 msec.
	Added new criterion, #16,"History of ILD or interstitial pneumonitis including radiation pneumonitis that required steroid treatment".	Added in order to exclude patients with a history of interstitial lung disease or interstitial pneumonitis to better reflect the requirements of the patient population.
6.1 Study Intervention(s) Administration, table	Added "and if local cetuximab label requires" to the information that a corticosteroid is given prior to the first infusion of cetuximab.	Added to indicate the use of corticosteroids, as a premedication, will be based on local requirements.
6.3.1 Study Intervention Assignment	Corrected the name of the system used to assign study numbers to participants.	Administrative change
6.5.1 Permitted Medicines	Added "and if local cetuximab label requires" to the information that a corticosteroid is given prior to the first infusion of cetuximab.	Added to clarify that if a corticosteroid would be given prior to cetuximab, will depend on the local cetuximab label.
6.5.4 Special Precautions 6.5.4.1 Cetuximab	Wording updated under Eye Disorders.	Updated for the signs and symptoms suggestive of keratitis.
6.5.4 Special Precautions 6.5.4.2 Tepotinib	Added instruction to refer to the newly inputted table on the recommended tepotinib dose modifications for edema.	Administrative change
6.6 Dose Selection and Modification 6.6.2 Tepotinib	Under Tepotinib: Recommended Dose (second paragraph), added indication that tepotinib is also approved in US as well as Japan.	Updated with the approval of tepotinib in the US.

Section # and Name	Description of Change	Brief Rationale
	Added further clarification (table) under the tepotinib treatment interruption section to include recommended dose modifications in case of adverse reactions of clinical interest. Also included a footnote that if AEs were to occur during the DLT period or the safety run-in that DLT rules for dose modification should apply.	Safety measure to provide detailed guidelines according to the severity grade of the toxicity observed, and the recommended tepotinib dose modifications. Reminder added for dose modification guidance for events occurring during the DLT period and the safety run-in.
6.6.3 Dose Limiting Toxicity	Added "Grade 4 vomiting or diarrhea" as DLT criteria.	Health authority request to include Grade 4 (life threatening) vomiting or diarrhea as DLT criteria.
6.7 Study Intervention after the End of the Study	Added details on provision of providing study intervention after the End of the Study. Updated section to reflect current Sponsor policy.	Updated to specify the terms for the provisioning of study drug(s) to participants who benefit at the End of Study.
7.1 Discontinuation of Study Intervention	Grade >3 QTc interval prolongation was added as reason for discontinuation of study intervention. Additionally, the initiation of close and appropriate ECG monitoring in hospital according to local standards is referred to.	Updated to provide clarification in event of QTcF findings.
7.2 Participant Discontinuation /Withdrawal from the Study	Based on recent protocol template revisions, replaced first four bullets with updated language.	Administrative change
8 Study Assessments and Procedures	Added with the screening evaluations bullet point, that screening laboratory tests should be performed within 7 days prior to Cycle 1 Day 1.	Added screening window to facilitate protocol adherence.
8.1.1 Tumor Assessments	Deleted sentence "Readers should use cytology results and, if not available, no progression solely on effusions or ascites should be determined".	Removed in order to align with current amended IRC charter guidance for investigators.
9.2 Sample Size Determination	Removed "if applicable" after Cohort B, removed "if initiated" after Cohort B, removed "(or 22 if Cohort A only)".	Removed as the enrollment of Cohort B is now in parallel with Cohort A, and not later as initially implied. Cohort A language unnecessary.
9.3 Populations for Analyses, table	Description of PK analysis set, changed from "…clinically important protocol deviations" to "..relevant protocol deviations".	All PK relevant protocol deviations will be considered now regardless if these are clinically important.
9.4.1 Efficacy Analyses, table	Added "Duration of response data will be censored … for participants with an event after the period of 2 scheduled tumor assessments (84 or 168 days) of the last tumor assessment".	Added further description of the derivation of duration of response.

Section # and Name	Description of Change	Brief Rationale
	Added to the description of the statistical analysis methods for the PFS endpoint: "Progression free survival is defined as … or death due to any cause within the period of 2 scheduled tumor assessments (84 or 168 days) after the last tumor assessment, whichever occurs first. PFS data will be censored …for participants with an event after the period of 2 scheduled tumor assessments (more than 84 or 168 days) after the last tumor assessment".	Added further description of the derivation of PFS.
9.4.2.1 Safety Run-In Period, DLTs, Stopping Rules, Dose Reduction and Escalation	Added reference to newly added Appendix 8 BOIN Design.	Administrative change
9.4.4 Sequence of Analyses	Relabeled main analysis to primary analysis.	Administrative change
Appendix 2 Study Governance	Under study administrative section, deleted "(sites in North America will only be included if Cohort B is initiated)".	Sites in North America will be included in this study. The language in the study administrative section has been changed to reflect this.
Appendix 4 Order of Key Activities on Day 1 of Cycles 1 and 2	Changed the screening ECG window from 20 to 60 minutes.	Updated to facilitate protocol adherence and reduce burden at sites due to logistical constraints in agreement with safety.
Appendix 6 Clinical Laboratory Tests	Added phosphorus to biochemistry parameters for assessment.	Health authority request in the study monitoring plan to include assessment of phosphorus in the biochemistry panel.
	Deleted the serum or urine alcohol and drug screen.	Removed as this additional safety parameter was deemed not necessary for safety evaluation.
Appendix 8 BOIN Design	Added appendix which includes flowchart and boundaries of the BOIN design.	Added more detailed information/specifications to be used for the BOIN design.
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

Table of Contents

1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase II single-arm study to investigate tepotinib combined with cetuximab in *RAS*/*BRAF* wild-type left-sided metastatic colorectal cancer (mCRC) patients having acquired resistance to anti-EGFR antibody targeting therapy due to *MET* amplification (PERSPECTIVE).

Short Title: Phase II single-arm study of tepotinib combined with cetuximab (PERSPECTIVE).

Rationale: The purpose of this study is to assess the preliminary antitumor activity, safety, and tolerability, and to explore the pharmacokinetics (PK) of tepotinib in combination with cetuximab in participants with *RAS*/*BRAF* wild-type left-sided mCRC having acquired resistance to anti-epidermal growth factor receptor (EGFR) antibody targeted therapy due to mesenchymal epithelial transition factor (*MET*) amplification. The dual therapeutic approach of giving tepotinib and cetuximab in combination is to control the disease via maintaining the inhibition of the EGFR pathway with cetuximab and targeting the emerging MET activated pathway with tepotinib.

Objectives and Endpoints:

Safety Run-in

Objectives	Endpoints
Primary	
To confirm the recommended Phase II dose (RP2D) of tepotinib when used in combination with cetuximab	Occurrence of dose limiting toxicities (DLTs)

Overall Study

Objectives	Endpoints
Primary	
To evaluate the preliminary efficacy of tepotinib (RP2D) in combination with cetuximab in terms of tumor response	Objective response (OR, confirmed complete response [CR] or partial response [PR]) determined according to RECIST Version 1.1 assessed by the Investigators
Secondary	
To further evaluate the efficacy of the combination of tepotinib (RP2D) and cetuximab in terms of	
duration of response (DoR)	DoR (months) according to RECIST Version 1.1 assessed by the Investigators.
progression-free survival (PFS)	PFS (months) according to RECIST Version 1.1 assessed by the Investigators.
overall survival (OS)	OS (months) assessed by the Investigators.
To evaluate the safety and tolerability of tepotinib in combination with cetuximab	• Occurrence of Adverse Events (AE) and treatment-related AEs • Occurrence of clinically significant changes in vital signs, laboratory parameters and 12-lead electrocardiogram (ECG) findings
To characterize the immunogenicity of cetuximab	Immunogenicity of cetuximab as measured by antidrug antibody (ADA) assays on Day 1 Cycle 1 and End of Treatment Visit

Overall Design: This is a Phase II, multicenter, single-arm, open-label study. An initial subset of at least 6 participants will, irrespective of therapy line, be enrolled in a safety run-in period to confirm that the dose of 500 mg once daily (QD) of tepotinib (currently used in Phase II studies) can be administered together with cetuximab at 250 mg/m^2 as a weekly intravenous administration. After the safety run-in period, the Safety Monitoring Committee (SMC) will decide and confirm the recommended Phase II dose (RP2D) of tepotinib to be used in combination with cetuximab in the whole study. Participants will receive a combination of the tepotinib dose confirmed by the SMC and cetuximab in cycles of 21 days duration until disease progression (according to RECIST Version 1.1), death, AE leading to discontinuation, study withdrawal, or withdrawal of consent, whichever occurs first.

Disclosure Statement: This is a single group treatment study with 1 arm that is open-label.

Number of Arms: 1

Blinding: No blinding.

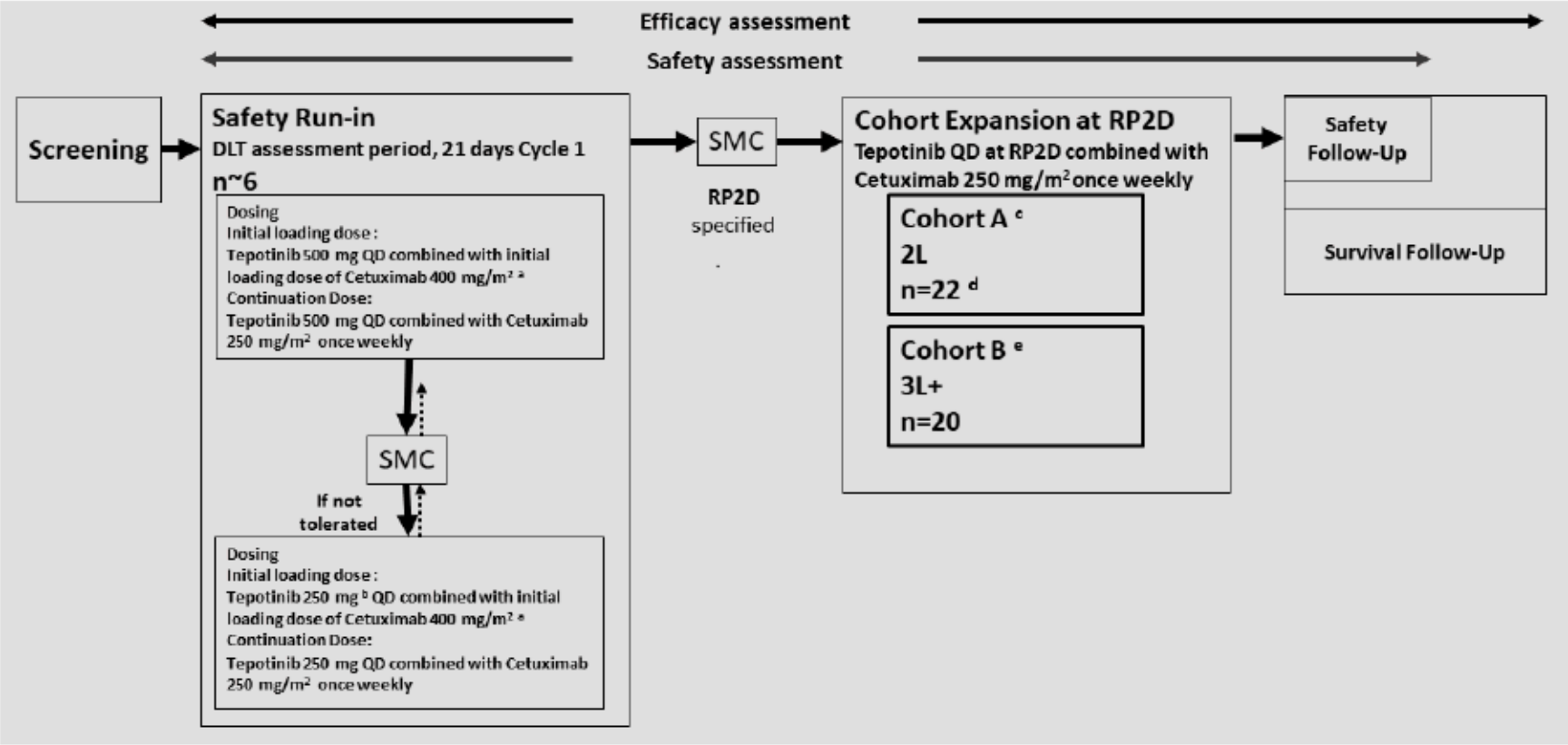
Number of Participants: In total, a maximum of 48 participants are planned to be assigned to study intervention such that approximately 22 (Cohort A) and 20 (Cohort B) participants will be treated at the RP2D.

Study Intervention Groups and Duration: For each participant, the study will include a Screening Period of up to 56 days, a Study Intervention Period consisting of 3-week cycles (Cycles are 21 days) of tepotinib combined with cetuximab until disease progression, an End-of-Study Intervention Visit, a Safety Follow-up Period of 30 days, and a 1-year post study follow-up. Therefore, assuming there are 5 cycles, the anticipated duration of treatment for each participant is 191 days or ~6.5 months with a 1-year follow-up period thereafter.

Involvement of Special Committee(s): Yes

1.2 Schema

A high-level schedule of visits / assessments is shown in Section 1.3. Number of participants to be screened is described in Section 9.2.



Abbreviations: 2L = 2nd Line; 3L+ = 3rd Line+; DLT = Dose Limiting Toxicity; QD = once daily; RP2D = Recommended Phase II Dose; SMC = Safety Monitoring Committee; US = United States.

a Required loading dose at an initial dose of 400 mg/m² body surface area if participant received the following:
- Panitumumab as prior line
- Cetuximab as prior line and last dose was more than 3 weeks ago.

No loading dose required if participant received cetuximab as prior line and last dose was given up to 3 weeks ago.

b The 250 mg once daily dose is the standard dose reduction. If a participant still does not tolerate the 250 mg once daily dose, or the AE does not resolve following treatment interruption, permanent treatment discontinuation or other dosing schemas should be discussed with the Sponsor.

c Cohort A will include participants from outside the US. A futility analysis is considered which will be performed after 12 participants are enrolled and monitored without stopping recruitment of further participants into this study.

d After the safety run-in period, at least 16 additional participants will be enrolled at the RP2D expansion in Cohort A, in addition to the 6 participants completing the safety run-in at RP2D.

e Cohort B will include US participants only.

1.3 Schedule of Activities

Activity / Assessment	Screening / Baseline	Intervention Period (in cycles of 3 weeks)									EoT	Safety Follow up / Discontinuation	Survival Follow-Up / EoS / 1-Year Follow-Up	Notes
	Day -56 to Day -1	Cycle 1 (21 days)			Cycle 2 (21 days)			Cycle 3 and subsequent cycles (21 days)			Within 14 days after decision to withdraw IMP	30 days after the last dose	After Safety Follow-Up, every 3 months, up to 1-year Site Visit or by Telephone	
Cycle Day		1	8	15	1	8	15	1	8	15				
Visit Window			± 3 days		± 3 days			± 3 days				- 3 to + 7 days	± 1 month	
Study Site Visits	X	X	X	X	X	X	X	X	X	X	X	X	X	At the Investigator's discretion, additional assessments may be performed at unscheduled time points if clinically indicated.
Written informed consent	X													
Inclusion and Exclusion Criteria	X													Recheck clinical status before 1st dose of study intervention. Screening labs for eligibility should be performed within 7 days prior to C1D1.
Demography	X													
Medical history	X													
HIV Screening	X													HIV testing is optional unless required locally.
Hepatitis B and C	X													

Activity / Assessment	Screening / Baseline	Intervention Period (in cycles of 3 weeks)									EoT	Safety Follow up / Discontinuation	Survival Follow-Up / EoS / 1-Year Follow-Up	Notes
	Day -56 to Day -1	Cycle 1 (21 days)			Cycle 2 (21 days)			Cycle 3 and subsequent cycles (21 days)			Within 14 days after decision to withdraw IMP	30 days after the last dose	After Safety Follow-Up, every 3 months, up to 1-year Site Visit or by Telephone	
Cycle Day		1	8	15	1	8	15	1	8	15				
Visit Window			± 3 days		± 3 days			± 3 days				- 3 to + 7 days	± 1 month	
Pregnancy Test (women of child bearing potential only)	X	X			X			X			X	X		Serum test at Screening, urine test thereafter. See Section 7.1 for EoT assessment due to occurrence of pregnancy
Physical examination	X	X	X	X	X		X	X		X	X	X		Symptom directed-physical examinations will be performed as clinically indicated per Investigator's judgment.
Vital signs	X	X	X	X	X		X	X			X	X		Includes height (collect at Screening only) and weight.
Standard 12-lead ECG including QTc	X	X			X						X			As triplicates. ECG assessment should be performed within 60 minutes prior to predose PK blood sample collection (See Appendix 4).
ECOG PS	X	X			X			X			X	X		

Activity / Assessment	Screening / Baseline	Intervention Period (in cycles of 3 weeks)									EoT	Safety Follow up / Discontinuation	Survival Follow-Up / EoS / 1-Year Follow-Up	Notes
	Day -56 to Day -1	Cycle 1 (21 days)			Cycle 2 (21 days)			Cycle 3 and subsequent cycles (21 days)			Within 14 days after decision to withdraw IMP	30 days after the last dose	After Safety Follow-Up, every 3 months, up to 1-year Site Visit or by Telephone	
Cycle Day		1	8	15	1	8	15	1	8	15				
Visit Window			± 3 days		± 3 days			± 3 days				- 3 to + 7 days	± 1 month	
AE and SAE assessment	X	Continuous												From the time of signing the ICF through Safety Follow-up Visit.
Concomitant medication and procedures review	X	Continuous												Procedures review includes the capture of cytology results.
Blood hematology, biochemistry	X	X	X	X	X		X	X		X	X	X		Including thrombocytes, after Cycle ≥ 2 only D1. Serum cystatin C (only for sites where the test is available).
Urinalysis	X	X	X		X			X			X	X		
Coagulation (PT, aPTT, INR)	X	X	X		X			X			X	X		
CCI														

Activity / Assessment	Screening / Baseline	Intervention Period (in cycles of 3 weeks)									EoT	Safety Follow up / Discontinuation	Survival Follow-Up / EoS / 1-Year Follow-Up	Notes
	Day -56 to Day -1	Cycle 1 (21 days)			Cycle 2 (21 days)			Cycle 3 and subsequent cycles (21 days)			Within 14 days after decision to withdraw IMP	30 days after the last dose	After Safety Follow-Up, every 3 months, up to 1-year Site Visit or by Telephone	
Cycle Day		1	8	15	1	8	15	1	8	15				
Visit Window			± 3 days		± 3 days			± 3 days				- 3 to + 7 days	± 1 month	
														CCI

CCI

Activity / Assessment	Screening / Baseline	Intervention Period (in cycles of 3 weeks)									EoT	Safety Follow up / Discontinuation	Survival Follow-Up / EoS / 1-Year Follow-Up	Notes
	Day -56 to Day -1	Cycle 1 (21 days)			Cycle 2 (21 days)			Cycle 3 and subsequent cycles (21 days)			Within 14 days after decision to withdraw IMP	30 days after the last dose	After Safety Follow-Up, every 3 months, up to 1-year Site Visit or by Telephone	
Cycle Day		1	8	15	1	8	15	1	8	15				
Visit Window			± 3 days		± 3 days			± 3 days				- 3 to + 7 days	± 1 month	
ADA cetuximab		X									X			Serum ADA samples will be collected predose (within 60 min before tepotinib dose) only on Cycle 1 Day 1 and at EoT (See Appendix 4) and Section 8.9.
CCI														

Activity / Assessment	Screening / Baseline	Intervention Period (in cycles of 3 weeks)									EoT	Safety Follow up / Discontinuation	Survival Follow-Up / EoS / 1-Year Follow-Up	Notes
	Day -56 to Day -1	Cycle 1 (21 days)			Cycle 2 (21 days)			Cycle 3 and subsequent cycles (21 days)			Within 14 days after decision to withdraw IMP	30 days after the last dose	After Safety Follow-Up, every 3 months, up to 1-year Site Visit or by Telephone	
Cycle Day		1	8	15	1	8	15	1	8	15				
Visit Window			± 3 days		± 3 days			± 3 days				- 3 to + 7 days	± 1 month	
ctDNA sample		X						Cycle 3, 5, 9 and 13 only			X			Collection predose (within 60 min prior to tepotinib dose), before premedication, if applicable (See Appendix 4)
Documentation of *RAS*/*BRAF* wild-type status, and high *MET* amp levels	X													Confirmed prior to enrollment and after disease progression on the previous anti-EGFR therapy by an established test.
Tepotinib until PD or intolerability		QD												Decided by the Sponsor and SMC: Dosing may be stopped at any time to review safety and PK data and allow for adjustments before dosing is resumed. Additional schedules may also be evaluated.
Cetuximab until PD or intolerability		Weekly (Day 1)												See Section 6.1 for details of premedication required prior to first infusion.

Activity / Assessment	Screening / Baseline	Intervention Period (in cycles of 3 weeks)									EoT	Safety Follow up / Discontinuation	Survival Follow-Up / EoS / 1-Year Follow-Up	Notes
	Day -56 to Day -1	Cycle 1 (21 days)			Cycle 2 (21 days)			Cycle 3 and subsequent cycles (21 days)			Within 14 days after decision to withdraw IMP	30 days after the last dose	After Safety Follow-Up, every 3 months, up to 1-year Site Visit or by Telephone	
Cycle Day		1	8	15	1	8	15	1	8	15				
Visit Window			± 3 days		± 3 days			± 3 days				- 3 to + 7 days	± 1 month	
Tumor Assessment (RECIST Version 1.1) based on MRI and/or CT scans and other protocol-defined imaging modalities.	X							X #)			X##)			See Section 8.1 Screening tumor assessment needs to happen within 28 days prior to dosing. All evaluations should be documented by the Investigator and images uploaded to the imaging repository, for a possible independent read at a later date. #): C3, C5, C7, C9, C11, C13, C15 and subsequently every 4 cycles until study closure, or disease progression regardless of study intervention modifications/discontinuation. If disease progression is not certain, consider continuing to image.

Activity / Assessment	Screening / Baseline	Intervention Period (in cycles of 3 weeks)									EoT	Safety Follow up / Discontinuation	Survival Follow-Up / EoS / 1-Year Follow-Up	Notes
	Day -56 to Day -1	Cycle 1 (21 days)			Cycle 2 (21 days)			Cycle 3 and subsequent cycles (21 days)			Within 14 days after decision to withdraw IMP	30 days after the last dose	After Safety Follow-Up, every 3 months, up to 1-year Site Visit or by Telephone	
Cycle Day		1	8	15	1	8	15	1	8	15				
Visit Window			± 3 days		± 3 days			± 3 days				- 3 to + 7 days	± 1 month	
														Note: Visit window is +7 days for C3 only. All other cycles, the visit window is ± 7 days. ##) before starting any new treatment
Chest X-Ray	X													Not necessary if thoracic CT is performed as part of the tumor assessment (RECIST Version 1.1) at screening. These evaluations should be documented by the Investigator and uploaded to the imaging repository, for a possible independent read at a later date.

AE = adverse event; ADA = Anti-drug antibody; aPTT = activated partial thromboplastin time; C = Cycle; CT = Computed tomography; ctDNA = circulating tumor DNA; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; EoT = End of Treatment; HIV = Human immunodeficiency virus; ICF = Informed Consent Form; IMP = investigational medicinal product; INR = International normalized ratio; MRI = Magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetic; PT = prothrombin time; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = Serious adverse event; SMC = Safety Monitoring Committee.

2 Introduction

Tepotinib is a small molecule, reversible adenosine triphosphate competitive inhibitor of the mesenchymal epithelial transition factor (MET). It is being developed as an antitumor agent in patients with a wide variety of human malignancies including carcinomas of the lung, liver, stomach, breast, ovary, kidney, and thyroid exhibiting aberrant MET activation such as high-level *MET* gene amplification or activating mutations. The proposed administered dose of 500 mg tepotinib corresponds to 500 mg tepotinib hydrochloride hydrate and is equivalent to 450 mg tepotinib (free base form). The 250 mg tepotinib corresponds to 250 mg tepotinib hydrochloride hydrate and is equivalent to 225 mg tepotinib (free base form).

Cetuximab commercial name Erbitux® is a chimeric human/mouse monoclonal antibody of the immunoglobulin G subclass that targets the human tyrosine kinase epidermal growth factor receptor (EGFR). Cetuximab is indicated for the treatment of patients with EGFR first-expressing, *RAS* wild-type metastatic colorectal cancer (mCRC) and squamous cell carcinoma of the head and neck.

Detailed information on the chemistry, pharmacology, efficacy, and safety of cetuximab is found in the Investigator's Brochure (IB)/US Package Inserts (PI)/Summary of Product Characteristics (SmPCs), and for tepotinib in the Investigator's Brochure (IB).

2.1 Study Rationale

The purpose of this study is to assess the preliminary antitumor activity, safety, and tolerability, and to explore the pharmacokinetics (PK) of tepotinib in combination with cetuximab in participants with *RAS/BRAF* wild-type left-sided mCRC having acquired resistance to anti-EGFR antibody targeted therapy due to *MET* amplification.

Prior to the treatment phase, the safety run-in period will be conducted administering tepotinib 500 mg once daily (QD) in combination with 250 mg/m^2 of cetuximab once weekly. Dose Limiting Toxicities (DLT) will be assessed to confirm the daily recommended Phase II dose (RP2D) as combination with cetuximab. As per the Investigator's Brochure/US PI/SmPC for cetuximab, an initial loading dose of 400 mg/m^2 of cetuximab will be given to participants who received panitumumab as prior line or cetuximab as prior line if the last dose of cetuximab was given more than 3 weeks prior to first dosing. No loading dose of cetuximab will be required if the participant received cetuximab as prior line and last dose was given up to 3 weeks prior to first dosing.

The dual therapeutic approach of giving tepotinib and cetuximab in combination is to control the disease via maintaining the inhibition of the EGFR pathway with cetuximab and targeting the emerging MET activated pathway with tepotinib.

The primary efficacy analysis will be based on all patients with *MET* amplification identified by a positive liquid and/or tissue-based *MET* amplification test, both with an appropriate regulatory status who were administered at least 1 dose at RP2D of tepotinib and/or cetuximab (full analysis set).

Participants with mCRC with only one prior treatment line will be enrolled into the study for 2nd line treatment (2L) into Cohort A (countries outside of US). Participants with two or more prior treatment lines will be enrolled for 3rd line + (3L+) treatment into Cohort B (US only).

For further discussion of the scientific rationale for study design, see Section 4.2, and for justification for dose, see Section 4.3.

2.2 Background

Cetuximab

Cetuximab blocks the binding of EGF and other ligands to the EGFR and prevents EGFR dimerization, thereby inhibiting ligand induced activation of this receptor tyrosine kinase. This results in the inhibition of cell growth, induction of apoptosis, and decreased production of matrix metalloproteinases and vascular endothelial growth factor (reviewed by Moosmann 2007 and Vincenzi 2008).

Cetuximab also stimulates EGFR internalization and eventual degradation, by removing the receptor from the cell surface and thereby preventing interaction with its ligand (Feng 2007, Perez-Torres 2006). In addition, cetuximab can mediate antibody-dependent cell-mediated cytotoxicity, a process dependent on both the affinity of cetuximab for the extracellular domain of EGFR and the level of cellular EGFR expression (Patel 2010).

Inhibition of tumor growth as a single agent, synergy with radiation, and utility in chemo resistant tumor cell lines made development of this antibody for anticancer therapy attractive (reviewed by Moosmann 2007 and Vincenzi 2008). Additionally, targeted biologic response agents might be less likely to damage normal cells than cytotoxic agents. They frequently have nonoverlapping toxicities with conventional cytotoxic agents, making them optimal candidates for combination therapies. Potential clinical benefits are objective clinical responses or stabilization of disease in patients with tumors that are EGFR-positive as the most likely clinical targets. Cetuximab is indicated for the treatment of patients with EGFR-expressing, *RAS* wild-type mCRC in first-line treatment and above (Van Cutsem 2015, Bokemeyer 2015, Karapetis 2008).

MET amplification as a mechanism of acquired resistance to anti-EGFR therapy has been demonstrated for cetuximab therapy. Amplification of the *MET* protooncogene is associated with acquired resistance in patients who do not develop KRAS mutations during anti-EGFR therapy. Incidence of *MET* amplification in EGFR-resistant colorectal cancer (CRC) has been observed and ranges between 4.1% to 22.6% (Bardelli 2013, LC-SCRUM, ASCO 2019 [Nakamura 2019], Raghav 2016, Siravegna 2015, Mohan 2014, Morelli 2014).

Tepotinib

The in vitro and in vivo primary pharmacology studies demonstrated that tepotinib is a potent and highly selective Type I, adenosine triphosphate-competitive inhibitor of the receptor tyrosine kinase MET. Tepotinib inhibited hepatocyte growth factor (HGF)-dependent and constitutive MET activation in biochemical and cellular assays with IC50 values being consistently in the single-digit nanomolar range. With the same potency, tepotinib inhibited MET-mediated signal

transduction, tumor cell proliferation and anchorage-independent growth in MET-dependent tumor cells.

Given the important role of aberrant MET/HGF signaling in cancer, several different therapeutic strategies, aimed at inhibiting MET/HGF signaling, have been developed and are being evaluated in clinical studies. These include agents that directly inhibit HGF and/or its binding to MET, antibodies targeted at MET, and small molecule MET tyrosine kinase inhibitors (TKIs) (Awad 2016, Comoglio 2018).

The resistance of advanced epithelial tumors to conventional standard chemotherapies has been linked to their genetic complexity; however recent findings indicate that many solid tumors are "addicted" to particular activated kinases. Targeting such kinases with selective inhibitors represents a promising anticancer approach. The role of MET in tumor progression and metastatic dissemination makes it a privileged candidate for therapeutic intervention. Functional studies demonstrate that MET activation confers resistance to anti-EGFR therapy both in vitro and in vivo. Notably, in patient-derived CRC xenografts, *MET* amplification correlated with resistance to EGFR blockade which could be overcome by MET kinase inhibitors.

Tepotinib and Cetuximab Combination

In non-small cell lung cancer (NSCLC) tumors with activating EGFR kinase domain mutations, the combination of tepotinib and EGFR-TKIs (e.g., gefitinib) was shown to overcome resistance to EGFR-TKI treatment mediated by *MET* amplification (Study EMR200095-006, tepotinib with gefitinib [a first generation EGFR-TKI]). The combination treatment led to tumor regressions of established NSCLC-derived human tumor xenografts and the antitumor activity was stronger with the combination treatment than with tepotinib alone. The data provides a rationale for the treatment of patients who developed resistance to anti-EGFR therapy due to *MET* amplification with the combination of tepotinib in an anti-EGFR resistant setting. Initial signals of efficacy of tepotinib in Phase I studies indicated the need to stratify patient populations based on predictive *MET* alterations for this highly selective drug. These results warrant further investigation of tepotinib not only in NSCLC but also other tumor types such as mCRC in combination therapy.

The general combination of anti-EGFR therapy with a MET inhibitor to treat mCRC has been investigated in several studies, indicating the medical need but also potential mechanism of action. In pretreated *KRAS* wild-type mCRC patients with no prior anti-EGFR inhibitor therapy, the combination of panitumumab (an anti-EGFR antibody) with rilotumumab (human monoclonal antibody against HGF) showed improved response compared with panitumumab alone. While patients were not selected for *MET* amplification, the therapy showed increased objective response rate (ORR) (21% versus 31%), median progression-free survival (PFS) (3.7 versus 5.2 months), and median overall survival (OS) (11.6 versus 13.8 months) (Van Cutsem 2014). Furthermore, tivantinib (questionable MET inhibitor regarding mode of action [Calles 2015]) was studied in combination with cetuximab plus irinotecan. The study enrolled patients with wild-type *KRAS* mCRC treated with one prior line of therapy, including an irinotecan-based regimen but not an EGFR inhibitor. While patients were not selected for *MET* amplification, patients in the tivantinib group showed improved ORR (45% versus 33%), median PFS (8.3 versus 7.3 months), and median OS (19.8 versus 16.9 months) compared with the placebo group, however this study did not reach statistical significance to conclude that adding tivantinib to cetuximab plus irinotecan leads to

improved PFS or OS (Eng 2016). The combination of tivantinib and cetuximab was investigated in patients with wild-type *KRAS*, EGFR-resistant MET-high (staining) mCRC, who had previously received more than 1 systemic therapy (last one contain anti-EGFR) and showed tumor progression on anti-EGFR therapy within 3 months prior to enrollment. The study did not meet its primary endpoint, with an ORR of 9.8%. Median PFS and OS were 2.6 and 9.2 months, respectively. Here, the majority of patients had more than 1 line of prior systemic therapies (Rimassa 2019). Savolitinib (a MET inhibitor) is currently being studied in a Phase II trial (NCT03592641) in patients with *MET*-amplified metastatic and/or unresectable CRC, with wild-type in *KRAS*/*NRAS*/*BRAF*. Patients are selected by liquid biopsy, however, do not undergo combination therapy with an anti-EGFR treatment. This study is ongoing and no data on this combination are available.

In summary, despite significant progress in the early detection, diagnosis, and treatment of tumors, the efficacy of most cancer treatments remains unsatisfactory, and remains an unmet medical need. In addition, the high selectivity of tepotinib (Bladt 2013) suggests that by combining tepotinib with other cancer therapies, the antitumor activity might be maximized with no or only limited increase in toxicity.

2.3 Benefit/Risk Assessment

Cetuximab - Benefit

In patients with *RAS* wild-type tumors, a significant benefit across all endpoints was associated with the addition of cetuximab to FOLFIRI (Van Cutsem 2015). The difference in median OS was 28.4 months in the cetuximab plus FOLFIRI arm versus 20.2 months in the FOLFIRI alone arm (hazard ratio = 0.69, 95% confidence interval: 0.54, 0.88; p = 0.002). Compared to the *RAS* evaluable population, all key efficacy endpoints were numerically better in the *RAS* wild-type population. In patients with other than KRAS exon 2 *RAS*-mutant tumors, no clear difference in efficacy outcomes between the treatment groups was seen.

The preclinical, clinical-pharmacological, and current clinical data on cetuximab suggest a favorable benefit/risk of cetuximab in combination with FOLFOX4 versus FOLFOX4 alone in the first-line treatment of mCRC participants with *RAS* wild-type status (Study EMR62202-057 (TAILOR)).

In the reporting period from the most current version of the Cetuximab IB (01 October 2019 to 30 September 2020) an estimated 85,599 patients (CRC: 51,143; squamous cell carcinoma of the head and neck: 34,455) were treated with commercially available cetuximab. The overall benefit/risk profile of cetuximab remains favorable for the approved indications.

Cetuximab – Risks

Very commonly occurring risks include mild to moderate infusion-related reactions (IRRs), skin reactions, hypomagnesemia, and increase in liver enzymes. More detailed safety information is provided in the IB/US PI/SmPC.

Tepotinib - Benefit

The 500 mg once daily dose is considered to be well tolerated and in the biologically active range, it was chosen as the dose for this study. Overall, in the ongoing and completed studies, tepotinib was well tolerated (refer to the current IB). To further improve the benefit/risk ratio of the study, only participants with *MET* amplification positive tumors will be enrolled, thus enabling investigation of the efficacy and safety of the compound in the most relevant population and limiting further exposure to the non-targeted population. Tepotinib efficacy compares favorably to available therapies in advanced NSCLC. In addition, tepotinib exhibits an acceptable, manageable, and tolerable safety profile compared to chemotherapy containing regimens, as well as the facilitation of treatment by once daily oral dosing is to be taken into consideration.

The primary endpoint of the pivotal VISION study (MS200095-0022, a single-arm [tepotinib], open-label Phase II trial in participants with NSCLC harboring *MET*ex14 alterations or *MET* amplification), is defined as objective response assessed by independent read. Thereby, for *MET*ex14 patients a relevant ORR of 46.5% (95% CI: 36.4, 56.8.) associated with a median duration of response (DoR) of 11.1 months (95% CI: 7.2, not estimable) as assessed by independent read after tepotinib monotherapy is observed in the overall population as of the data cutoff date 01 January 2020 (patients in the ITT group dosed before 02 April 2019 with 9 months of follow-up). Moreover, a consistent proportion of responders is seen across lines of therapy, with ORRs ranging between 44% to 48.5%, which again supports the notion of *MET*ex14 skipping alterations being an oncogenic driver for NSCLC.

Clinical efficacy and safety information of combinations of MET inhibitors with EGFR inhibitors is already available from several studies. This includes information of tepotinib with the 1st generation EGFR TKI gefitinib in patients with advanced NSCLC after failure to previous EGFR TKI treatment (NCT01982955, Cheng 2018). In particular, the subgroup of participants with *MET*-amplified, T790M negative tumors, demonstrated positive efficacy signals including an ORR of 67% and a median PFS of 16.6 months were seen. Furthermore, 60 participants were exposed to tepotinib with the EGFR inhibitor. While all participants receiving this treatment experienced treatment-emergent adverse events (TEAEs), the majority of these TEAEs were mild or moderate. A comparison of tepotinib plus gefitinib versus chemotherapy showed 9.7% versus 4.3% having TEAEs leading to permanent discontinuation, 3.2% versus 0% of TEAEs leading to death (none of the TEAEs was related), 16.1% versus 30.4% had serious related TEAEs, 51.6% versus 52.2% had Grade $\geq$ 3 related TEAEs, and 12.9% versus 8.7% had lipase/amylase increase Grade $\geq$ 3 not accompanied by pancreatitis or respective symptoms. Overall, tepotinib in combination with gefitinib was considered safe and well tolerated (Cheng 2018).

CCI [redacted]

Bardelli et al. demonstrated that MET activation in CRC tumor cells conferred resistance to anti-EGFR therapy in vitro and in vivo. In patient-derived CRC xenografts, *MET* amplification correlated with resistance to EGFR blockade which could be overcome by MET kinase inhibitors (Bardelli 2014).

Tepotinib - Risks

Interstitial lung disease (ILD) is considered a risk in patients with advanced NSCLC, as well as edema (mainly peripheral edema), creatinine increased, hypoalbuminemia, amylase and lipase increased, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increased, diarrhea, and nausea and vomiting. All these risks have been adverse reactions to tepotinib. More detailed safety information on classification of risks is provided in the IB.

As long as safety measures described in the protocol are strictly followed, it is reasonable to believe that the potential benefit of tepotinib outweighs its risk in participants with mCRC who have progressed on anti-EGFR antibody targeting therapy due to *MET* amplification. Furthermore, a SMC will regularly monitor safety throughout the study.

Benefit/Risk Assessment: Combination of tepotinib with cetuximab

In this study, possible overlapping toxicities for the combination of tepotinib plus cetuximab are diarrhea, increase in liver enzymes: AST and ALT, and ILD.

Diarrhea, ALT and AST increase are generally mild to moderate in severity. For both drugs these are risks that are well manageable. As per cetuximab label, increase in liver enzymes levels are very common, however in a monotherapy study they were not among the most common adverse events (AEs) reported ($\geq$ 15%). Inclusion will be only allowed for participants with adequate hepatic function.

Though ILD is a risk for both products, it was seen only in patients with NSCLC (1.9%) when treated with tepotinib. For cetuximab it is an uncommon (< 1%) event. Thus, the likelihood of a participant to experience an ILD in this study is considered low. Overall, the risk from overlapping toxicities is considered as manageable and adequate measurements such as eligibility criteria and dose modifications are in place. Participants with a history of ILD or who develop ILD will be excluded from the study.

More detailed information about the known and expected benefits and risks for the use combination of tepotinib with cetuximab, see Section 4.2 and more detail on the reasonably expected adverse events of tepotinib and cetuximab may be found in the respective IBs and SmPC/US PI for cetuximab.

Based on the available tepotinib and cetuximab nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

Moreover, a Safety Run-in Period has been planned to allow for a detailed evaluation of the combination regimen by a Safety Monitoring Committee (SMC) after the first 3 patients before more participants are enrolled into the study.

3 Objectives and Endpoints

Safety Run-in

Objectives	Endpoints
Primary	
To confirm the recommended Phase II dose (RP2D) of tepotinib when used in combination with cetuximab	Occurrence of dose limiting toxicities (DLTs)

Overall Study

Objectives	Endpoints
Primary	
To evaluate the preliminary efficacy of tepotinib (RP2D) in combination with cetuximab in terms of tumor response	Objective response (OR, confirmed complete response [CR] or partial response [PR]) determined according to RECIST Version 1.1 assessed by the Investigators
Secondary	
To further evaluate the efficacy of the combination of tepotinib (RP2D) and cetuximab in terms of	
duration of response (DoR)	DoR (months) according to RECIST Version 1.1 assessed by the Investigators
progression-free survival (PFS)	PFS (months) according to RECIST Version 1.1 assessed by the Investigators
overall survival (OS)	OS (months) assessed by the Investigators
To evaluate the safety and tolerability of tepotinib in combination with cetuximab	• Occurrence of Adverse Events (AE) and treatment-related AEs • Occurrence of clinically significant changes in vital signs, laboratory parameters and 12-lead electrocardiogram (ECG) findings
To characterize the immunogenicity of cetuximab	Immunogenicity of cetuximab as measured by antidrug antibody (ADA) assays on Cycle 1 Day 1 and End of Treatment Visit
CCI [redacted]	

4 Study Design

4.1 Overall Design

Please also see cross-references to Section 1.2, Section 1.3, and Section 6.7.

This is a Phase II, multicenter, single-arm, open-label study. A tolerable dose of tepotinib and cetuximab will be defined in the safety run-in period. It will assess the preliminary antitumor activity, safety, tolerability, and explore the PK of the MET inhibitor tepotinib combined with cetuximab (a chimeric monoclonal immunoglobulin G anti-EGFR monoclonal antibody) in *RAS*/*BRAF* wild-type mCRC participants having acquired resistance to anti-EGFR antibody targeted therapy due to *MET* amplification. Visits and duration of treatment are described as follows:

Screening

After having given written informed consent for screening procedures, *MET* amplification status will be assessed by a liquid and/or tissue-based *MET* amplification test in participants with mCRC with documented relapse on previous EGFR-monoclonal antibody treatment. Tissue and/or liquid biopsy samples provided for the inclusion testing will have to be collected after disease progression of the previous anti-EGFR therapy. Please see Section 8.8 for more detail on requirements and tests for *MET* amplification status and *RAS*/*BRAF* wild-type status.

RAS/*BRAF* wild-type status will be confirmed for eligibility before enrolling the participant, and after disease progression on the previous anti-EGFR therapy by an established test.

After having given written informed consent, eligibility criteria will be assessed prior to tepotinib and cetuximab coadministration on Day 1. If, at screening, the participant meets all the protocol-defined inclusion criteria and none of the exclusion criteria, the participant will be enrolled into either Cohort A (2L treatment, outside US) or Cohort B (3L+ in the US only) in the study; US participants are only allowed to be enrolled into Cohort B.

The screening period will include a Baseline tumor RECIST Version 1.1 assessment based on computed tomography (CT) or magnetic resonance imaging (MRI) and the confirmation of measurable tumor disease by the Investigator within 28 days before dosing. All radiological images will be collected, quality checked and stored for a potential post-study centralized read. Participants who fail to meet the protocol-specified criteria or who discontinue the study before start of study intervention will be considered screening failures.

Treatment Period

Eligible participants will receive a combination of the tepotinib dose confirmed by the SMC and cetuximab in cycles of 21 days duration until disease progression (according to RECIST Version 1.1), death, AE leading to discontinuation of both study interventions, study withdrawal, or withdrawal of consent, whichever occurs first.

Safety Run-in

An initial subset of at least 6 participants will, irrespective of therapy line, be enrolled in a safety run-in period to confirm that the dose of 500 mg QD of tepotinib (currently used in Phase II studies) can be administered together with cetuximab at 250 mg/m^2 as a weekly intravenous administration. Cohorts of 3 participants will be enrolled before SMC evaluation. Under certain conditions, depending on prior therapy, an initial loading dose of 400 mg/m^2 of cetuximab is required before the weekly 250 mg/m^2 dose is given. See Section 6.1 which provides the guidance to when the initial loading dose is given and when not to give. If the dose of tepotinib is not tolerated, the dose will be changed based on observed DLTs for the second run-in cohort. This decision will be taken by a SMC consisting of Sponsor representatives including, but not limited to the Patient Safety Strategy Lead (chair), the Medical Responsible, and the Biostatistician, and the coordinating Investigators or their deputies, based on safety data, and if available, PK data. If not tolerated, the dose of tepotinib will be adjusted to a dose that will be given to at least 6 additional participants during the safety run-in period. Further details on the Bayesian optimal interval (BOIN) model are shown in Section 9.4.2.1.

The first participant of the safety run-in period will be closely monitored for at least 3 days by the enrolling Investigator, with safety phone calls each day, before the second participant can be treated. Interruption of enrollment and a related SMC meeting may be requested at any time by any SMC member(s) if a safety or tolerability signal requires expedited discussions. The SMC can provide further treatment regimen suggestions as i.e. holiday schedules or tepotinib every second day.

Cohort expansion at RP2D

The SMC will decide and confirm the recommended Phase II dose (RP2D) of tepotinib to be used in combination with cetuximab in the whole study. The SMC may also decide to reduce the tepotinib dose to 250 mg QD based on the data collected during the safety run-in and for the whole study. If the dose of 250 mg QD is in general not tolerated, dosing in this study might be stopped. Dosing can also be stopped at any time to review safety and, if available, PK data, to allow for adjustments before dosing is resumed which will be decided by the Sponsor and the SMC. Safety run-in period can include participants from Cohorts A and/or B. The SMC's rules for assessing dose escalation and stopping rules are described under Section 9.4.2.1.

Follow-up Period

All participants are to be followed up after stop of treatment with tepotinib and cetuximab, including an End of Treatment (EoT) Visit within 14 days of the last dose of tepotinib and/or cetuximab. A Safety Follow-up Visit will occur 30 (- 3 to + 7) days after the last dose of tepotinib and/or cetuximab for all participants who discontinued the study intervention permanently. After the Safety Follow-up Visit, the Survival Follow-up is to be performed every 3 months (±1 month) at clinic visits or by telephone contact for up to 1 year. Participants' survival information will be collected. Any subsequent anticancer therapy given to the participant until death should be recorded.

Participants who discontinue treatment for reasons other than progressive disease (PD) or death will have additional visits for tumor assessments every 6 weeks until 9 months and every 12 weeks thereafter until disease progression, death, or withdrawal of consent. A ± 7-day time window is permitted for these additional follow-up visits until 9 months, and ± 14 days thereafter.

Duration of study for each participant, and duration of the study intervention period

For each participant, the study will include a Screening Period of up to 56 days, a Study

Intervention Period consisting of 3-week cycles (Cycles are 21 days) of tepotinib combined with cetuximab until disease progression, an End-of-Study Intervention Visit, a Safety Follow-up Period of 30 days, and a 1-year post study follow-up. Therefore, assuming there are 5 cycles, the anticipated duration of treatment for each participant is 191 days or ~6.5 months with a 1-year follow-up period thereafter.

Participants who discontinue the study for any reason, except for participant withdrawal, will complete the End-of-Study Intervention (End of Treatment), and Safety Follow-up Visit. See Section 1.3.

4.2 Scientific Rationale for Study Design

Dysregulation of MET signaling is an oncogenic driver in a number of tumors and interfering with the activity of MET is an effective way to induce tumor regression and stabilization. The high frequency of over 50% of 12 months and longer lasting tumor responses reported in NSCLC patients with tumors carrying a *MET*ex14 skipping mutation demonstrated this (Paik 2019). Furthermore, tepotinib clinical activity was reported in tumors overexpressing *MET*, such as *EGFR*-mutated NSCLC progressing on EGFR inhibitors and hepatocellular carcinomas (Decaens 2018, Ryoo 2018, Yang 2019). Especially in tumors such as gastric tumors, melanoma, papillary renal cell carcinoma, head and neck tumors, ovarian cancer, glioma and bladder cancer, *MET* amplification was observed and might be a target for specific therapy resistance CCI [redacted]

It has been observed that de novo *MET* amplification occurs rarely in mCRC (1% to 2%), (Raghav 2016). However, acquired *MET* amplification can be identified by circulating tumor DNA (ctDNA) in a significant subset of mCRC patients that are refractory to anti-EGFR antibodies (Bardelli 2013, LC-SCRUM, ASCO 2019 [Nakamura 2019], Raghav 2016, Siravegna 2015, Mohan 2014, Morelli 2014). Therefore, *MET* amplifications most likely play an important role in acquired anti-EGFR resistance. These findings have clear implications for identifying patient populations and for designing appropriate clinical trials using MET inhibitors in mCRC and potentially serve as a useful predictive biomarker of MET inhibitor response in mCRC clinical trials (Raghav 2016). EGFR targeted monoclonal antibodies are effective in a subset of mCRC. Inevitably, all patients develop resistance, which occurs through emergence of *RAS* mutations in approximately 50% of the cases. Participants with these *RAS* mutations will be excluded in this study population. Amplification of the *MET* protooncogene is an additional mechanism associated with acquired resistance in patients who do not develop *RAS* mutations during anti-EGFR therapy. Acquired *MET* amplification was seen in 3 out of 7 patients with post anti-EGFR treatment samples. *MET* amplification was detected in ctDNA before relapse became clinically evident

(Bardelli 2013). In vitro and in vivo studies demonstrated that MET activation conferred resistance to anti-EGFR therapy. In patient-derived CRC xenografts, *MET* amplification correlated with resistance to EGFR blockade which could be overcome by MET kinase inhibitors such as tepotinib and others (Bardelli 2013). The emergence of *MET* amplification in ctDNA of mCRC patients after treatment with cetuximab or panitumumab was confirmed in further independent studies: it was found in 2 out of 10 (20%) patients (Mohan 2014), 3 out of 16 (19%) patients (Siravegna 2015), 12 out of 53 (23%) patients (Raghav 2016), and 10 out of 71 (14%) patients (Nakamura 2019). *MET* amplification was specifically detected after anti-EGFR therapy, but not after anti-VEGF treatment, chemotherapy or regorafenib (Raghav 2016). *RAS*-mutant tumor status is known to be a very strong negative predictor for EGFR antibody therapy whilst, *RAS* wild-type tumor status is a relatively strong predictive marker for the efficacy of EGFR antibody therapy. *BRAF* tumor mutations are strong negative prognostic markers but also predictive markers for alternative therapy options. *RAS*/*BRAF* wild-type was potentially chosen as all guidelines discourage the use of anti-EGFR monoclonal antibodies in patients with *BRAF*-mutant disease despite of a still inconclusive evidence situation.

The dual therapeutic approach to control the disease via maintaining the inhibition of the EGFR pathway with cetuximab and at the same time targeting the emerging MET activated pathway with tepotinib offers a potential treatment option for those patients. There is currently no personalized treatment option available for these selected mCRC patients and therefore constitutes a clinical condition with high unmet medical need. Since it is described that anti-EGFR resistant clones decay exponentially after stopping the anti-EGFR therapy post-progression (Parseghian 2019), a timely initiation of the dual therapy is required.

Due to the different nature of the two drugs (small molecule and protein) and the consequent different metabolic pathways, the potential for PK interactions between both drugs is considered low. Also, the risk for overlapping toxicity is considered low, however, this will be closely monitored.

The proposed study investigates tepotinib combined with cetuximab in *RAS*/*BRAF* wild-type mCRC patients who have acquired resistance to anti-EGFR antibody therapy due to *MET* amplification.

The prognostic impact of the primary tumor location in metastatic CRC has been discussed extensively, including a meta-analysis which has been initiated by ESMO and provided evidence in the first-line treatment setting to reinforce the use of EGFR antibody therapy in patients with mCRC and left-sided *RAS* wild-type tumors (Arnold 2017 and ESMO Asia guidelines [Yoshino 2018]). Patients with left-sided tumors had a markedly better prognosis than those with right-sided tumors in the *RAS* wild-type populations of CRYSTAL (Phase III Cetuximab Combined With Irinotecan in First-line Therapy for mCRC [CRYSTAL]) study and FIRE-3 (Phase III, The FOLFIRI Plus Cetuximab Versus FOLFIRI Plus bevacizumab as First-Line Treatment For Patients With mCRC [FIRE-3]). First-line FOLFIRI plus cetuximab clearly benefitted patients with left-sided tumors (versus FOLFIRI or FOLFIRI plus bevacizumab), significantly improving OS (CRYSTAL: hazard ratio [HR] = 0.65; 95% CI: 0.50, 0.86 and FIRE-3: HR = 0.63; 95% CI: 0.48, 0.85) within the *RAS* wild-type populations of both studies in multivariable models that also included sex, prior adjuvant therapy, and *BRAF* mutational status

(Tejpar 2017). Patients with right-sided tumors derived limited benefit from standard treatments (i.e. FOLFIRI, FOLFIRI plus bevacizumab, and FOLFIRI plus cetuximab (Tejpar 2017). These differences are based on the different genetic phenotype of both primary tumor locations. Therefore, participants with advanced (locally advanced or metastatic) left-sided colorectal cancer are included in this study.

While cetuximab and panitumumab are approved as treatment options for patients in a first-line and later line setting, different standard of cares are established between US and Europe and other regions. In Europe, cetuximab is more commonly used in first-line, whereas in US it is more often used after bevacizumab + chemotherapy. Therefore, the study will include participants with a prior first-line of anti-EGFR containing therapy outside of US (Cohort A), and in US participants with more than one prior line of therapies (with the most recent line being an anti-EGFR containing therapy, Cohort B). A separate analysis evaluating the safety and responses will be performed for all cohorts.

4.3 Justification for Dose

Cetuximab will be used according to the approved label, with an initial dose of 400 mg/m^2 (if needed, followed by repetitive weekly doses of 250 mg/m^2, see Section 6.1 for guidance). Detailed information on the PK of cetuximab in humans can be found in the IB/US PIs/SmPCs.

Tepotinib will be used at a starting dose of 500 mg QD in a 21-day cycle, which is the recommended dose and has been investigated in other studies. For potential dose de-escalation, the available 250 mg dose strength will be used in case 500 mg QD in combination with weekly cetuximab is not tolerated. No drug-drug interactions are expected (See Section 4.2). The anticipated initial dose levels for combination therapy take into consideration a potentially overlapping toxicity of interstitial lung disease. Diarrhea, ALT, and AST increase are mainly mild to moderate in severity, risks for both drugs and well manageable with standard therapy.

The proposed clinical dose of 500 mg tepotinib once daily was defined by a translational model-based approach that utilized nonclinical PK and pharmacodynamics (Pd) data (inhibition of the MET pathway), nonclinical efficacy data (inhibition of tumor growth), and clinical PK and Pd data, and was confirmed by clinical safety and efficacy data.

According to the translational PK/Pd model, daily administration of 500 mg tepotinib is predicted to achieve a steady state ≥ 95% MET inhibition in greater than 90% of the population. The dose reduction-level of 250 mg is predicted to maintain the target Pd response in greater than 80% of the population.

4.4 End of Study Definition

A participant has completed the study if he/she has completed all study parts, including the Safety Follow-up Visit after end of treatment and the Survival Follow-up, for up to 1-year.

The end of the study is defined as the date when the last participant has completed the last visit in the Survival Follow-up.

Participants will not be followed for the 1-year Survival Follow-up if the Sponsor terminates the study early for any reason.

See also Section 7.2.

5 Study Population

The criteria in Sections 5.1 and 5.2 are designed to enroll only participants, who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative (where allowed by local laws and regulations) has provided written informed consent, as indicated in Appendix 2.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Are ≥ 18 years of age (or having reached the age of majority according to local laws and regulations, if the age of majority is > 18 years of age) at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Advanced (locally advanced or metastatic, unresectable) left-sided (from splenic flexure to rectum – National Comprehensive Cancer Network CRC Version 1.2021 guidelines) CRC with *RAS*/*BRAF* wild-type at study entry confirmed prior to enrollment, with previous anti-EGFR therapy and acquired resistance on the most recent anti-EGFR monoclonal antibody therapy (panitumumab or cetuximab) by radiological documentation of disease progression according to RECIST Version 1.1.

3. *MET* amplification detected by a positive liquid biopsy and/or tissue with appropriate regulatory status (collected after disease progression of the previous anti-EGFR therapy).

4. Measurable disease by Investigator in accordance with RECIST Version 1.1.

5. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

6. Life expectancy > 3 months.

7. Participants having at least one systemic treatment for mCRC including 1 anti-EGFR monoclonal antibody therapy as the most recent line of therapy for mCRC before study treatment and must have shown a radiologically confirmed by RECIST Version 1.1 complete response (CR) or partial response (PR), both for at least 4 months or stable disease (SD) for at least 6 months to that therapy prior to disease progression.

a. For Cohort A in sites outside of US, participants must only have had one prior systemic treatment for mCRC.

b. For Cohort B in sites in the US only, participants must have had at least two prior systemic treatments for mCRC. First-line treatment must include a fluoropyrimidine and oxaliplatin or irinotecan and second-line treatment must include a fluoropyrimidine, oxaliplatin, or irinotecan.

8. Less than 2 months between the last administration of the most recent EGFR containing regimen and first dosing in this study.

9. Adequate hematological function in the absence of transfusions in 7 days before testing defined by white blood cell count $\geq 3 \times 10^9$/L with absolute neutrophil count, $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin ≥ 8.5 g/dL.

10. Adequate hepatic function defined by a total bilirubin level $\leq 1.5 \times$ upper limit of normal (ULN), AST $\leq 3 \times$ ULN, and ALT $\leq 3 \times$ ULN. For participants with liver metastases: total bilirubin $\leq 1.5 \times$ ULN, AST/ALT $\leq 5 \times$ ULN.

11. Adequate renal function defined by an estimated glomerular filtration rate > 30 mL/min according to the 4-component Modification of Diet in Renal Disease (MDRD) equation (GFR [mL/min/1.73 m^2] = 175 × serum creatinine $(Scr)^{-1.154} \times age^{-0.203} \times 1.212$ [if African American] × 0.742 [if female]).

Sex

12. Are male or female

Contraceptive use by males or females will be consistent with local regulations on contraception methods for those participating in clinical studies.

a. Male Participants:

Agree to the following during the study intervention period and for at least 4 months after the last dose of study intervention:

- Refrain from donating sperm

PLUS, either:

- Abstain from intercourse with a woman of child bearing potential

OR

- Use a male condom:
  - When having sexual intercourse with a woman of child bearing potential, who is **not** currently pregnant, **and** advise her to use a highly effective contraceptive method with a failure rate of <1% per year, as described in Appendix 3, since a condom may break or leak.

b. Female Participants:

- Are **not** pregnant or breastfeeding, and at least one of the following conditions applies:
  - **Not** a woman of child bearing potential

  OR

- If a woman of child bearing potential, use a highly effective contraceptive method (i.e., with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 3 for the following time periods:
  - Before the first dose of the study intervention(s), if using hormonal contraception:
    - Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses

      OR

    - Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay.

      AND

      A barrier method, as described in Appendix 3.
  - During the intervention period
  - After the study intervention period (i.e., after the last dose of study intervention is administered) for at least 2 months after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period.
  - The investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
  - Have a negative serum or highly sensitive urine pregnancy test, as required by local regulations, within 24 hours before the first dose of study intervention. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required.
- Additional requirements for pregnancy testing during and after study intervention are in Section 8.2.4.
- The investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

Informed Consent

13. Capable of giving signed informed consent, as indicated in Appendix 2 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participants with symptomatic central nervous system (CNS) metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS metastases. Also excluded are participants with carcinomatous meningitis.

2. Participants who have brain metastasis as the only measurable lesion.

Prior/Concomitant Therapy

3. Prior chemotherapy, biological therapy, radiation therapy, hormonal therapy for anti-cancer purposes, targeted therapy, or other investigational anticancer therapy (not including palliative radiotherapy at focal sites) within 21 days prior to the first dose of study intervention, except for the anti-EGFR containing regimen including associated chemotherapy if applicable, which may be continued until enrollment of the participant in the study.

4. Any unresolved toxicity Grade 2 or more according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0, from previous anticancer therapy excluding neuropathy, alopecia and rash.

Other Exclusions

5. Known severe hypersensitivity reactions to monoclonal antibodies (Grade $\geq$ 3 NCI-CTCAE v 5.0), any history of anaphylaxis, or uncontrolled asthma (i.e., 3 or more occurrences of partially controlled asthma).

6. Discontinuation of the most recent cetuximab or panitumumab containing therapy due to an adverse event.

7. Prior treatment with other agents targeting the HGF/MET pathway.

8. Impaired cardiac function:

    a. Left ventricular ejection fraction < 45% defined by echocardiography (a screening assessment not required for participants without a history of congestive heart failure unless clinically indicated)

b. Serious arrhythmia

c. Unstable angina pectoris

d. New York Heart Association heart failure Class III and IV

e. Myocardial infarction within the last 12 months prior to study entry

f. Symptomatic pericardial effusion

g. Corrected QT interval by Fridericia (QTcF) > 480 ms

9. Hypertension uncontrolled by standard therapies (not stabilized to < 150/90 mmHg).

10. Past or current history of neoplasm other than mCRC, except for curatively treated non-melanoma skin cancer, in situ carcinoma of the cervix, or other cancer curatively treated and with no evidence of disease for at least 5 years.

11. Medical history of difficulty swallowing, malabsorption, or other chronic gastrointestinal disease, or conditions that may hamper compliance and/or absorption of the test products.

12. Major surgery within 28 days prior to Day 1 of study intervention.

13. Known infection with human immunodeficiency virus, or an active infection with hepatitis B or hepatitis C virus.

14. Substance abuse, active infection, or other acute or chronic medical or psychiatric condition or laboratory abnormalities that might increase the risk associated with study participation at the discretion of Investigators.

15. IMP use in another study within 3 weeks of the first dose of study intervention.

16. History of ILD or interstitial pneumonitis including radiation pneumonitis that required steroid treatment.

5.3 Lifestyle Considerations

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., watching television or reading).

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants will be assigned a new participant number and will undergo all Screening procedures as planned by the protocol, except liquid biopsy/ tissue biopsy testing. Rescreening is permitted only for participants with confirmed *MET* amplification if they do not meet 1 of the other inclusion or exclusion criteria and after discussion with the Sponsor. For Rescreening no repetition for *MET* amplification status is needed.

6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Intervention(s) Administration

Duration of study for each participant, and flexibility on dosing schedule is covered under Section 4.1.

ARM Name	Not applicable	
Intervention Name	Tepotinib	Cetuximab
Type	Combination	
Dose Formulation	Film-coated tablets	Solution for intravenous infusion
Unit Dose Strength(s)	250 mg	Vial of 20 mL containing 100 mg cetuximab (5 mg/mL) outside of US. Vial of 50 mL or 100 mL containing 100 mg or 200 mg cetuximab (2 mg/mL) respectively for US participants only.
Dose Amount and Frequency	After food intake, e.g. a normal breakfast, once a day. Tepotinib will be used initially at 500 mg QD (2 tablets of 250 mg QD). For potential dose de-escalation, the available 250 mg dose strength will be used (1 tablet once daily). Please see also Section 6.6 Tepotinib will be given approximately 30 mins before the start of each cetuximab infusion.	Administered once a week. Prior to the first infusion, participants must receive premedication with an antihistamine and if local cetuximab label requires, a corticosteroid at least 1 hour prior to administration of cetuximab. This premedication is recommended prior to all subsequent infusions. When to start with a loading dose: Required loading dose at an initial dose of 400 mg/m^2 body surface area if participant received the following: Panitumumab as prior line Cetuximab as prior line and last dose was more than 3 weeks ago. No loading dose required if participant: received cetuximab as prior line and last dose was given up to 3 weeks ago. Loading dose (where required): Cetuximab, is administered at an initial dose of 400 mg/m^2 body surface area, over a recommended infusion period of 120 minutes and a maximum infusion rate of 5 mg/min, followed by or starting with weekly infusions at a dose of 250 mg/m^2 over a recommended infusion period of 60 minutes and a maximum infusion rate of 10 mg/min
Route of Administration	Oral	Intravenous
Use	Experimental	Experimental
IMP and Non- Investigational Medicinal Product	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Tepotinib will be provided in CCI tablets. Each wallet containing the CCI tablets will be labeled per country requirement	Cetuximab will be provided in vials. Each vial will be labeled per country requirement
Current/Former Name(s) or Alias(es)	Not applicable	Erbitux

Abbreviations: IMP = investigational medicinal product; QD = daily; US = United States.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee will confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Pharmacy Manual.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) will be stored in a secure, environmentally controlled, and monitored (manual or automated) area, per the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, container numbers, expiry dates, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) will not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Due to the nature of the single-arm study design, this study is performed open-label.

An Interactive Web Response System (IWRS) will be employed to assign a study number to participants and facilitate supply and resupply of study intervention at study sites.

Participant numbers will be assigned in the appropriate format and will reflect study number, site number and participant identification. Participant numbers will not be reassigned to other participants or reused in this study. If a participant is allowed to be rescreened for the study, a new participant number will have to be assigned.

Study using IWRS	After confirmation of participant's eligibility, participants will be centrally assigned to unique participant numbers. Before the study is initiated, the directions for the IWRS will be provided to each site. The site will contact the IWRS prior to starting study intervention administration for each participant.

6.3.2 Blinding

This is an open-label single arm study. Potentially, a re-assessment of tumor measurements will be performed by an independent review committee to reduce bias.

6.4 Study Intervention Compliance

Acceptable compliance for this study will be defined in the Monitoring Plan.

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic CRF (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tepotinib tablets during the site visits and documented in the source documents and eCRF. Any deviation(s) from the prescribed dosage regimen are recorded in the eCRF.

A record of the number of tepotinib tablets dispensed to and taken by each participant will be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

Participants may be withdrawn from the study interventions in the event of noncompliance that is deemed by the Investigator or Sponsor to compromise participant safety or study integrity (see Section 7.1 and Section 8.4).

6.5 Concomitant Therapy

Record in the eCRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion.

Standard supportive therapy should follow general principles in oncology (refer to American Society of Clinical Oncology guidelines for supportive care). Use of hematopoietic growth factors is permitted where indicated in accordance with the American Society of Clinical Oncology guideline.

6.5.1 Permitted Medicines

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

The Investigator will record all concomitant medications/procedures taken by the participant during the study, from the date of signature of main informed consent, in the appropriate section of the eCRF.

Cetuximab

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

See Appendix 3 for contraceptive methods.

For any skin AE of Grade 1 to 3, topical and/or oral antibiotics are permitted. Participants with Grade 3 or higher reactions should be referred to a dermatologist for advice and management if needed.

Tepotinib

The following are permitted:

- Concomitant medications that have a narrow therapeutic window and are known to be transported by P-gp (e.g., rivaroxaban, apixaban, ranolazine, talinolol, digoxin), BCRP (e.g., rosuvastatin), OCT2, MATE1, and MATE2 (e.g., dofetilide, metformin) and OCT1 are permitted, but should be used with caution. Tepotinib is a substrate for P-gp. Strong P-gp inducers may have the potential to decrease tepotinib exposure. Concomitant use of strong P-gp inducers (e.g., carbamazepine, phenytoin, rifampicin, and St. John's wort) should be avoided. Monitoring the clinical effects of P-gp-dependent substances with a narrow therapeutic index (e.g., digoxin) is recommended during coadministration with tepotinib. Tepotinib can inhibit the transport of sensitive substrates of BCRP. Monitoring the clinical effects of sensitive BCRP substrates (e.g., rosuvastatin) is recommended during co-administration with tepotinib. Based on in vitro data, tepotinib and its metabolite may have the potential to increase the AUC of co administered metformin in humans, through inhibition of its renal excretion mediated via OCT1 and OCT2, and MATE1 and MATE2. Monitoring of the effect of metformin is recommended during co-administration with tepotinib.
- The Investigator may decide not to include a participant in the study, if the participant cannot withdraw the drugs that have a narrow therapeutic range and that are known to be transported via P-gp.
- If the Investigator decides to enroll a participant who is treated with a drug that is transported via P-gp and has a narrow therapeutic range, close safety monitoring is advised.
- Refer to Appendix 3 Contraception for contraceptive methods.
- Supportive treatment, e.g., bisphosphonates, agents for improving appetite, if initiated prior to study entry, is allowed to continue. Change in dose/schedule on study is discouraged. Initiation of bisphosphonates with prophylactic purpose during study intervention should be avoided.
- Symptomatic treatment of brain metastasis with anticonvulsants known to have a reduced risk for drug interactions such as lamotrigine, levetiracetam, pregabalin or valproic acid is allowed.

6.5.2 Prohibited Medicines

If the administration of a nonpermitted concomitant drug becomes necessary during the study, e.g., for AEs or in an urgent medical situation, it is at the Investigator's discretion. In such a case, this participant has to be withdrawn from study intervention and detailed information needs to be recorded.

Cetuximab

Cetuximab is contraindicated in participants with known severe (Grade 3 or 4) hypersensitivity reactions to cetuximab.

Tepotinib

The following are not permitted during the study:

- Any other cancer therapy, including chemotherapy, biological therapy, traditional Chinese

medicine, hormonal therapy for anticancer purposes, targeted therapy, or any investigational product other than tepotinib and cetuximab as defined in this protocol.

- Drug(s), for which the package insert/summary of product characteristics includes a contraindication for P-gp (e.g., dabigatran, aliskiren), BCRP, OCT1, OCT2, MATE1, and MATE2 inhibiting drugs.
- Drug(s) that are known to induce P-gp and thereby may decrease efficacy of tepotinib (e.g., avasimibe, carbamazepine, phenytoin, rifampin and St. John's wort).

6.5.3 Other Interventions

Tepotinib

Localized radiation therapy to alleviate symptoms such as bone pain is allowed provided that the total dose delivered is in a palliative range according to institutional standards and does not involve any target lesion(s) utilized for response determination.

Cetuximab

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

6.5.4 Special Precautions

6.5.4.1 Cetuximab

Infusion-related reactions

Severe IRRs, including anaphylactic reactions, may commonly occur, in some cases with fatal outcome. Occurrence of a severe IRR requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment. Some of these reactions may be anaphylactic or anaphylactoid in nature or represent a cytokine release syndrome (CRS). Symptoms may occur during the first infusion and for up to several hours afterwards or with subsequent infusions. It is recommended to warn patients of the possibility of such a late onset and instruct them to contact their physician if symptoms or signs of an IRR occur. Symptoms may

include bronchospasm, urticaria, increase or decrease in blood pressure, loss of consciousness or shock. In rare cases, angina pectoris, myocardial infarction or cardiac arrest have been observed.

Anaphylactic reactions may occur as early as within a few minutes of the first infusion e.g. due to preformed Immunoglobulin E (IgE) antibodies cross-reacting with cetuximab. These reactions are commonly associated with bronchospasm and urticaria. They can occur despite the use of premedication.

The risk for anaphylactic reactions is much increased in patients with a history of allergy to red meat or tick bites or positive results of tests for IgE antibodies against cetuximab (α-1-3-galactose). In these patients cetuximab should be administered only after a careful assessment of benefit/risk, including alternative treatments, and only under close supervision of well-trained personnel with resuscitation equipment ready.

The first dose should be administered slowly, and the speed must not exceed 5 mg/min whilst all vital signs are closely monitored for at least two hours. If during the first infusion, an IRR reaction occurs within the first 15 minutes, the infusion should be stopped. A careful benefit/risk assessment should be undertaken including consideration whether the patient may have preformed IgE antibodies before a subsequent infusion is given. If an IRR develops later during the infusion or at a subsequent infusion further management will depend on its severity:

a) Grade 1: continue slow infusion under close supervision

b) Grade 2: continue slow infusion and immediately administer treatment for symptoms

c) Grade 3 and 4: stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab. See Cetuximab: Dose Modifications under Section 6.6.1.

A CRS typically occurs within one hour after infusion and is less commonly associated with bronchospasm and urticaria. CRS is normally most severe in relation to the first infusion.

Mild or moderate IRRs are very common comprising symptoms such as fever, chills, dizziness, or dyspnea that occur in a close temporal relationship mainly to the first cetuximab infusion. If the patient experiences a mild or moderate infusion-related reaction, the infusion rate may be decreased. It is recommended to maintain this lower infusion rate in all subsequent infusions.

A close monitoring of patients, particularly during the first administration, is required. Special attention is recommended for patients with reduced performance status and pre-existing cardio-pulmonary disease.

Respiratory Disorders and ILD

Cases of ILD, which can be fatal, have been reported with the majority of patients from the Japanese population. Confounding or contributing factors, such as concomitant chemotherapy known to be associated with ILD, and pre-existing pulmonary diseases were frequent in fatal cases. Such patients should be closely monitored. In the event of symptoms (such as dyspnea, cough, fever) or radiographic findings suggestive of ILD, prompt diagnostic investigation should occur.

Patients with acute onset or worsening of pulmonary symptoms should be closely monitored. If interstitial lung disease is diagnosed, cetuximab must be discontinued and the patient be treated appropriately.

Skin Reactions

If a patient experiences a severe skin reaction (≥Grade 3; CTCAE), cetuximab therapy must be interrupted. Treatment may only be resumed if the reaction has resolved to Grade ≤ 2.

If the severe skin reaction occurred for the first time, treatment may be resumed without any change in dose level. With the second and third occurrences of severe skin reactions, cetuximab therapy must again be interrupted. Treatment may only be resumed at a lower dose level (200 mg/m^2 BSA after the second occurrence and 150 mg/m^2 after the third occurrence), if the reaction has resolved to Grade ≤ 2.

If severe skin reactions occur a fourth time or do not resolve to Grade ≤ 2 during interruption of treatment, permanent discontinuation of cetuximab treatment is required.

Electrolyte Abnormalities

Progressively decreasing serum magnesium levels have been observed. Other electrolyte disturbances have also been observed and may lead to severe hypomagnesemia. In addition, hypokalemia may develop. Hypocalcemia may also occur; in particular in combination with platinum-based chemotherapy the frequency of severe hypocalcemia may be increased. Determination of serum electrolyte levels is recommended prior to and periodically during cetuximab treatment. Electrolyte repletion is recommended, as appropriate.

Eye Disorders

Cases of keratitis and ulcerative keratitis have been reported with the use of cetuximab. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

If a diagnosis of ulcerative keratitis is confirmed, treatment with cetuximab should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.

Cetuximab should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.

Patients with *RAS*-mutant Metastatic Colorectal Cancer

The additional analyses of pivotal studies conclude that patients with other than *KRAS* exon 2 *RAS*-mutant tumors may be less likely to benefit from cetuximab. Given the available RAS data, the totality of the evidence is sufficient to recommend administration of cetuximab only in patients with *RAS*-wild-type mCRC.

Colorectal Cancer Patients with *RAS*-mutant Tumors

Cetuximab should not be used in the treatment of colorectal cancer patients whose tumors have *RAS* mutations or for whom *RAS* tumor status is unknown. Results from clinical studies show a negative benefit-risk balance in tumors with *RAS* mutations, in particular, in combination with continuous infusional 5-fluorouracil/folinic acid plus oxaliplatin.

Special Populations

The effectiveness of cetuximab in pediatric patients has not been established. No new safety signals were identified in pediatric patients as reported from a Phase I study.

There is limited experience in the use of cetuximab in combination with radiation therapy in CRC.

Pregnancy and Lactation

Animal data do not suggest a teratogenic effect. However, an increased incidence of abortion was observed in monkeys administered doses greater than human exposure. There are no adequate and well-controlled studies in pregnant or lactating women.

6.5.4.2 Tepotinib

Interstitial Lung Disease

Interstitial lung disease or ILD-like adverse reactions have been reported in the clinical study program with tepotinib in patients with NSCLC.

Participants should be monitored for pulmonary symptoms indicative for ILD or ILD-like reactions. Tepotinib should be withheld and participants should be promptly investigated for alternative diagnosis or specific etiology of ILD. Tepotinib must be permanently discontinued if ILD is confirmed and the participant be treated appropriately.

Edema

Edema has been reported frequently in the study program. It is an identified risk for treatment with tepotinib. To gain further information, to the occurrence and resolution of edema, any AEs of edema, the current edema status or AE resolution is to be specifically documented at each visit.

In the case of edema, please follow the advice in the Recommended Dose Modifications for Tepotinib table in Section 6.6.2.

Asymptomatic Pancreatic Enzyme Elevation

If an asymptomatic lipase/amylase elevation of Grade ≥ 3 occurs, the participant will undergo clinical evaluation for the presence of signs and symptoms typical of acute pancreatitis and for other risk factors for pancreatitis. In addition, a CT scan and/or MRI of the abdomen will be performed to assess the pancreas. The Sponsor (or delegate) will be notified of the outcome of the CT/MRI. Dosing with study intervention can continue during the evaluation period unless the

clinical evaluation indicates pancreatitis. However, the continuation of study intervention for the participant will be individually discussed with the Investigator on a participant by participant basis.

Lipase and amylase elevations are considered adverse reactions and may occur during or beyond Cycle 1, and 3 different scenarios are forecasted:

- Persistent asymptomatic lipase/amylase elevation at the same grade of Grade ≥ 3
- Recurrent asymptomatic lipase/amylase elevation of Grade ≥ 3, after an initial Grade ≥ 3 elevation with subsequent resolution; and
- Asymptomatic lipase/amylase elevation of Grade ≥ 3 with persistent elevation at the same grade, followed by subsequent further increase in grade.

In all cases, the participant will undergo clinical evaluation for the presence of signs and symptoms typical of acute pancreatitis and for other risk factors for pancreatitis. A gastrointestinal consult should be requested and additional investigations (e.g., repeated abdominal CT scan) should be considered, as appropriate. The case will be discussed with the Sponsor (or delegate). Treatment with tepotinib may be continued during the evaluation period, at the discretion of the treating physician and depending on the circumstances of the individual case.

If there is no clinical or radiological evidence of pancreatitis, treatment with tepotinib should be continued, particularly if there is a potentially positive benefit for the individual participant. Evaluation of potential clinical benefit will be based on evidence from the literature, nonclinical models, and/or current experience with tepotinib in the participant or other participants with this tumor type. Otherwise, treatment with tepotinib should be discontinued.

In case of dose reduction Section 6.6, the Investigator should notify the Sponsor immediately and each case should be discussed on a case-by-case basis, providing the reason for dose reduction.

Embryo-fetal Toxicity

Tepotinib can cause fetal harm when administered to pregnant women.

Women of childbearing potential or male participants with female partners of childbearing potential should be advised of the potential risk to a fetus.

6.6 Dose Selection and Modification

See also Section 4.3 for justification of the tepotinib and cetuximab doses. The recommendation to proceed to an intermediate dose level, to decrease the dose will be made by the SMC based on safety, tolerability, and available PK data.

6.6.1 Cetuximab

Cetuximab: Recommended Dose

In all indications, cetuximab is administered once a week. The very first dose is 400 mg cetuximab per m^2 body surface area (if needed, see Section 6.1 for guidance). All subsequent weekly doses are 250 mg/m^2 each.

Cetuximab: Dose Modification

In case a dose reduction is necessary, the study intervention will be administered as follows and described in the 'Investigator's Brochure Appendix' (part of the cetuximab IB, that refers to the Merck core company data sheet).

Infusion-related Reactions

If during the first infusion, an IRR occurs within the first 15 minutes, the infusion should be stopped. A careful benefit/risk assessment should be undertaken including consideration whether the participant may have performed IgE antibodies before a subsequent infusion is given. If an IRR develops later during the infusion or at a subsequent infusion further management will depend on its severity:

a) Grade 1: continue slow infusion under close supervision

b) Grade 2: continue slow infusion and immediately administer treatment for symptoms

c) Grade 3 and 4: stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab.

Skin Reactions

- If a participant experiences a severe skin reaction (≥Grade 3; CTCAE), cetuximab therapy must be interrupted. Treatment may only be resumed if the reaction has resolved to Grade ≤ 2.
- If the severe skin reaction occurred for the first time, treatment may be resumed without any change in dose level. With the second and third occurrences of severe skin reactions, cetuximab therapy must again be interrupted. Treatment may only be resumed at a lower dose level (200 mg/m^2 after the second occurrence and 150 mg/m^2 after the third occurrence), if the reaction has resolved to Grade ≤ 2.
- If severe skin reactions occur a fourth time or do not resolve to Grade ≤ 2 during interruption of treatment, permanent discontinuation of cetuximab treatment is required.

6.6.2 Tepotinib

Tepotinib: Recommended Dose

The proposed clinical dose of 500 mg tepotinib once daily was defined by a translational model-based approach that utilized nonclinical PK and Pd data (inhibition of the MET pathway), nonclinical efficacy data (inhibition of tumor growth), and clinical PK and Pd data, and was confirmed by clinical safety and efficacy data.

In the ongoing Phase II single-arm pivotal study (VISION) that aims to investigate tepotinib in advanced (Stage IIIB/IV) NSCLC with *MET*ex14 skipping alterations or *MET* amplification, daily doses of 500 mg tepotinib were administered after breakfast and shown to be efficacious with an acceptable safety profile, confirming the selected clinical dose and regimen, and this is the labeled dose in US and Japan for patients with NSCLC with *MET*ex14 skipping alterations.

The exposure-efficacy analysis for the primary clinical endpoint in VISION, objective response (OR), shows similar OR rates across the exposure range achieved with administration of the clinical dose of 500 mg. This confirms the simulations from the translational PK/Pd model that predicted biologically meaningful target inhibition in a large proportion of the patient population at the clinical dose of 500 mg.

Tepotinib: Dose Modification

Dependent on circumstances, the Investigator could either temporarily interrupt tepotinib treatment, or continue tepotinib treatment at a lower dose level until the AE related to tepotinib recovers to ≤ Grade 2 or to Baseline values.

Dose Reduction

In case a dose reduction is necessary, the study intervention will be administered as follows:

The 250 mg once daily dose is the standard dose reduction. If a participant does not tolerate the 250 mg once daily dose, or the AE does not resolve following treatment interruption, permanent treatment discontinuation or other dosing schemas (i.e. holiday schedules or tepotinib every 2nd day) should be discussed with the Sponsor.

Treatment Interruption

The maximum permitted period of continuous treatment interruption is 21 days. Following a treatment interruption, participants can be re-challenged at the initial dose level. Re-exposure at different dose level after a treatment interruption is subject to case by case decisions; the Sponsor should be informed of any such decisions.

Recommended Dose Modifications for Tepotinib

Target organ	Adverse event[a]	Dose modification
Pulmonary	Confirmed ILD/pneumonitis	Permanently discontinue tepotinib.
Cardiac	QTc interval prolongation of Grade ≥3	Discontinue tepotinib
Body	Edema Grade 1 or 2	Dose level of tepotinib can be maintained
	Edema Grade 3	The dose of tepotinib must be interrupted until edema recovers to ≤ Grade 2 or baseline but for no more than 21 days. After recovery the patient can restart at the same dose or at 250 mg daily. If edema Grade 3 reoccurs the tepotinib dose must be interrupted again until edema recovers to ≤ Grade 2 or baseline but for no more than 21 days. After recovery, tepotinib must then be dose reduced to 250 mg daily (if the previous dose was 500 mg daily). If edema Grade 3 reoccurs at 250 mg dose, tepotinib must be permanently discontinued.
	Generalised edema Grade 4	Permanently discontinue tepotinib.
Pancreas	Pancreatic enzyme elevation Grade ≥3	See detailed instruction in Section 6.5.4.2.
Other	Any other related adverse event of Grade 3	The dose of tepotinib must be interrupted until event resolves to ≤ Grade 2 or baseline but for no more than 21 days. After recovery, tepotinib may be restarted at 1 dose level below; 250 mg daily. If any other related AE of Grade 3 reoccurs at 250 mg dose, tepotinib must be permanently discontinued
	Grade 4	Permanently discontinue tepotinib

Abbreviation: AE = adverse event; .
Also consider DLT rules during DLT period and Safety Run-in.
a Adverse events graded by NCI-CTCAE v5.0.

Following dose modifications, the dose of tepotinib may be increased again to the initial dose level at the discretion of the Investigator.

Clinical circumstances which are not covered by above criteria may be grounds for dose reductions or treatment interruptions and should be discussed with the Sponsor on a case-by-case basis.

6.6.3 Dose Limiting Toxicity

Dose-limiting toxicities will be evaluated using the NCI-CTCAE v5.0. Limits for dose escalations will be considered in accordance to Bayesian Optimal Interval design (BOIN) based on a maximum target toxicity rate of 30% and a maximum number of 12 participants (Yuan 2016).

In the safety run-in part of the study, DLTs are defined as any of the following toxicities and judged by the Investigator and/or the Sponsor to be not attributable to the disease or disease-related processes under investigation:

1. Grade 4 neutropenia for more than 7 days
2. Grade ≥ 3 febrile neutropenia with absolute neutrophil count < 1000/mm^3 and a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour
3. Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with non-traumatic bleeding
4. Grade 3 uncontrolled nausea/vomiting and/or diarrhea that has not improved within 72 hours despite adequate and optimal treatment
5. Grade 4 vomiting and/or diarrhea
6. Grade ≥ 3 skin toxicity that has not resolved to Grade 2 after 14 days of adequate treatment
7. Any other Grade ≥ 3 non-hematological AE will be defined as DLT. Exceptions are alopecia or an isolated lipase and/or amylase elevation of Grade ≥ 3 without clinical or radiological evidence of pancreatitis
8. Occurrence of Hy's law cases (defined as aminotransferases > 3 × ULN, total bilirubin ≥ 2 × ULN, and alkaline phosphatase (ALP) < 2 × ULN, with no other reason to account for these abnormalities)
9. Interstitial lung disease (ILD)/pneumonitis.

All participants enrolled in the safety run-in period who miss > 25% of the planned doses of tepotinib and/or cetuximab within Cycle 1 will be replaced if the dose reduction/interruption was not caused by any safety reasons/DLTs. Participants who experience at least one DLT during the DLT assessment period are included regardless of the cumulative dose administered.

All participants enrolled in the study are selected based on the same inclusion and exclusion criteria as specified in the eligibility criteria.

6.7 Study Intervention after the End of the Study

If the study is prematurely terminated or suspended, participants who continue to demonstrate clinical benefit will be eligible to receive study intervention. Study intervention will be provided via an extension of the study, a rollover study requiring approval by the responsible health authority and independent ethics committee, or mechanisms i.e., single patient post study access, or patient support, or other access programs as per local regulations, at the discretion of the Sponsor. The Sponsor reserves the right to terminate access to study intervention if any of the following occur: a) the study is terminated due to safety concerns, or b) a marketing authorization is granted in the local market and the corresponding medication is reimbursed by the public social security system making it accessible to the participant.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for what is specified in the Schedule of Activities (SoA) (Section 1.3). The SoA indicates data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

- The participant must be withdrawn from study intervention in the event of any of the following:
  - Withdrawal of consent.
  - Development of unacceptable toxicity.
  - Occurrence of progressive disease according to RECIST Version 1.1 or initiation of any other anticancer therapy.
  - Occurrence of an inclusion or exclusion criterion that is clinically relevant and affects the participant's safety, if discontinuation is considered necessary by the Investigator and / or Sponsor prior to study intervention completion.
  - Occurrence of pregnancy, which at the EoT visit is done as a serum test only for confirmation as urine test will be positive, before being discharged from the study.
  - Use of a nonpermitted concomitant drug (including any other drug with known anticancer activity unless specified otherwise), if discontinuation is considered necessary by the Investigator and/or the Sponsor.
  - Noncompliance that is deemed by the Investigator or the Sponsor to compromise participant safety or study integrity.

The Investigator will consider discontinuation of study intervention for abnormal liver function when a participant meets one of the conditions outlined and not meeting inclusion criterion 10 under Section 5.1 or if the Investigator believes that it is in best interest of the participant.

The Investigator must consider discontinuation of study intervention for an ILD-like event when a participant meets one of the conditions outlined in Section 6.5.4.1 and Section 6.5.4.2 under Respiratory Disorders and ILD, or if the Investigator believes that it is in best interest of the participant.

If a clinically significant finding is identified (including changes from Baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. If the participant has a Grade ≥ 3 QTc interval prolongation study intervention must be discontinued. Additionally, close and appropriate ECG monitoring in hospital

according to local standard should be initiated. This review of the ECG printed at the time of collection will be documented. Any new clinically relevant finding is reported as an AE.

The SoA (Section 1.3) specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed. Withdrawals will be documented in the eCRF as per the SoA (Section 1.3).

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may discontinue from the study at any time, at his/her own request or at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of study discontinuation, if possible, a discontinuation visit will be conducted, as listed in the SoA. The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.
- If the participant revokes consent for the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- A participant has the right at any time to request destruction of any biological samples taken. The investigator will document this in the site study records and the CRF and inform the Sponsor. The samples will be destroyed.
- Additional participants must be enrolled for each participant who withdraws from the study after signing consent and successfully meeting entry criteria but did not receive tepotinib and/or cetuximab. Additionally, participants excluded from the DLT analysis set may be replaced; the decision will be made by the SMC.
- The Investigator will secure the safety of the study participants and make every attempt to collect data.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the

appropriate consent, contact the participant's general practitioner for information. These contact attempts will be documented in the participant's medical record.

- If the participant continues to be unreachable, he/she will be deemed as "lost to follow-up".

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA (Section 1.3). A summary of key study activities on Day 1 of Cycles 1 and 2 is provided in Appendix 4.
- No protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. Laboratory tests for eligibility should be performed within 7 days prior to C1D1. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- A maximum of approximately 250 mL of blood will be collected in any one-month period from each participant in the study, including any extra assessments that may be required.
- Date of birth, sex (gender), race, and ethnicity will be collected only where allowed by local law/regulations.

8.1 Efficacy Assessments and Procedures

For assessment time points and procedures for primary, secondary, and CCI [redacted] efficacy endpoints, see Section 1.3.

8.1.1 Tumor assessments

Computed tomography/magnetic resonance imaging scans will be performed and collected until disease progression is assessed by the Investigators according to RECIST Version 1.1 or start of new anti-cancer therapy. Radiographic images and physical findings (physical assessments) will be used by the Investigators for the local determination of disease progression and patient's treatment decisions. A Baseline bone scan should be performed in participants known or suspected to have bone metastases at Baseline. At Baseline, tumor lesions will be categorized in target and non-target lesions as described in RECIST Version 1.1. Results for these evaluations will be recorded with as much specificity as possible so that pre- and post-treatment results will provide the best opportunity for evaluating tumor response.

CT or MRI of the chest, abdomen, and pelvis should be conducted to evaluate disease in these locations. Imaging (preferably MRI and including T2/FLAIR) of the head at Baseline for participants who have or are suspected to have central nervous system metastases should be conducted. All lesions in the brain should be considered non-target lesions. Additional anatomic areas should be investigated in case of suspicion of presence of metastases based on signs and symptoms of individual participants. All assessments should be provided by the same physician or radiologist if possible, during the study.

For patients who are enrolled in the study and present with brain metastasis MRI assessments of brain lesions should be performed if possible. When possible, the MRI assessment shall include Coronal 3D Gd-T1WI, Axial TSE/T2WI, Axial FLAIR, Axial T1WI, and Axial Gd-T1WI.

Skeletal lesions identified at Baseline should continue to be imaged at subsequent imaging scheduled visits using localized CT, MRI, or X-ray (using the same method used at Baseline for all visits for any given lesion). After Baseline, whole body bone scans need not be repeated, unless positive at Baseline or clinically indicated.

All protocol-required images should be uploaded to the imaging repository, maintained by or on behalf of an Imaging Research Organization for a potential independent read which may be done at any appropriate time, including at the end of study or later.

Cytology results will be collected when available. Enlarging pleural/pericardial effusion and/or ascites (fluid collections) may or may not denote progression. The radiologist can utilize cytology findings (if available) to decide if significant new fluid or unequivocal and significant enlarging fluid is an indication of progression.

The Investigator may perform scans in addition to a scheduled study scan for medical reasons or if the Investigator suspects PD. Participants who withdraw from the study for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort should be made to confirm a clinical diagnosis of PD by imaging according to RECIST Version 1.1.

Participants will be assessed every 6 weeks starting from Cycle 3 Day 1 visit until 9 months, and every 12 weeks thereafter according to RECIST Version 1.1, until disease progression, death, withdrawal of consent, or study closure. Details on how to perform RECIST Version 1.1

assessments are provided in Appendix 5. Investigator assessments will be conducted. Any CR or PR should be confirmed, preferably at the scheduled 6-week interval or at the next scheduled imaging visit, but no sooner than 4 weeks after the initial documentation of CR or PR. In the case of symptoms suggesting progression, participants should be evaluated by imaging thereafter for documentation and confirmation of the tumor responses.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Baseline and during the study. If a chest X-ray indicates metastatic disease while the participant is enrolled in this study, a CT of the chest is required for confirmation. All assessments should be provided by the same physician or radiologist if possible during the study.

Participants who withdraw from the treatment for reasons other than progressive disease will have additional visits for tumor assessments every 6 weeks until 9 months, and every 12 weeks thereafter until disease progression. A ± 7-day time window is permitted for these additional follow-up visits until 9 months, and ± 14 days thereafter. Reasons for study termination should be recorded if this visit is the last visit for the participant. Recording of any new anticancer therapy will be made (a tumor assessment is mandatory before initiating the new therapy).

Survival Follow-up is to be performed every 3 months ± 1 month at a clinic visit or by telephone contact for up to 1-year. Participants' survival information will be collected. Any subsequent anticancer therapy given to the participant until death should be recorded.

The imaging endpoints to be assessed for efficacy evaluation according to RECIST Version 1.1 include:

- Radiographic response: best overall response (BOR), DoR, and progression-free survival (PFS) per Investigator according to RECIST Version 1.1.
- Tumor assessment during follow-up: See SoA (Section 1.3). Participants without progressive disease according to RECIST Version 1.1 at the End of Treatment Visit will be followed for disease progression according to the SoA (Section 1.3) until PD was confirmed or the maximum duration of study intervention has been reached or the study ended, whatever is reached first.

8.1.2 Collection and storage of images

All study-related images will be collected by an Imaging Research Organization, then quality-checked and stored for a possible later independent review of imaging.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of Baseline medical conditions, AEs, physical examination findings, vital signs, electrocardiograms, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The

Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1.

Apart from the Investigator, safety data will also be assessed continuously by the Sponsor medical monitoring activities, as well as by the following committees:

- SMC during the safety run-in (refer to Section 4.1).

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. In addition, skin examination is to be performed.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system and abdomen (liver).
- Investigators will pay special attention to clinical signs related to previous serious illnesses, including ILD, pancreatitis, and cardiovascular diseases.

8.2.2 Vital Signs

- Height (measured at Screening only) and weight will be measured and recorded.
- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed. The method used for temperature assessment will be recorded.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured preferably in a sitting position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate. The participant position will be recorded.

8.2.3 Electrocardiograms

- Triplicate12-lead ECG will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Participants will rest for 5 minutes in a semi-supine or supine position before the reading is taken. For study discontinuation criteria involving clinically significant QTcF findings, refer to Section 7.1.

8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 6 at the time points listed in the SoA (Section 1.3). All samples will be clearly identified.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.

The tests will be performed by local laboratories. It is required that these local laboratories are certified, perform and document interlaboratory testing at regular time intervals and provide a list of normal range laboratory values including units as defined by international system of units (SI). The Sponsor will receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study will be forwarded to the Sponsor.

- The Investigator will review each laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports will be filed with the source documents.
- Methods for sample identification during shipping and handling, as well as sampling methods, processing and storage of samples are detailed in the local Laboratory Manuals.
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted as shown in the SoA (Section 1.3).
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at the end of relevant systemic exposure of the study intervention and correspond with the time frame for female participant contraception in Section 5.1.

8.3 Adverse Events and Serious Adverse Events

- The definitions of an Adverse Event (AE) and a Serious Adverse Event (SAE) are in Appendix 7.
- The Investigator and any qualified designees (e.g., Sub-Investigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up AEs that are serious or that caused the participant to discontinue the study intervention or study, as specified in Section 8.3.3.

- Requests for follow-up will usually be made via the Study Monitor, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

- All SAEs will be collected from the signing of the ICF until the Safety Follow-up Visit at the time points specified in the SoA (Section 1.3). Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.
- All AEs will be collected from the signing of the ICF until the Safety Follow-up Visit at the time points specified in the SoA (Section 1.3).
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 7. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.
- Investigators are not obligated to actively solicit AEs or SAEs after the end of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 7. All SAEs and all nonserious AEs of special interest (AESI) (see Section 8.3.7) must be additionally documented and reported using the appropriate Report Form as specified in Appendix 7.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 8.3.7) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). No new information is expected. Reasonable attempts to obtain this information will be made and documented. It is also the Investigator's responsibility to ensure that

any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is in Appendix 7.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE (particularly life-threatening and deaths) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Individual Case Safety Reports will be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

An Investigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g., Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will review and then file it along with the Investigator Brochure in the Investigator's Site File and will notify the IRB/IEC, if appropriate according to local requirements.

In this global clinical multicenter study, the Sponsor is in the best position to determine an unanticipated problem (as defined in US Regulations 21 CFR 312.66). The Sponsor will immediately notify all Investigators of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IRB's approval/favorable opinion to continue the study. An unanticipated problem is a serious adverse event that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report, specified in Section 2.3.

AESIs specified in Section 8.3.7 will be reported to the Sponsor (or delegate) in an expedited manner as described in Appendix 7.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, female partners of male participants will be collected after the start of study intervention and until the Safety Follow-up Visit.
- If a pregnancy is reported, the Investigator will inform the Sponsor within 24 hours of learning of the pregnancy and will follow the procedures specified below for collection of pregnancy information.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner, who becomes pregnant while the participant is in this study. This applies only to participants who receive study intervention.
- After obtaining signed consent from the pregnant female partner directly, the Investigator will record the pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while she is in the study. The initial information will be recorded on the appropriate

form and submitted to the Sponsor within 24 hours of learning of the pregnancy.

- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or stillbirth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events are common in participants with metastatic colorectal cancer and can be serious/life threatening:

- Progressive disease

Because these events are typically associated with the disease under study (e.g., progressive disease), they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded on the applicable eCRF page within the appropriate time frame.

However, if either of the following conditions applies, then the event will be recorded and reported as an SAE (instead of a disease-related events):

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The Investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.7 Adverse Events of Special Interest

For this study, AESIs include only the following:

- AEs suggestive of drug-induced liver injury including hepatic/liver failure and hepatitis (non-infectious) are considered AESIs.

AESIs will be reported to the Sponsor (or delegate) in an expedited manner as described in Appendix 7.

8.4 Treatment of Overdose

For this study, any dose of tepotinib or cetuximab greater than the dose that is defined in this clinical study protocol will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

Even if not associated with an AE or a SAE, any overdose is recorded in the eCRF and reported to global patient safety in an expedited manner. Overdoses are reported on a SAE and Overdose Report Form, following the procedure in Appendix 7.

8.5 Pharmacokinetics

CCI

[redacted]

CCI

- Liquid biopsy (whole blood) and/or tissue biopsy samples will be collected to test *MET* amplification that should be detected by a positive test with appropriate regulatory status (collected after disease progression of the previous anti-EGFR therapy). Local *MET* amplification testing of tissue and/or Sponsor overseen central liquid biopsy sample testing will be allowed for enrolment only with an assay with appropriate validation and regulatory status. If local *MET* amplification tests do not have the appropriate regulatory status or if the samples are not analyzed locally, central confirmation of *MET* amplification is offered and needed before enrolling. Participants should have shown benefit from the previous anti-EGFR therapy by CR or PR, both at least for 4 months or SD for at least 6 months prior to disease progression.

CCI

CCI [redacted]

8.9 Immunogenicity Assessments

Whole blood samples of approximately 3.5 mL will be collected for detection of antibodies against cetuximab in serum. Collection times are specified in the SoA (Section 1.3).

The detection of antibodies to cetuximab will be performed using a validated immunoassay method with tiered testing of screening, confirmatory and titration. Confirmed positive antibodies may be further characterized.

CCI [redacted]

Details on processes for collection and handling of these samples are in a Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

8.10 Medical Resource Utilization and Health Economics

Not applicable. There is no health economic objective, nor any resource utilization outcomes measures for this study.

9 Statistical Considerations

Analysis of all data will be performed by the Sponsor or its designee. The results of all study parts will be reported in the clinical study report. Analyses will be performed separately for each cohort. Details of the analysis of safety, efficacy, PK, and biomarker data will be presented in the Integrated Analysis Plan (IAP), which will be finalized before the database is locked for analysis.

9.1 Statistical Hypotheses

No formal statistical hypothesis will be tested, as the study is designed to be exploratory.

9.2 Sample Size Determination

The number of participants to be screened is expected to be around 342 participants to account for the described heterogenicity for *MET* amplification in the planned setting (Pietrantonio 2017; Pietrantonio 2015; Raghav 2016; Liu 2019; Mohan 2014; Siravegna 2015; Morelli 2014; Montagut 2018; LC-SCRUM, ASCO 2019 [Nakamura 2019]).

In total, a maximum of 48 participants are planned to be assigned to study intervention such that approximately 22 (Cohort A) and 20 (Cohort B) participants will be treated at RP2D. The 42 participants will be under the same dose level. The sample size calculation of 42 participants is based on the full analysis set (FAS).

The aim is to have 22 participants treated with the RP2D of tepotinib for 2L line treatment (Cohort A) and 20 participants treated with the RP2D for the 3L+ treatment (Cohort B) with at least 6 participants in the safety run-in period, irrespective of cohort.

It is anticipated that 6 eligible participants irrespective of therapy line, will be enrolled into the first part of the study for the determination of RP2D of tepotinib depending on DLTs observed. If 250 mg tepotinib is to be used the number of participants enrolled for the determination of RP2D will increase up to 12 (See Section 9.4.2.1).

2nd Line treatment (Cohort A):

A sample size of 22 participants treated with the RP2D of tepotinib (including those RP2D-dosed participants from the safety run-in), is chosen for the following reasons:

The probability to observe 5 or more responders (confirmed CR or PR) out of 22 treated participants (5/22 = 22.7% response rate) is 80.8% under the assumption of a true response rate of 30% (relevant clinical effect); whereas, if the true responder rate is 10% (non-relevant clinical effect regarding further development of this combination therapy in this indication), the probability to observe 5 or more responders is 5.7%. In these calculations, a futility analysis is considered which will be performed after 12 participants are enrolled and monitored without stopping recruitment of further participants into this study: If there are less than 2 responders within the first 12 treated participants, the enrollment of 2L participants for the study will be stopped for futility. Under the assumption of a true rate of 30%, the probability of a false stop will be 8.5%; whereas in case of a true rate of 10%, the probability of a correct stop will be 65.9%.

The overall threshold of >20% responders at the end of the study was set based on the development consideration for 2L where bevacizumab + chemotherapy showed a response rate of 22.7% (Giantonio 2007).

3rd Line+ treatment (Cohort B):

A sample size of 20 participants treated with the RP2D of tepotinib (including those RP2D-dosed participants from the safety run-in), is required, so that the probability to observe 2 or more responders (confirmed CR or PR) out of 20 treated participants (2/20 = 10.0% response rate) is 82.4% under the assumption of a true response rate of 15% (relevant clinical effect); whereas, if the true response rate is 2.5% (non-relevant clinical effect regarding further development of this combination therapy in this indication), the probability to observe 2 or more responders is 8.8%. No futility analysis is planned here due to the low rate of expected responders in the 3L+ setting.

The threshold of ≥10% for 3L+ was set based on data for regorafenib or trifluridine/tipiracil, which showed a response rate of maximum 4% (Li 2015, Mayer 2015).

9.3 Populations for Analyses

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock.

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's study intervention status in the study.
Full (FAS)/Safety (SAF)	All participants, who were administered at least one dose of any study intervention.
DLT	All participants treated in the safety run-in period who received at least 75% of the tepotinib and cetuximab planned dose and complete the DLT period (3 weeks after start of treatment with study intervention), or who experience a DLT during the DLT period regardless of the received amount of each study intervention.
PK	All participants, who receive at least one dose of study intervention, have no relevant protocol deviations or important events affecting PK, and provide at least one measurable post-dose concentration. Participants will be analyzed per the actual study intervention they received.
Immunogenicity	All participants who receive at least one dose of study intervention and have at least one valid ADA result. All ADA analyses will be based on this analysis set.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

All efficacy analyses will be performed on the FAS population unless otherwise specified. These analyses will be done by cohort and assigned dose level of tepotinib. There is no formal significance level for this study and all analyses are considered descriptive.

Endpoint	Statistical Analysis Methods
Primary	
Objective response determined according to RECIST Version 1.1 by Investigator Assessment	Best Overall Response (BOR) based on confirmed responses will be derived as follows: • Complete Response (CR) defined as at least two determinations of CR at least 4 weeks apart (with no PD in between) • Partial Response (PR) defined as at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart (and not qualifying for a CR), with no PD in between • Stable Disease (SD) defined as at least one SD assessment (or better) [≥ 6 weeks] after start date (and not qualifying for confirmed CR or PR. • Non-CR/non-PD (applicable only to participants with non-measurable disease at Baseline) = at least one non-CR/non-PD assessment (or better) [≥ 6 weeks] after start date (and not qualifying for CR or PR). • PD = PD ≤ 12 weeks after start date (and not qualifying for CR, PR, non-CR/non-PD or SD). • Not Evaluable (NE): all other cases. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from Baseline no longer holds. If this occurs the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the minimum duration for SD definition has been met. Objective Response (OR) is defined as a BOR of complete response (CR) or partial response (PR) according to RECIST Version 1.1. Objective response rate (confirmed CR or PR) and the corresponding 2-sided exact Clopper-Pearson 95% CI will be presented.
Secondary	
DoR (months) according to RECIST Version 1.1 assessed by the Investigators.	For participants with objective response, duration of response is the time from when the CR/PR (whichever is first) criteria are first met until PD or death due to any cause within the period of 2 scheduled tumor assessments (84 or 168 days) after the last tumor assessment, whichever occurs first. Duration of response data will be censored on the date of the last adequate tumor assessment for participants who do not have an event (PD or death) or for participants with an event after the period of 2 scheduled tumor assessments (84 or 168 days) of the last tumor assessment. Participants who do not have a tumor assessment after objective response will be censored at the date CR/PR criteria are first met. Duration of response will be summarized descriptively. Kaplan-Meier plots as well as the corresponding number of events, 1st and 3rd quartile (Q1 and Q3), median, minimum and maximum from the Kaplan-Meier product-limit estimates of the survival function and survival rates at 3, 6, 9, 12, 15, and 18 months together with corresponding 95% CI will be presented.

Endpoint	Statistical Analysis Methods
PFS (months) according to RECIST Version 1.1 assessed by the Investigators.	Progression free survival is defined as the time (in months) from first administration of study intervention to the date of the first documentation of PD or death due to any cause within the period of 2 scheduled tumor assessments (84 or 168 days) after the last tumor assessment, whichever occurs first. PFS data will be censored on the date of the last evaluable tumor assessment for participants who do not have an event (PD or death) or for participants with an event after the period of 2 scheduled tumor assessments (more than 84 or 168 days) after the last tumor assessment. Participants who do not have a Baseline tumor assessment or who do not have any post Baseline tumor assessments will be censored at the date of the start of study intervention. PFS will be summarized descriptively. Kaplan-Meier plots as well as the corresponding number of events, first and third quartile (Q1 and Q3), median, minimum and maximum from the Kaplan-Meier product-limit estimates of the survival function and survival rates at 3, 6, 9, 12, 15, and 18 months together with corresponding 95% CI will be presented.
OS (months) assessed by the Investigators	Overall survival is defined as the time (in months) from first administration of study intervention to the date of death. For participants not known to be deceased at time of analysis, OS time will be censored at the last date the participant was known to be alive. If this date is after the data cutoff, participants will be censored at the date of data cutoff. Overall survival will be summarized descriptively. Kaplan-Meier plots as well as the corresponding number of events, first and third quartile (Q1 and Q3), median, minimum and maximum from the Kaplan-Meier product-limit estimates of the survival function and survival rates at 3, 6, 9, 12, 15, and 18 months together with corresponding 95% CI will be presented.
CCI	

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis population unless otherwise specified. All analyses will be presented by cohort and dose level, if applicable. The safety analyses will also be done purely descriptively. Further details will be provided in the IAP.

Endpoint	Statistical Analysis Methods
Primary	
Occurrence of DLTs	The number and percentage of participants in the DLT analysis set during the DLT observation period will be tabulated.
Secondary	
Occurrence of Adverse Events (AEs) and treatment-related AEs	Adverse events will be coded according to the latest available version of the Medical Dictionary for Regulatory Activities version 21.0 or higher. Severity of AEs will be graded using the NCI-CTCAE (v5.0) toxicity grades. Adverse events related to study intervention will be defined as any AE considered as related to tepotinib and/or cetuximab. Missing classifications concerning study intervention relationships will be considered related to the study intervention. Any TEAEs will be summarized, i.e., those events that are emergent during treatment having been absent prior to treatment or worsened relative to the pretreatment state and with onset dates occurring within the first dosing day of study intervention until 30 days after the last dose of study intervention. Following subtypes of TEAEs will be presented in summaries and tables according to System Organ Classes and Preferred Terms: • TEAEs • SAEs

Endpoint	Statistical Analysis Methods
	• TEAEs related to tepotinib and/or cetuximab • SAEs related to tepotinib and/or cetuximab • NCI-CTCAE Grade 3 or higher TEAEs • NCI-CTCAE Grade 3 or higher TEAEs related to tepotinib and/or cetuximab • TEAEs leading to tepotinib and/or cetuximab interruptions • TEAEs leading to permanent tepotinib and/or cetuximab discontinuation • TEAEs leading to deaths • AEs leading to withdrawal, dose modifications, or permanent study intervention discontinuation • AESIs Deaths (primary cause) during the study will also be presented in summaries and tables. Deaths within 30 days from last dose administration and deaths beyond this period up to 90 days follow-up and reasons for them will also be tabulated. AESIs are defined as events suggestive of drug-induced liver injury including hepatic/liver failure and hepatitis (non-infectious).
Laboratory variables	Descriptive summaries over time of actual (absolute) laboratory values and changes from Baseline will be presented. Gradable laboratory results will be classified by grade according to NCI-CTCAE (v5.0); non-gradable parameters will be classified as normal, high or low. Shift tables will be presented where applicable.
Physical examination,	Clinically significant, abnormal findings from the physical examination are to be reported as AEs. Separate summaries of the physical examination during and after treatment will not be provided.
Vital signs, body weight, ECOG	Increase/decrease in vital signs (body temperature, heart rate, blood pressure and respiratory rate), ECOG performance status and body weight will be categorized and summarized descriptively in shift tables from Baseline to minimum and maximum on-treatment values.
ECG	Clinically significant, abnormal findings from 12-lead ECG during the treatment phase will be presented descriptively. Change from Baseline to worst on-treatment value will be summarized descriptively for the QTcF interval in accordance to ICH E14 criteria.

9.4.2.1 Safety Run-In Period, DLTs, Stopping Rules, Dose Reduction and Escalation

In the safety run-in period, a BOIN (**B**ayesian **O**ptimal **IN**terval) design (Yuan 2016) will support dose decisions starting with a tepotinib dose of 500 mg with the option to decrease to 250 mg, with a target DLT rate of 30% and a maximum number of 12 participants (see Appendix 8 for additional information).

Action	Number of DLT evaluable participants treated at the current dose					
	1	2	3	4	5	6
* Deescalate from 500 mg to 250 mg in case the number of DLTs is ≥	1	1	2	2	2	3
Allows to escalate back from 250 mg to 500 mg in case the number of DLTs is ≤	0	0	0	0	1	1

* The scheme will also be used for 250 mg as stopping rule.

At least 6 treated participants on a dose level are regarded as necessary to select a dose for the RP2D part of the study. Cohorts of 3 participants will be enrolled. SMC meetings will take place at a time of 3 treated participants within a cohort; on request additional SMC meetings might take place. Participants who are not DLT evaluable will be replaced.

9.4.3 Other Analyses

CCI , CCI and CCI analyses will be specified in the Integrated Analysis Plan finalized before database lock. Integrated analyses across studies, such as the population PK analysis will be presented separately from the main CSR.

General Considerations

The following statistics will be used to summarize the study data (for example, Baseline Characteristics) unless otherwise specified:

- Continuous variables: number of non-missing observations, mean, standard deviation, median, minimum, and maximum, 95% confidence intervals for the mean, as appropriate.
- Categorical variables: frequencies and percentages

CCI

CCI

9.4.4 Sequence of Analyses

Primary analysis is planned around 5 months after last patient first visit. A futility analysis for the 2L is planned (see Section 9.2). Unplanned analyses may be performed in this single arm study. The final analysis will be performed after end of study.

A SMC, consisting of permanent members from the Sponsor and Clinical Research Organization, the Coordinating Investigator, and other optional members with expertise in the management of cancer participants, will review the safety data on a regular basis throughout the study. The SMC will decide by consensus and provide their recommendation on the continuation or suspension of enrollment after an initial safety run-in of cetuximab in combination with tepotinib and will review all available safety data. The specific working procedures will be described in an SMC charter, which will be established prior to the start of recruitment.

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11 Appendices

Appendix 1 Abbreviations

2L	Second line
3L+	Third line +
ADA	Antidrug antibody
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the curve
BOIN	Bayesian optimal interval
BOR	Best overall response
BUN	Blood urea nitrogen
CIOMS	Council for International Organizations of Medical Sciences
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computed tomography
CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DLT	Dose limiting toxicity
DoR	Duration of response
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EoT	End of Treatment
FAS	Full analysis set
GCP	Good Clinical Practice

HGF	Hepatocyte growth factor
IAP	Integrated Analysis Plan
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
ILD	Interstitial lung disease
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRR	Infusion-related reaction
IWRS	Interactive Web Response System
ITT	Intention-to-Treat
mCRC	Metastatic colorectal cancer
MET	Mesenchymal epithelial transition
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
OS	Overall survival
Pd	Pharmacodynamics
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PPD	Protected personal data
PR	Partial response
QD	Once daily
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors

RP2D	Recommended Phase II dose
SAE	Serious Adverse Event
SD	Stable Disease
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment emergent adverse events
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
US PI	United States prescribing information

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with enough, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (where allowed by local laws and regulations) and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants or their legally-authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent will also sign the ICF.
- If the ICF is updated during their participation in the study, participants will be re-consented to the most current, approved version.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and pregnant partners (if applicable), who will be required to give consent for their data to be used, as specified in the informed consent.
- The participant will be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

Study sites in Europe, Northern Asia and North America are planned to participate in this study. Additional regions/countries might be added according to recruitment needs.

The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH Good Clinical Practice (GCP). The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

The study will appear in the following clinical studies registries:

- ClinicalTrials.gov: number is not available at the time of protocol finalization
- EudraCT: 2020-001776-15

A procedure for independent review of radiological images might be established at a later timepoint.

The Clinical Research Organization, Covance, will be responsible for the activities delegated on the Transfer of Responsibilities & Obligations (TORO) and outlined in separate operational manuals (i,e., Project Management Plan, Laboratory Manual, Monitoring Plan, etc.). Details of structures and associated procedures will be defined in a separate Project Management Plan.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The Investigator will submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC will review and approve them before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
  - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures

- Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).

- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor (or designee) physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor (or designee) physician to assist with the medical emergency.

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions will meet good local standards, as applicable.

Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Coordinating Investigator.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.

- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by agreement.

- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

Any publications and presentations of the results either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication but maintains the right to delay publication to protect intellectual property rights.

Posting of data on ClinicalTrials.gov and EudraCT will occur at an appropriate date to meet applicable requirements.

Data Quality Assurance

- All participant study data will be recorded on electronic eCRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the eCRF. Details for managing eCRFs are in the Project Management Plan.
- The Investigator will maintain accurate documentation (source data) that supports the information in the eCRF.
- The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.
- Study Monitors will perform ongoing source data verification to confirm that data in the eCRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records

may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator will keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file will identify each participant, contain the following demographic and medical information for the participant, and will be as complete as possible:
  - Participant's full name, date of birth, sex, height, and weight
  - Medical history and concomitant diseases
  - Prior and concomitant therapies (including changes during the study)
  - Study identifier (i.e., the Sponsor's study number) and participant's study number.
  - Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
  - Any medical examinations and clinical findings predefined in the protocol
  - All AEs
  - Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.
- Data recorded on printed or electronic eCRFs that are transcribed from source documents will be consistent with the source documents or the discrepancies will be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records will be available.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in the Monitoring Plan.

Study and Site Start and Closure

First Act of Recruitment

- The study start date is the date when the clinical study will be open for recruitment.
- The first act of recruitment is when the first site is opened (first site initiation visit) and will be the study start date.

Study Closure and Site Termination

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
  - Inadequate recruitment of participants by the Investigator.
  - Discontinuation of further development of the Sponsor's compound.
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 3 Contraception

Definitions:

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

A woman of child bearing potential is **not**:

1. Premenarchal
2. A premenopausal female with 1 of the following:

   Documented hysterectomy

   Documented bilateral salpingectomy

   Documented bilateral oophorectomy

   Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

   For a female with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.

3 A postmenopausal female

   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

   A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.

   A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

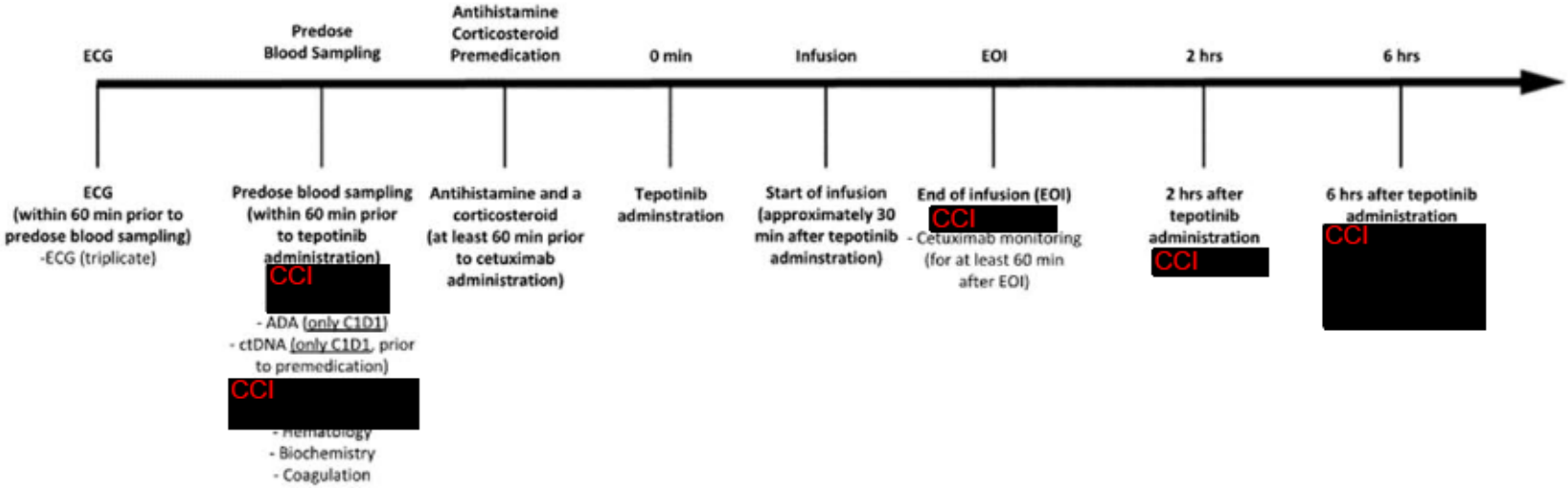
Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods That Have Low User Dependency • Implantable progestogen-only hormone contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a woman of child bearing potential and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  • Oral
  • Intravaginal
  • Transdermal
  • Injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation
  • Oral
  • Injectable
• Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.

Notes: Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants. Highly effective methods are those with a failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are **not** acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure with friction).

Appendix 4 Order of Key Activities on Day 1 of Cycles 1 and 2



Abbreviations: ADA = Anti-drug antibody; C1D1 = Cycle 1 Day 1; ctDNA = circulating tumor DNA; DNA = Deoxyribonucleic acid; ECG = electrocardiogram; EOI = End of infusion; CCI .

Appendix 5 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

The text below was obtained from the following reference: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer. 2009;45:228-47.

Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the RECIST Committee (Version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

- Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
- 10 mm caliper measurement by clinical exam (when superficial)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At Baseline and in follow-up, only the short axis will be measured and followed

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered nonmeasurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other local regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as **target lesions** and 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 involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the Baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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. If lymph nodes are to be

included in the sum, then as noted above, only the short axis is added into the sum. The Baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation, using calipers if clinically assessed. All Baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at Baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

No photographs, no skin lesion measurement by calipers and no measurements on chest X-ray will be done in this study.

Computed tomography, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II of the original source article cited above, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from 1 assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following CR or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit; however, they must normalize for a participant to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in 1st-line studies in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential AE of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or (SD in order to differentiate between response (or SD) and PD.

RESPONSE CRITERIA

Evaluation of Target Lesions

Complete response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the Baseline sum diameters.

Progressive disease: 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. (Note: the appearance of 1 or more new lesions is also considered progression).

Stable disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the Baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Electronic case report forms eCRFs or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at Baseline should have their actual measurements recorded at each subsequent

evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at Baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete response: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-Complete response/Non-Progressive disease: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive disease: Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

When the participant also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the participant has only non-measurable disease. This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concept applies here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the participant should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (e.g., some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the participant's Baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at Baseline is considered a new lesion and will indicate PD. An example of this is the participant who has visceral disease at Baseline and while on study has a brain CT or MRI ordered which reveals metastases. The participant's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at Baseline.

If a new lesion is equivocal, e.g., because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fludeoxyglucose positron emission tomography (FDG-PET) response assessments need additional studies, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at Baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at Baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The best overall response (BOR) is the best response recorded from the start of the study intervention until the end of treatment taking into account any requirement for confirmation.

On occasion, a response may not be documented until after the end of therapy, so protocols should be clear if post treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The participant's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either 1 the 'BOR'.

The BOR is determined once all the data for the participant is known. Best response determination in studies where confirmation of CR or PR IS NOT required: Best response in these studies is defined as the best response across all time points (for example, a participant who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When SD is believed to be best response, it must also meet the protocol-specified minimum time from Baseline. If the minimum time is not met when SD is otherwise the best time point response, the participant's best response depends on the subsequent assessments. For example, a participant who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same participant lost to follow-up after the first SD assessment would be considered inevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CRa	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[a] CR: complete response; NE: Not evaluable; PD: progressive disease; PR: partial response; SD: stable disease;. See text for more details.

Note:

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of 'zero' on the eCRF.

In studies where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of response and progression. For example, in most studies, it is reasonable to consider a participant with time point responses of PR-NE-PR as a confirmed response.

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy.

Conditions that define 'early progression, early death, and inevaluability' are study-specific and should be clearly described in each protocol (depending on treatment duration, and treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. The use of FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure the responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies. However, in all other circumstances, i.e., in randomized studies (Phase II or III) or studies where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of the study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 to 8 weeks) that is defined in the study protocol.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the Baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of participants achieving SD for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

Note: The duration of response and SD as well as the progression-free survival are influenced by the frequency of follow-up after Baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

Appendix 6 Clinical Laboratory Tests

Laboratory Assessments	Parameters			
Hematology	Platelet count		Mean corpuscular volume (MCV)	White Blood Cell Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Hemoglobin		Mean corpuscular hemoglobin (MCH)	
	Hematocrit			
Coagulation	Prothrombin time	Activated partial thromboplastin time	International normalized ratio	
Biochemistry	Blood Urea Nitrogen	Potassium	Aspartate aminotransferase	Total bilirubin
	Urea[a]	Creatinine	Sodium	Alanine aminotransferase
	Glucose	Calcium	Alkaline phosphatase	Protein
	Total amylase	Lipase	Gamma-glutamyl transpeptidase	Albumin
	Magnesium	Serum cystatin C (for sites where the test is available)	Phosphorus	
Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.				
Routine Urinalysis	• Specific gravity, physical appearance, color • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone (FSH) and estradiol (as needed if **not** a woman of child bearing potential only) • Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for a woman of child bearing potential). • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • All of the safety labs will be performed locally			

a Urea can be calculated using blood urea nitrogen (BUN), as follows:

If BUN is expressed in mmol/L then urea=BUN (factor = 1 for conversions in mmol (1 mole N2 = 2 moles N per mole of urea) then urea [mmol/L] = BUN [mmol/L])

If BUN is expressed in mg/dL it needs to be converted according to the following formula: urea [mg/dL] = BUN [mg/dL] × 2.1428. (conversion factor derived by: MW of urea = 60, MW of urea nitrogen = 14 × 2 => 60/28 = 2.1428)

If BUN is expressed in mmol/L and needs to be converted to urea mg/dL, the following formula must be used: urea (mg/dL) = BUN (mmol/L) × 0.357.

Appendix 7 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. • Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or a SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or a SAE if they fulfil the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Unless judged by the Investigator to be more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings, other abnormal safety assessments that are associated with the underlying disease, the disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) will not be reported as AEs/SAEs, unless the participant's general condition is more severe than expected for the his/her condition and/or if the investigator considers that there is a reasonable possibility that the event was related to study intervention.

Other Adverse Events to be Reported Using a Specialized Procedure or Form

- Overdoses (see Section 8.4) as described under "Reporting of SAEs" below.
- Pregnancies (see Section 8.3.5) as described under "Reporting of Pregnancies" below.
- DLTs (see Section 6.6.3) as described under "Reporting of DLTs" below.
- AESIs (see Section 8.3.7) as described under "Reporting of "AESIs" below.

SAE Definition

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE will be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is **not** considered an AE. • However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

A SAE is defined as any untoward medical occurrence that, at any dose:

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is **not** intended to include 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 do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are usually considered as serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- As needed, the Sponsor or its designee may ask for copies of certain medical records (e.g., autopsy reports, supplemental lab reports, documents on medical history/concomitant medications, discharge letters), as supporting source documentation. All participant identifiers, except the participant number, will be redacted on these copies before submission to the Sponsor or its designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- If an AE constitutes a DLT this is documented accordingly.
- Specific guidance is in the eCRF Completion and Monitoring Conventions.

Assessment of Intensity

Investigators will reference the National Cancer Institute - Common Terminology Criteria for AEs (CTCAE), Version 5.0 (publication date: 27 Nov 2017), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death will be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might then be reported as an SAE.

Assessment of Causality

- The Investigator will assess the relationship between study intervention and each AE/SAE occurrence:
  - Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention. A reasonable alternative explanation will be available.
  - Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.

Assessment of Causality

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator will document in the medical notes that he/she has reviewed the AE/SAE and assessed causality.
- There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. To meet the reporting timeline, the causality assessment is not required for the initial report.
- The Investigator may change his/her causality assessment after considering follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the Sponsor or its designee to elucidate the nature and/or causality of the AE or SAE, as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or its designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor or its designee within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting by an Electronic Data Collection Tool
1. The primary mechanism for reporting an SAE to the Sponsor or its designee will be the electronic data collection tool. 2. If the electronic system is unavailable, then the site will use the paper SAE data collection tool, specified below, to report the event within 24 hours. 3. The site will enter the SAE data into the electronic system as soon as it becomes available. 4. After the study is completed at a site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. 5. If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Sponsor's safety department. 6. By exception, an SAE (or follow-up information) may be reported by telephone. The site will complete the electronic SAE data entry immediately thereafter.
SAE Reporting by a Paper Form
1. SAE reporting on a paper report form is used as a back-up method for an electronic data capture system failure. The form includes completion instructions for the Investigator, names, addresses, and telephone and fax numbers. All information from the paper form will be transcribed into the electronic form as soon as the system becomes available. 2. Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee. 3. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the form sent by overnight mail or courier service. 4. Initial notification via telephone does not replace the need for the Investigator to complete and sign the form within 24 hours after becoming aware of the event. 5. Additional documents (e.g. laboratory reports, autopsy report, hospital discharge letter) and relevant pages from the eCRF may be required in addition (e.g. medical history, concomitant medication). The data provided will be consistent with the information in the eCRF.

Recording and Reporting of DLTs

1. Each event that meets the DLT criteria, as specified in Section 6.6.3, will be recorded in the eCRF within 24 hours after awareness of the event.
2. Serious DLTs will be reported in an expedited manner, using the SAE reporting process, as specified above.
3. Notification of each DLT related event (non-serious and serious) will be reported to the Sponsor or its designee within 24 hours from the date of awareness.

Reporting of AESIs

1. For a non-serious AESI, the site will complete the specific AESI report form and notify the Sponsor immediately (within 24 hours), using the same process for reporting SAEs, as specified above.
2. For a serious AESI, the site will complete an SAE report form, using the SAE reporting process, specified above.

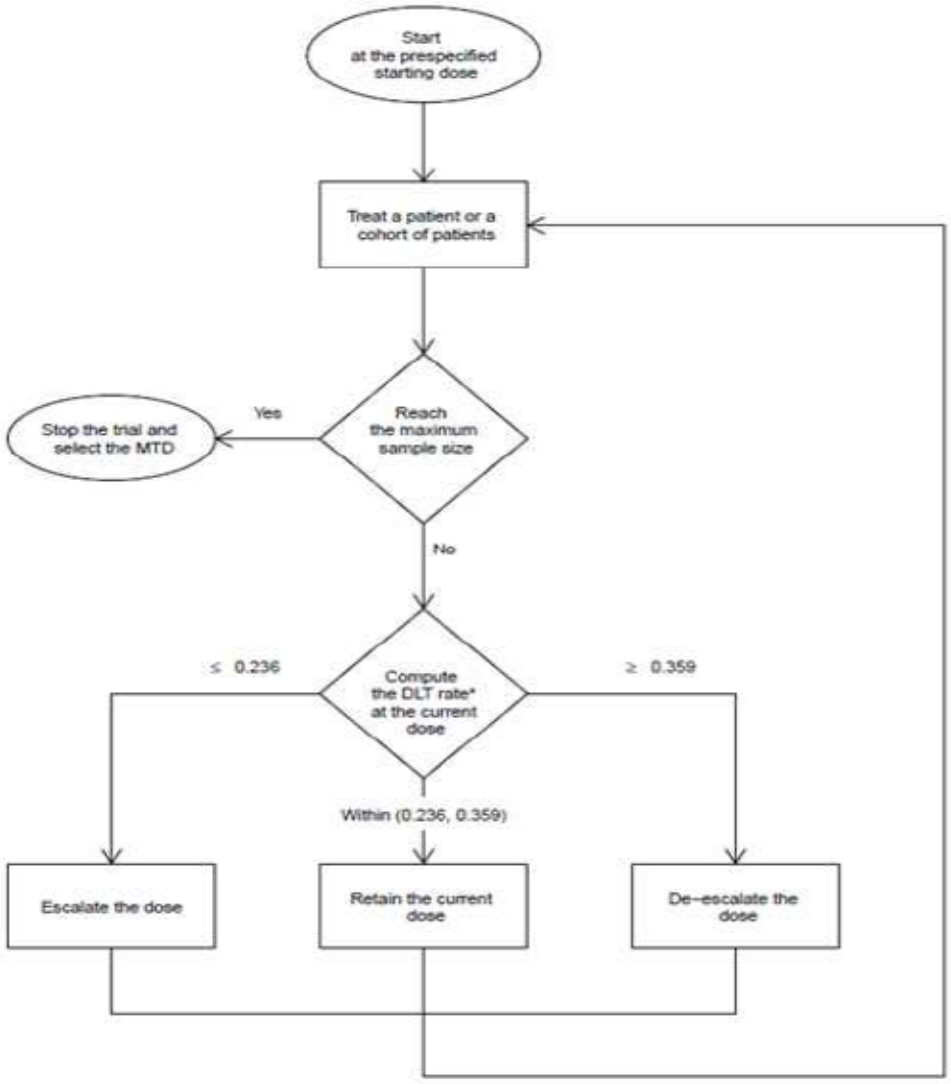
Reporting of Pregnancies

1. Pregnancy will be reported whether related to the study intervention using the applicable paper form.
2. The applicable form will be used to report if an abnormal outcome of the pregnancy occurs and the child/fetus sustains an event.
3. Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.

Appendix 8 BOIN Design

In Section 9.4.2.1 the BOIN design by Yuan 2016 is introduced. The target toxicity for this study is 30%; the maximum total number of participants for the Safety Run-in is 12 (maximum number of participants for a certain dose level is 6). The respective boundaries are provided in Yuan 2016 (Table 1 in that article and the figure below) as well as the rules for escalation and de-escalation (see Table 2 in that article and the respective table in Section 9.4.2.1 in this protocol) will be used. Yuan 2016 also performed simulations to investigate the operation characteristic of the BOIN design in comparison to other designs for certain situations (see Figure 3 in that article).

Flowchart of the BOIN design



$$\text{* DLT rate} = \frac{\text{Total number of patients who experienced DLT at the current dose}}{\text{Total number of patients treated at the current dose}}$$

Appendix 9 Protocol Amendment History

The information for the current amendment is on the title page.

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	27-Apr-2020
1.1-USA	Country-specific Amendment	30-Jul-2020
1.2-FRA	Country-specific Amendment	06-Oct-2020

Country-specific Amendment Version 1.2-FRA to Protocol Version 1:

Protocol Version [1.2 FRA] (06 October 2020)

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

Changes made to improve the clarity of the study in line with comments raised by IEC/IRBs and national regulatory authorities.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	To criterion #2, and clarified that advanced tumors are also unresectable.	Updated to clarify tumors are unresectable to better reflect the requirements of the patient population.
5.2 Exclusion Criteria	Added new criterion, #16,"History of ILD or interstitial pneumonitis including radiation pneumonitis that required steroid treatment."	Exclusion of patients with a history of interstitial lung disease (ILD) or interstitial pneumonitis to better reflect the requirements of the patient population
6.5.4 Special Precautions 6.5.4.1 Cetuximab	Wording updated under Eye disorders.	Updated to align with the wording from the EU Summary of Product Characteristics (SmPC) for cetuximab.
6.5.4 Special Precautions 6.5.4.2 Tepotinib	Added specific details for edema.	Provided detailed guidelines according to the severity grade of the toxicity observed, and the recommended for tepotinib dose modifications.
6.6 Dose Selection and Modification 6.6.2 Tepotinib	Added further clarification under the tepotinib treatment interruption section to include recommended dose modifications in case of adverse reactions of clinical interest.	Provided detailed guidelines according to the severity grade of the toxicity observed, and the recommended for tepotinib dose modifications.
6.7 Study Intervention after the End of the Study	Added details on provision of providing study intervention after the End of the Study.	Updated to specify the terms for the free of charge provision of study intervention for participants who benefit at the End of the Study.
7.1 Discontinuation of Study Intervention	Updated this section to clarify further in event of QTcF findings.	QTc interval prolongation were added as reasons for discontinuation of study intervention. Additionally, the initiation of close and appropriate ECG monitoring in hospital according to local standards is referred to.
Appendix 8 Country-specific Requirements	Reference to changes described in this table.	Administrative update.
Appendix 9 Protocol Amendment History	Refers to changes made to previous local country specific amendments.	Administrative update.
Appendix 10 Sponsor Signature Page	Clinical study protocol version updated.	Administrative update.

Section # and Name	Description of Change	Brief Rationale
Appendix 11 Coordinating Investigator Signature Page	Clinical Study protocol version updated.	Administrative update.
Appendix 12 Principal Investigator Signature Page	Clinical study protocol version updated.	Administrative update.

Country-specific Amendment Version 1.1-USA to Protocol Version 1:

Protocol Version [1.1 USA] (30 July 2020)

Overall Rationale for the Amendment

The purpose of this amendment is to incorporate FDA request received on 06 July 2020, and on 24 July 2020.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Removed "if applicable" after Cohort B	Update for clarification on Health authority feedback.
1.2 Schema	Removed "and might be initiated at a later time point" after Cohort B will include US participants only	
2 Introduction	Added text "The proposed administered dose of 500 mg tepotinib corresponds to 500 mg tepotinib hydrochloride hydrate and is equivalent to 450 mg tepotinib (free base form) throughout the document. The 250 mg tepotinib corresponds to 250 mg tepotinib hydrochloride hydrate and is equivalent to 225 mg tepotinib (the free base form)."	Health authority feedback to revise the protocol to clarify the amount of tepotinib free base administered.
2.1 Study Rationale	Removed "if Cohort B is initiated"	Update for clarification on Health authority feedback.
4.1 Overall Design	Removed "if Cohort B is initiated"	Update for clarification on Health authority feedback.
5.1 Inclusion Criteria	To criterion #2, added that left-sided CRC tumors, "from splenic flexure to rectum." Made reference to current National Comprehensive Cancer Network (NCCN) CRC v4.2020 guidelines	Health authority feedback to define left sided tumors.
	To criterion #7b, added "First-line treatment must include a fluoropyrimidine and oxaliplatin or irinotecan and second-line treatment must include a fluoropyrimidine, oxaliplatin, or irinotecan."	Health authority feedback to clarify that first-line treatment must include a fluoropyrimidine and oxaliplatin or irinotecan and second-line treatment must include a fluoropyrimidine, oxaliplatin, or irinotecan.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Addded to criterion #8 as point "g. Corrected QT interval by Fridericia (QTcF > 480 ms)"	Health authority feedback to clarify that we exclude patients with QTc intervals >480 msec.
	Added new criterion, #16,"History of ILD or interstitial pneumonitis including radiation pneumonitis that required steroid treatment."	Health authority feedback for exclusion of patients with a history of ILD or interstitial pneumonitis.
6.1 Study Intervention(s) Administration	Added, "and if local cetuximab label requires", a corticosteroid is given prior to the first infusion of cetuximab	Health authority feedback to acknowledge the difference between USA and outside the USA requirements related to premedication. To specify the use of corticosteroids will be based on local requirements.
6.5.1 Permitted Medicines	Added, "and if local cetuximab label requires", a corticosteroid is given prior to the first infusion of cetuximab	
6.6.3 Dose Limiting Toxicity	Added "Grade 4 vomiting or diarrhea" as DLT criteria.	Health authority feedback to implement that that DLT criteria will be revised so Grade 4 (life threatening) vomiting or diarrhea are considered as DLT criteria.
9.2 Sample Size Determination	Removed "if applicable" after Cohort B, and removed "if initiated" after Cohort B	Health authority feedback addressed to clarify that enrollment of Cohort B is now targeted to initiate immediately in the USA, and not possibly later as initially implied.
Appendix 2 Study Governance	Under study administrative section, deleted "(sites in North America will only be included if Cohort B is initiated)"	
Appendix 6 Clinical Laboratory Tests	Added phosphorus to biochemistry parameters for assessment.	Health authority feedback in the study monitoring plan to include assessment of phosphorus in the biochemistry panel.

Appendix 10 Sponsor Signature Page

Study Title:	A Phase II single-arm study to investigate tepotinib combined with cetuximab in *RAS/BRAF* wild-type left-sided metastatic colorectal cancer (mCRC) patients having acquired resistance to anti-EGFR antibody targeting therapy due to *MET* amplification (PERSPECTIVE)
Regulatory Agency Identifying Numbers:	EudraCT: 2020-001776-15 IND: CCI
Clinical Study Protocol Version:	08 Mar 2021 /Version 2.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	Medical Director
Institution:	Merck Healthcare KGaA
Address:	Frankfurter Str. 250 Darmstadt, Germany
Telephone number:	PPD
Fax number:	Not Applicable
E-mail address:	PPD

Appendix 11 Coordinating Investigator Signature Page

Study Title:	A Phase II single-arm study to investigate tepotinib combined with cetuximab in *RAS*/*BRAF* wild-type left-sided metastatic colorectal cancer (mCRC) patients having acquired resistance to anti-EGFR antibody targeting therapy due to *MET* amplification (PERSPECTIVE)
Regulatory Agency Identifying Numbers:	EudraCT: 2020-001776-15 IND: CCI
Clinical Study Protocol Version:	08 Mar 2021/Version 2.0
Site Number:	

I approve the design of the clinical study, am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

_____ 09-MAR-2021

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	
Institution:	
Address:	
Telephone number:	
Fax number:	
E-mail address:	

Appendix 12 Principal Investigator Signature Page

Study Title:	A Phase II single-arm study to investigate tepotinib combined with cetuximab in *RAS*/*BRAF* wild-type left-sided metastatic colorectal cancer (mCRC) patients having acquired resistance to anti-EGFR antibody targeting therapy due to *MET* amplification (PERSPECTIVE)
Regulatory Agency Identifying Numbers:	EudraCT: 2020-001776-15 IND: CCI [redacted]
Clinical Study Protocol Version:	08 Mar 2021/Version 2.0
Site Number:	

I am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: