Clinical trial results:
A single-arm, open-label, multicenter, multinational, safety and efficacy Phase IIIb trial of BI 695502 plus mFOLFOX6 in patients with previously untreated metastatic colorectal cancer

Summary

EudraCT number	2015-003718-25
Trial protocol	ES
Global end of trial date	03 October 2018

Results information

Result version number	v1 (current)
This version publication date	17 October 2019
First version publication date	17 October 2019

Trial information

Trial identification

Sponsor protocol code	1302.3

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02776683
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.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	12 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2018
Global end of trial reached?	Yes
Global end of trial date	03 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to evaluate the safety and tolerability of BI 695502 in combination with leucovorin/5-fluorouracil (5FU)/oxaliplatin (mFOLFOX6) and as maintenance therapy (when applicable).
The secondary objectives of this trial were to evaluate the following efficacy parameters: Progression-free survival (PFS), objective response rate (proportion of patients with complete response [CR] plus partial response [PR]), duration of response (DOR), time to progression (TTP), and overall survival (OS).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented in all trials whereby doses would be reduced if required. Thereafter, if further events were reported, the subject would be withdrawn from the trial. Symptomatic treatment of tumour associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 June 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 68
Country: Number of subjects enrolled	Japan: 41
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Ukraine: 63
Worldwide total number of subjects	182
EEA total number of subjects	10

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	114
From 65 to 84 years	67
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This was Phase IIIb, open-label, multicenter, multinational, single-arm trial. Patients with previously untreated metastatic colorectal cancer (mCRC) were enrolled. From 21December2017, Sponsor recommended that patients should be switched from BI 695502 to the reference product Avastin® as soon as it was available at the respective clinical site.

Pre-assignment

Screening details:

All patients were screened for eligibility to participate in the trial. Patients attended specialist sites which would then ensure that they (the patients) met all strictly implemented inclusion/exclusion criteria. Patients were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Pre-switch period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label trial. Blinding was not performed for this trial.

Arms

Arm title	BI 695502

Arm description:

All patients were to receive BI 695502 (5 milligrams per kilogram [mg/kg]) solution for intravenous (i.v.) infusion in combination with mFOLFOX6 chemotherapy every 2 weeks. Patients were to continue to receive treatment during the pre-switch period until disease progression, death, unacceptable toxicity, or the end of the trial, whichever occurred earlier. Based on patient tolerability, at least 8 cycles of mFOLFOX6 were to be given to all patients.

Arm type	Experimental
Investigational medicinal product name	BI 695502
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A dose of 5 mg/kg body weight of BI 695502 was administered by i.v. infusion every 2 weeks.

Investigational medicinal product name	mFOLFOX6
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For mFOLFOX6 chemotherapy, oxaliplatin 85 mg/m2 i.v. over 2 hours on Day 1 of cycle, leucovorin 400 mg/m2 i.v. (or levoleucovorin 200 mg/m2 i.v.) over 2 hours on Day 1 of cycle, 5-fluorouracil 400 mg/m2 i.v. bolus on Day 1 of cycle, then 1200 mg/m2/day x 2 days (total 2400 mg/m2 over 46-48 hours) i.v. continuous infusion were to be administered. 1 cycle = 2 weeks.

Number of subjects in period 1[1]	BI 695502
Started	123
Completed	43
Not completed	80
Consent withdrawn by subject	9
Physician decision	7
Adverse event, non-fatal	21
Progressive disease	39
Other than listed	3
Protocol deviation	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Period 2

Period 2 title	Post-switch period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label trial. Blinding was not performed for this trial.

Arms

Arm title	BI 695502 to Avastin®

Arm description:

At the switch visit, patients were to be switched from BI 695502 to Avastin®. Post-switch, patients were to receive Avastin® (5 mg/kg) solution for i.v. infusion in combination with mFOLFOX6 chemotherapy every 2 weeks. Patients were to continue to receive treatment until disease progression, death, unacceptable toxicity, or the end of the trial, whichever occurred earlier.

Arm type	Experimental
Investigational medicinal product name	mFOLFOX6
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For mFOLFOX6 chemotherapy, oxaliplatin 85 mg/m2 i.v. over 2 hours on Day 1 of cycle, leucovorin 400 mg/m2 i.v. (or levoleucovorin 200 mg/m2 i.v.) over 2 hours on Day 1 of cycle, 5-fluorouracil 400 mg/m2 i.v. bolus on Day 1 of cycle, then 1200 mg/m2/day x 2 days (total 2400 mg/m2 over 46-48 hours) i.v. continuous infusion were to be administered. 1 cycle = 2 weeks.

Investigational medicinal product name	Avastin®
Investigational medicinal product code	
Other name	Bevacizumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A dose of 5 mg/kg body weight of Avastin® was administered by i.v. infusion every 2 weeks.

Number of subjects in period 2	BI 695502 to Avastin®
Started	43
Completed	0
Not completed	43
Consent withdrawn by subject	2
Physician decision	3
Adverse event, non-fatal	3
Progressive disease	20
Other than listed	15

Baseline characteristics

Reporting groups	
Reporting group title	BI 695502

Reporting group description:

All patients were to receive BI 695502 (5 milligrams per kilogram [mg/kg]) solution for intravenous (i.v.) infusion in combination with mFOLFOX6 chemotherapy every 2 weeks. Patients were to continue to receive treatment during the pre-switch period until disease progression, death, unacceptable toxicity, or the end of the trial, whichever occurred earlier. Based on patient tolerability, at least 8 cycles of mFOLFOX6 were to be given to all patients.

Reporting group values	BI 695502	Total	
Number of subjects	123	123	
Age categorical			
Units: Subjects			
Age Continuous			
Treated set (TS): The TS contained all participants who signed informed consent and who received at least one dose of trial medication.			
Units: years			
arithmetic mean	58.0		
standard deviation	± 11.87	-	
Sex: Female, Male			
TS			
Units: Subjects			
Female	55	55	
Male	68	68	
Race (NIH/OMB)			
TS			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	33	33	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	6	6	
White	82	82	
More than one race	0	0	
Unknown or Not Reported	2	2	
Ethnicity (NIH/OMB)			
TS			
Units: Subjects			
Hispanic or Latino	15	15	
Not Hispanic or Latino	106	106	
Unknown or Not Reported	2	2	

End points

End points reporting groups

Reporting group title	BI 695502

Reporting group description:

All patients were to receive BI 695502 (5 milligrams per kilogram [mg/kg]) solution for intravenous (i.v.) infusion in combination with mFOLFOX6 chemotherapy every 2 weeks. Patients were to continue to receive treatment during the pre-switch period until disease progression, death, unacceptable toxicity, or the end of the trial, whichever occurred earlier. Based on patient tolerability, at least 8 cycles of mFOLFOX6 were to be given to all patients.

Reporting group title	BI 695502 to Avastin®

Reporting group description:

At the switch visit, patients were to be switched from BI 695502 to Avastin®. Post-switch, patients were to receive Avastin® (5 mg/kg) solution for i.v. infusion in combination with mFOLFOX6 chemotherapy every 2 weeks. Patients were to continue to receive treatment until disease progression, death, unacceptable toxicity, or the end of the trial, whichever occurred earlier.

Primary: Percentage of Patients with Treatment-Emergent Adverse Events (TEAEs) in the Specified Categories Selected for Primary Endpoint Assessment

End point title	Percentage of Patients with Treatment-Emergent Adverse Events (TEAEs) in the Specified Categories Selected for Primary Endpoint Assessment[1]

End point description:

The primary safety endpoint of the trial was patients with any of the following selected adverse events (AEs): · Infusion reactions (anaphylactic/hypersensitivity/infusion-related reactions), · Thromboembolic events (arterial or venous), · Gastrointestinal perforations, · Hypertension, · Proteinuria, · Pulmonary hemorrhage · All hemorrhages (including pulmonary hemorrhages) · Wound-healing complications/abscess/fistulas · Posterior reversible encephalopathy syndrome · Ovarian failure. All AEs with an onset between start of treatment and end of the residual effect period (REP), a period of 18 weeks after the last dose of trial medication were considered for the primary safety analysis. Confidence interval was calculated using Wilson score method. TS: The TS contained all patients who signed informed consent and who received at least one dose of trial medication.

End point type	Primary

End point timeframe:

From baseline up to 18 weeks after the last dose of trial medication prior to the Switch Visit. Maximum duration of up to 32 treatment cycles + safety follow up (up to 82 weeks overall).

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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	BI 695502			
Subject group type	Reporting group			
Number of subjects analysed	123[2]			
Units: Percentage of participants (%)				
number (confidence interval 95%)				
Patients with any of the selected AEs	58.50 (49.70 to 66.86)			
Infusion reactions	18.70 (12.80 to 26.50)			
Thromboembolic events	12.20 (7.53 to 19.15)			
Gastrointestinal perforations	2.40 (0.83 to 6.93)			

Hypertension	28.50 (21.23 to 36.99)			
Proteinuria	9.80 (5.67 to 16.28)			
Pulmonary Haemorrhage	0.00 (0.00 to 3.03)			
Hemorrhages	22.80 (16.25 to 30.93)			
Wound-healing complications	1.60 (0.45 to 5.74)			
Reversible Encephalopathy Syndrome	0.00 (0.00 to 3.03)			
Ovarian failure	0.00 (0.00 to 6.53)			

Notes:

[2] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as Assessed by Central Imaging Review

End point title	Duration of Response (DOR) as Assessed by Central Imaging Review

End point description:

DOR was the time from first documented Complete Response (CR) (CR is disappearance of all target lesions) or Partial Response (PR) (PR is at least a 30% decrease in the sum of diameters (SoD) of target lesions taking as reference the baseline sum diameters) until time of progression as assessed by central imaging review per Response evaluation criteria in solid tumors (RECIST) 1.1. RECIST is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize") or worsen ("progress") during treatment. DOR was calculated using the Kaplan-Meier technique. Confidence interval was calculated based on the Brookmeyer and Crowley method. 99999= NA= The upper limit confidence interval was not determined as it was not reached. Only patients with complete or partial objective response were included in the analysis.

End point type	Secondary

End point timeframe:

Tumor scans were performed at baseline then every ~8 weeks up to 34 weeks, then every ~12 weeks thereafter until confirmed disease progression. Analysis performed for the pre-switch period only; maximum duration of up to 32 treatment cycles (64 weeks).

End point values	BI 695502			
Subject group type	Reporting group			
Number of subjects analysed	77[3]			
Units: Months				
median (confidence interval 95%)	9.1 (7.3 to 99999)			

Notes:

[3] - TS (complete or partial objective response)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP) as Assessed by Central Imaging Review

End point title	Time to Progression (TTP) as Assessed by Central Imaging Review

End point description:

TTP was defined as the time from first administration of trial medication to the date of tumor progression as assessed by central imaging review per RECIST 1.1 (RECIST is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize") or worsen ("progress") during treatment.). TTP was calculated using the Kaplan-Meier technique. Confidence interval was calculated based on the Brookmeyer and Crowley method.

End point type	Secondary

End point timeframe:

Tumor scans were performed at baseline then every ~8 weeks up to 34 weeks, then every ~12 weeks thereafter until confirmed disease progression. Analysis performed for the pre-switch period only; maximum duration of up to 32 treatment cycles (64 weeks).

End point values	BI 695502			
Subject group type	Reporting group			
Number of subjects analysed	123[4]			
Units: Months				
median (confidence interval 95%)	11.1 (9.5 to 12.9)			

Notes:

[4] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response (OR) Rate as Assessed by Central Imaging Review

End point title	Objective Response (OR) Rate as Assessed by Central Imaging Review

End point description:

OR rate was defined as the percentage of patients who achieved at least one visit response of CR (CR is disappearance of all target lesions) or PR (PR is at least a 30% decrease in the sum of diameters (SoD) of target lesions taking as reference the baseline sum diameters) after the start of treatment. The response criteria evaluation was carried out according to RECIST 1.1. RECIST is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize") or worsen ("progress") during treatment. Confidence interval was calculated using Wilson score method. OR = CR + PR.

End point type	Secondary

End point timeframe:

Tumor scans were performed at baseline then every ~8 weeks up to 34 weeks, then every ~12 weeks thereafter until confirmed disease progression. Analysis performed for the pre-switch period only; maximum duration of up to 32 treatment cycles (64 weeks).

End point values	BI 695502			
Subject group type	Reporting group			
Number of subjects analysed	123[5]			
Units: Percentage of participants				
number (confidence interval 95%)	61.0 (52.1 to 69.1)			

Notes:

[5] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Time

End point title	Overall Survival (OS) Time

End point description:

OS was defined as the time from first administration of trial medication until death from any cause. OS was calculated using the Kaplan-Meier technique. Confidence interval was calculated based on the Brookmeyer and Crowley method.

End point type	Secondary

End point timeframe:

From baseline until death due to any cause. Analysis performed for the pre-switch period only; maximum duration of up to 32 treatment cycles (64 weeks).

End point values	BI 695502			
Subject group type	Reporting group			
Number of subjects analysed	123[6]			
Units: Months				
median (confidence interval 95%)	19.4 (16.7 to 21.1)			

Notes:

[6] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Time as Assessed by Central Imaging Review

End point title	Progression-Free Survival (PFS) Time as Assessed by Central Imaging Review

End point description:

PFS was defined as the time from first administration of trial medication until disease progression as assessed by central imaging review or death due to any cause. Disease progression was assessed according to RECIST 1.1. RECIST is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize") or worsen ("progress") during treatment. Progression was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of at least 5 mm. PFS was calculated using the Kaplan-Meier technique. Confidence interval was calculated based on the Brookmeyer and Crowley method.

End point type	Secondary

End point timeframe:

Tumor scans were performed at baseline then every ~8 weeks up to 34 weeks, then every ~12 weeks thereafter until confirmed disease progression. Analysis performed for the pre-switch period only; maximum duration of up to 32 treatment cycles (64 weeks).

End point values	BI 695502			
Subject group type	Reporting group			
Number of subjects analysed	123[7]			
Units: Months				
median (confidence interval 95%)	10.5 (9.4 to 11.8)			

Notes:

[7] - TS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of first dose of trial medication until last date of trial medication + 18 weeks (REP). Up to a maximum of 32 treatment cycles + safety follow up (up to 82 weeks overall).

Adverse event reporting additional description:

All-Cause mortality is defined as death due to any cause (including disease progression) and is reported for the overall study period, including both the pre-switch period for BI 695502 treatment and post-switch period for Avastin® treatment. Serious and Other(non-serious) TEAE data is reported for the BI695502 treatment period only(ie pre-switch).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	BI 695502

Reporting group description:

All patients were to receive BI 695502 (5 milligrams per kilogram [mg/kg]) solution for intravenous (i.v.) infusion in combination with mFOLFOX6 chemotherapy every 2 weeks. Patients were to continue to receive treatment during the pre-switch period until disease progression, death, unacceptable toxicity, or the end of the trial, whichever occurred earlier. Based on patient tolerability, at least 8 cycles of mFOLFOX6 were to be given to all patients.

Serious adverse events	BI 695502		
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 123 (26.83%)		
number of deaths (all causes)	41		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningioma benign			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour necrosis			

subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Accelerated hypertension			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brachiocephalic vein thrombosis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic venous thrombosis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Subclavian vein thrombosis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vena cava thrombosis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			

subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	6 / 123 (4.88%)		
occurrences causally related to treatment / all	3 / 6		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cervical radiculopathy			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myelopathy			

subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	2 / 123 (1.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Disseminated intravascular coagulation				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypersplenism				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Splenomegaly				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				

Sudden hearing loss				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Ileus				
subjects affected / exposed	2 / 123 (1.63%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal hernia				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intra-abdominal fluid collection				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal stenosis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mesenteric vein thrombosis				

subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Jaundice cholestatic			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver disorder			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Portal vein thrombosis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin necrosis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Renal haematoma			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bacterial sepsis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Biliary tract infection			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vulval abscess			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	BI 695502		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	118 / 123 (95.93%)		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	25 / 123 (20.33%)		
occurrences (all)	77		
Platelet count decreased			
subjects affected / exposed	18 / 123 (14.63%)		
occurrences (all)	42		
Weight decreased			
subjects affected / exposed	18 / 123 (14.63%)		
occurrences (all)	23		
White blood cell count decreased			
subjects affected / exposed	18 / 123 (14.63%)		
occurrences (all)	48		
Gamma-glutamyltransferase increased			
subjects affected / exposed	12 / 123 (9.76%)		
occurrences (all)	28		
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 123 (5.69%)		
occurrences (all)	17		
Weight increased			
subjects affected / exposed	7 / 123 (5.69%)		
occurrences (all)	8		
Vascular disorders			
Hypertension			
subjects affected / exposed	34 / 123 (27.64%)		
occurrences (all)	55		
Nervous system disorders			

Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	44 / 123 (35.77%) 137		
Neuropathy peripheral subjects affected / exposed occurrences (all)	21 / 123 (17.07%) 35		
Dysgeusia subjects affected / exposed occurrences (all)	18 / 123 (14.63%) 25		
Headache subjects affected / exposed occurrences (all)	14 / 123 (11.38%) 22		
Dizziness subjects affected / exposed occurrences (all)	8 / 123 (6.50%) 11		
Neurotoxicity subjects affected / exposed occurrences (all)	7 / 123 (5.69%) 42		
Blood and lymphatic system disorders			
Neutropenia subjects affected / exposed occurrences (all)	32 / 123 (26.02%) 97		
Anaemia subjects affected / exposed occurrences (all)	21 / 123 (17.07%) 31		
Thrombocytopenia subjects affected / exposed occurrences (all)	20 / 123 (16.26%) 46		
Leukopenia subjects affected / exposed occurrences (all)	7 / 123 (5.69%) 9		
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	57 / 123 (46.34%) 104		
Diarrhoea			

subjects affected / exposed	41 / 123 (33.33%)		
occurrences (all)	105		
Stomatitis			
subjects affected / exposed	37 / 123 (30.08%)		
occurrences (all)	67		
Constipation			
subjects affected / exposed	27 / 123 (21.95%)		
occurrences (all)	42		
Vomiting			
subjects affected / exposed	19 / 123 (15.45%)		
occurrences (all)	34		
Abdominal pain			
subjects affected / exposed	17 / 123 (13.82%)		
occurrences (all)	23		
Abdominal pain upper			
subjects affected / exposed	12 / 123 (9.76%)		
occurrences (all)	14		
Dyspepsia			
subjects affected / exposed	9 / 123 (7.32%)		
occurrences (all)	12		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	18 / 123 (14.63%)		
occurrences (all)	22		
Rhinorrhoea			
subjects affected / exposed	8 / 123 (6.50%)		
occurrences (all)	9		
Dyspnoea			
subjects affected / exposed	7 / 123 (5.69%)		
occurrences (all)	9		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	16 / 123 (13.01%)		
occurrences (all)	16		
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed occurrences (all) Skin hyperpigmentation subjects affected / exposed occurrences (all)	11 / 123 (8.94%) 14 7 / 123 (5.69%) 9		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 9 / 123 (7.32%) 9		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all)	 11 / 123 (8.94%) 15 45 / 123 (36.59%) 83 17 / 123 (13.82%) 26 10 / 123 (8.13%) 19 9 / 123 (7.32%) 37		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 9 / 123 (7.32%) 11 9 / 123 (7.32%) 9 7 / 123 (5.69%) 9		
Infections and infestations			

Urinary tract infection subjects affected / exposed occurrences (all)	8 / 123 (6.50%) 9		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	 26 / 123 (21.14%) 70 10 / 123 (8.13%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2016	'Locally advanced' was removed from the trial title and inclusion criteria to allow all patients with untreated metastatic colorectal cancer to be included in the trial. The Benefit-Risk Assessment was updated to alert Investigators of the risks of fetal harm in women taking Avastin and to update the protocol in line with the revised labelling. The overall design section was updated to remove provision of an interim analysis, as this was no longer needed for the trial. Changes to the mFOLFOX6 regimen were to be allowed following agreement by the Sponsor due to some sites not being able to obtain leucovorin. Inclusion criteria were updated to exclude patients with measurable lesions that had been irradiated within 12 weeks prior to enrollment. Exclusion criterion 4 was updated to provide more detailed information in exclusion in patients with brain metastases. Exclusion criterion 10 was updated to allow use of corticosteroids as antiemetics for oxaliplatin and 5-fluorouracil according to regular institutional practice. Exclusion criterion 15 was updated to allow inclusion of patients with history of gastroduodenal ulcer more than 18 months prior to Screening. Radiotherapy was added as a restriction to prevent concomitant radiotherapy during the trial. Restrictions information was updated to prevent trial medication being given within 28 days of any surgical procedure needed to obtain a biopsy. The description of the safety laboratory parameters was clarified. Coagulation tests were added to the Chemistry parameter. Number of electrocardiograms (ECGs) was updated to clarify that 2 consecutive ECGs were to be performed. A full definition of TEAEs suggestive of hepatic injury was added to assist Investigators in deciding whether the drug-induced liver injury checklist needed to be completed. Pharmacokinetic (PK) analyses were updated to remove population PK modeling and to state that plasma BI 695502 levels were to be compared to historical controls instead.
25 May 2016	• It was clarified that coagulation tests were to be performed post-screening.
13 April 2017	• The rectal examination was made optional since it is not routinely done in all United States practices.
26 October 2017	• The trial number was updated to include the new brand name, INVICTAN®-3. • The timing of the tumor assessments was clarified, specifically that if an assessment was done at Visit 27 then another assessment was not required at Visit 28. • The criteria for dose deviations which were to be considered protocol deviations were clarified. • The mandatory concentration of BI 695502 for i.v. infusion was updated.

17 January 2018	• As a consequence of the observation of particles for certain investigational medicinal product batches, the Sponsor recommended that patients were switched from BI 695502 to the reference medicinal product as soon as it was available at the respective clinical site. The protocol was updated throughout to clarify that trial medication may be either BI 695502 or Avastin®. • It was clarified that the REP was 18 weeks after the last dose of trial medication and thus this was when the Safety Follow-up (SFU) should be performed. Patients who were still being seen at the site every 3 weeks did not need an additional SFU Visit. • The end of trial definition was updated to take account of patients that may continue to receive Avastin® beyond the 18-week SFU Visit. • It was clarified that filters were still to be used for Avastin® administration the same as for BI 695502 administration. • The statistical methods were updated to clarify the period covered by the main analyses plus that appropriate censoring methods were to be applied at the time of switching from BI 695502 to Avastin®. • The visits required at the Switch Visit were clarified in the flow chart. • Additional information was added to describe the 5 Data Safety Monitoring Board meetings that had been held for trial 1302.5 and that they had all recommended continuation of that trial without modification. • The reasons for patient discontinuation of trial medication were updated to include 'Congestive heart failure, any degree'. • Clarification on the dose of Avastin and the administration instructions was added. • Clarification of the Avastin supply and labeling, storage conditions, and accountability was added to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

From 21 December 2017, the Sponsor recommended for patients to be switched from BI 695502 to Avastin®. The main analyses for reporting primary and secondary endpoints was clarified as the pre-switch period (i.e., all receiving BI 695502).

Notes: