

**Clinical trial results:****A Phase II Single-Arm Study to Investigate Tepotinib Combined With Cetuximab in RAS/BRAF Wild-Type Left-Sided mCRC Patients Having Acquired Resistance to Anti-EGFR Antibody Targeting Therapy Due to MET Amplification (PERSPECTIVE)****Summary**

EudraCT number	2020-001776-15
Trial protocol	GB FR CZ BE IT
Global end of trial date	31 March 2022

Results information

Result version number	v1 (current)
This version publication date	28 September 2022
First version publication date	28 September 2022

Trial information**Trial identification**

Sponsor protocol code	MS202202-0002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04515394
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Healthcare KGaA, Darmstadt Germany
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre, Merck Healthcare KGaA, Darmstadt Germany, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre, Merck Healthcare KGaA, Darmstadt Germany, +49 6151725200, service@merckgroup.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 March 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to assess the preliminary antitumor activity, safety and tolerability of tepotinib in combination with cetuximab in subjects with RAS/BRAF wild-type left-sided Metastatic Colorectal Cancer (mCRC) having acquired resistance to anti-epidermal growth factor receptor (EGFR) antibody targeted therapy due to mesenchymal epithelial transition (MET) amplification.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	3
EEA total number of subjects	1

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1
From 65 to 84 years	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 57 subjects were screened. Out of which, 3 subjects were enrolled and 2 subjects received treatment in this study..

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Tepotinib + Cetuximab
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Arm description:

Subjects received Tepotinib film-coated tablets at a dose of 500 milligrams (mg) orally, once daily (QD) in combination with weekly intravenous infusions of Cetuximab at a dose of 250 milligrams per square meter (mg/m²) until disease progression (according to Response Evaluation Criteria in Solid Tumors Version 1.1 [RECIST v1.1]), death, Adverse event (AE) leading to discontinuation, study withdrawal, or withdrawal of consent, whichever occurs first.

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	MSB0010442D
Other name	Erbitux
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received weekly intravenous infusions of Cetuximab at a dose of 250 mg/m² until disease progression (according to [RECIST v1.1]), death, AE leading to discontinuation, study withdrawal, or withdrawal of consent, whichever occurs first.

Investigational medicinal product name	Tepotinib
Investigational medicinal product code	MSC2156119J
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Tepotinib initially at 500 mg QD until disease progression (according to [RECIST v1.1]), death, AE leading to discontinuation, study withdrawal, or withdrawal of consent, whichever occurs first.

Number of subjects in period 1	Tepotinib + Cetuximab
Started	3
Treated	2
Completed	2
Not completed	1
Subjects did not receive treatment	1

Baseline characteristics

Reporting groups

Reporting group title	Tepotinib + Cetuximab
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Reporting group description:

Subjects received Tepotinib film-coated tablets at a dose of 500 milligrams (mg) orally, once daily (QD) in combination with weekly intravenous infusions of Cetuximab at a dose of 250 milligrams per square meter (mg/m²) until disease progression (according to Response Evaluation Criteria in Solid Tumors Version 1.1 [RECIST v1.1]), death, Adverse event (AE) leading to discontinuation, study withdrawal, or withdrawal of consent, whichever occurs first.

Reporting group values	Tepotinib + Cetuximab	Total	
Number of subjects	3	3	
Age Categorical			
Units: subjects			
<=18 years	0	0	
Between 18 and 65 years	1	1	
>=65 years	2	2	
Sex: Female, Male			
Units: subjects			
Female	1	1	
Male	2	2	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	3	3	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	3	3	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Tepotinib + Cetuximab
Reporting group description: Subjects received Tepotinib film-coated tablets at a dose of 500 milligrams (mg) orally, once daily (QD) in combination with weekly intravenous infusions of Cetuximab at a dose of 250 milligrams per square meter (mg/m ²) until disease progression (according to Response Evaluation Criteria in Solid Tumors Version 1.1 [RECIST v1.1]), death, Adverse event (AE) leading to discontinuation, study withdrawal, or withdrawal of consent, whichever occurs first.	
Subject analysis set title	Tepotinib + Cetuximab
Subject analysis set type	Full analysis
Subject analysis set description: Subjects received Tepotinib film-coated tablets at a dose of 500 milligrams (mg) orally, once daily (QD) in combination with weekly intravenous infusions of Cetuximab at a dose of 250 milligrams per square meter (mg/m ²) until disease progression (according to Response Evaluation Criteria in Solid Tumors Version 1.1 [RECIST v1.1]), death, Adverse event (AE) leading to discontinuation, study withdrawal, or withdrawal of consent, whichever occurs first.	

Primary: Number of Subjects Who Experienced Dose Limiting Toxicities (DLTs) According to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) Version 5.0

End point title	Number of Subjects Who Experienced Dose Limiting Toxicities (DLTs) According to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) Version 5.0 ^[1]
End point description: DLTs: any of following toxicities and judged by Investigator and/Sponsor to be not attributable to disease/disease-related processes under investigation: Grade (Gr)4 neutropenia for more than 7 days; Gr greater than or equal to [\geq] 3 febrile neutropenia with absolute neutrophil count <1000 per cube millimeter (per mm ³) and a single temperature of >38.3 degree Celsius/a sustained temperature of ≥ 38 degree Celsius for more than 1 hour; Gr4/3 thrombocytopenia with non-traumatic bleeding; Gr3 uncontrolled nausea/vomiting/diarrhea that has not improved within 72 hours despite adequate and optimal treatment; Gr4 vomiting/diarrhea; Gr ≥ 3 skin toxicity that has not resolved to Gr2 after 14 days of adequate treatment. DLT analysis set: all subjects treated in safety run-in period who received at least 75% of tepotinib and cetuximab planned dose and completed DLT period/experienced a DLT during DLT period regardless of received amount of each study intervention.	
End point type	Primary
End point timeframe: Day 1 to Day 21 of Cycle 1 (each cycle is of 21 days)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics was planned for this endpoint.

End point values	Tepotinib + Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Objective Response (OR) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) Assessed by Investigators

End point title	Number of Subjects with Objective Response (OR) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) Assessed by Investigators ^[2]
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End point description:

OR is defined as a best overall response (BOR) of complete response (CR) or partial response (PR). CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all target lesions. Full analysis set (FAS) include all subjects who were administered at least one dose of any study intervention.

End point type	Primary
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End point timeframe:

Time from first study treatment assessed up to 218 days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics was planned for this endpoint.

End point values	Tepotinib + Cetuximab			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) Assessed by Investigator

End point title	Duration of Response (DoR) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) Assessed by Investigator
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End point description:

For subjects with objective response, DoR is the time from when the complete response (CR) or partial response (PR) (whichever is first) criteria are first met until progression disease (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. PD is defined as at least a 20 percent (%) increase in the sum of the longest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions.

End point type	Secondary
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End point timeframe:

Time from the first dose of study drug until occurrence of PD, death due to any cause or last tumor assessment (assessed up to 218 days)

End point values	Tepotinib + Cetuximab			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[3]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[3] - None of the subjects showed objective response.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) Assessed by Investigators

End point title	Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) Assessed by Investigators
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End point description:

PFS is defined as the time (in months) from first administration of study intervention to the date of the first documentation of progression disease (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. PD is defined as at least a 20 percent (%) increase in the sum of the longest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. Due to early termination of study based on a limited number of subjects (N=2), no data was analyzed statistically, and no derived subject data was generated.

End point type	Secondary
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End point timeframe:

Time from the first dose of study drug until occurrence of PD, death due to any cause or last tumor assessment (assessed up to 218 days)

End point values	Tepotinib + Cetuximab			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[4]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[4] - No data was analyzed statistically and no derived subject data was generated.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Assessed by Investigators

End point title	Overall Survival (OS) Assessed by Investigators
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End point description:

OS is defined as the time (in months) from first administration of study intervention to the date of death. Due to early termination of study based on a limited number of subjects (N=2), no data was analyzed statistically, and no derived subject data was generated.

End point type	Secondary
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End point timeframe:

Time from first study treatment until death, assessed up to 218 days

End point values	Tepotinib + Cetuximab			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[5]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[5] - No data was analyzed statistically, and no derived subject data was generated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related TEAEs

End point title	Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Treatment-Related TEAEs
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End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a subject/clinical study subject, temporally associated with the use of study intervention, whether considered related to the study intervention or not. A serious AE was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. TEAEs were defined as events that started or worsened after first dose of study intervention until 30 days after last dose. TEAEs included both serious and non-serious TEAEs. Treatment-related TEAEs is defined as reasonably related to the study intervention. Safety analysis set (SAF) included all subjects who were administered at least one dose of any study intervention.

End point type	Secondary
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End point timeframe:

Time from first study treatment up to 30 days after the last dose, assessed up to 226 days

End point values	Tepotinib + Cetuximab			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: subjects				
TEAEs	2			
Treatment-related TEAEs	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinically Significant Changes from Baseline in Vital Signs

End point title	Number of Subjects with Clinically Significant Changes from Baseline in Vital Signs
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End point description:

Vital sign assessment included assessments of height, weight, temperature, pulse rate, respiratory rate, and blood pressure. Clinical significance was determined by the investigator. Number of subjects who had any clinically significant changes from baseline in vital signs were reported. Due to early termination of study based on a limited number of subjects (N=2), no data was analyzed statistically, and no derived subject data was generated.

End point type	Secondary
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End point timeframe:

Time from first study treatment up to 30 days after the last dose, assessed up to 226 days

End point values	Tepotinib + Cetuximab			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[6]			
Units: subjects				
number (not applicable)				

Notes:

[6] - No data was analyzed statistically, and no derived subject data was generated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinically Significant Changes from Baseline in Laboratory Parameters

End point title	Number of Subjects with Clinically Significant Changes from Baseline in Laboratory Parameters
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End point description:

Laboratory investigation included hematology, biochemistry, coagulation, routine urinalysis and other screening tests (Follicle-stimulating hormone (FSH) and estradiol, Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test, Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) and all of the safety labs were performed locally. Clinical significance was determined by the investigator. The number of subjects with clinically significant changes from baseline in laboratory parameters were reported. Due to early termination of study based on a limited number of subjects (N=2), no data was analyzed statistically, and no derived subject data was generated.

End point type	Secondary
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End point timeframe:

Time from first study treatment up to 30 days after the last dose, assessed up to 226 days

End point values	Tepotinib + Cetuximab			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[7]			
Units: subjects				
number (not applicable)				

Notes:

[7] - No data was analyzed statistically, and no derived subject data was generated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinically Significant Changes from Baseline in 12-Lead Electrocardiogram (ECG) Findings

End point title	Number of Subjects with Clinically Significant Changes from Baseline in 12-Lead Electrocardiogram (ECG) Findings
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End point description:

12-lead ECG recordings included heart rate and measures PR, QRS, QT and QTcF intervals. 12-lead ECG recordings were obtained after the participants have rested for at least 5 minutes in semi-supine or supine position. Clinical significance was determined by the investigator. The number of subjects with clinically significant changes from baseline in 12-lead ECG findings were reported. Due to early termination of study based on a limited number of subjects (N=2), no data was analyzed statistically, and no derived subject data was generated.

End point type	Secondary
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End point timeframe:

Time from first study treatment up to 30 days after the last dose, assessed up to 226 days

End point values	Tepotinib + Cetuximab			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[8]			
Units: subjects				
number (not applicable)				

Notes:

[8] - No data was analyzed statistically, and no derived subject data was generated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects With At Least 1 Postive Anti-Drug Antibodies (ADAs) for Cetuximab

End point title	Number of subjects With At Least 1 Postive Anti-Drug Antibodies (ADAs) for Cetuximab
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End point description:

Serum samples were analyzed by a validated electrochemiluminescence immunoassay method to detect the presence of antidrug antibodies (ADA). Number of subjects with positive ADA were reported. Immunogenicity analysis set included all subjects who received at least one dose of study intervention and had at least one valid antidrug antibody (ADA) result.

End point type	Secondary
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End point timeframe:

At Day 1 of cycle 1 (each cycle is of 21 days) and at End of Treatment (14 days after last dose, assessed up to 210 days)

End point values	Tepotinib + Cetuximab			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time from first study treatment up to 30 days after the last dose, assessed up to 226 days

Adverse event reporting additional description:

Safety analysis set (SAF) included all subjects who were administered at least one dose of any study intervention.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	Tepotinib + Cetuximab
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Reporting group description:

Subjects received Tepotinib film-coated tablets at a dose of 500 milligrams (mg) orally, once daily (QD) in combination with weekly intravenous infusions of Cetuximab at a dose of 250 milligrams per square meter (mg/m²) until disease progression (according to Response Evaluation Criteria in Solid Tumors Version 1.1 [RECIST v1.1]), death, Adverse event (AE) leading to discontinuation, study withdrawal, or withdrawal of consent, whichever occurs first.

Serious adverse events	Tepotinib + Cetuximab		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Tepotinib + Cetuximab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Investigations			
Weight increased			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		

General disorders and administration site conditions			
oedema peripheral			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
diarrhea			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Skin toxicity			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
drug eruption			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
dry skin			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Infections and infestations			
paronychia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Product issues			

Device dislocation subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Metabolism and nutrition disorders			
Hypoalbuminaemia subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Hypomagnesaemia subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Hypocalcaemia subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Iron deficiency subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2021	<ul style="list-style-type: none">• Added the study acronym "PERSPECTIVE" to study title and short title. Added row on title page indicating the study acronym "PERSPECTIVE".• Added screening window to facilitate protocol adherence.• For ECG assessments, allowed a 60-minute window (from the previous 20-minute window).• 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)".• To inclusion 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.• To inclusion criterion #2, clarified that advanced tumors are also unresectable.• To inclusion 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".• To inclusion criterion #11, corrected to add the superscripted numbers to the estimated glomerular filtration rate formula.• Added to exclusion criterion #8 as point "g. Corrected QT interval by Fridericia (QTcF > 480 milliseconds [ms])• Added new exclusion criterion, #16," History of ILD or interstitial pneumonitis including radiation pneumonitis that required steroid treatment".• Added "Grade 4 vomiting or diarrhea" as DLT criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 March 2022	This study was terminated early due to operational challenges identifying suitable participants for screening in the study.	-

Notes:

Limitations and caveats

None reported