Clinical trial results:
A Randomised, Parallel, Double Blinded Study to Compare the Efficacy and Safety of FKB238 to Avastin® In 1st Line Treatment for Patients with Advanced/Recurrent Non Squamous Non-Small Cell Lung Cancer in Combination of Paclitaxel and Carboplatin

Summary

EudraCT number	2015-004104-33
Trial protocol	DE HU ES GR BG HR IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	09 February 2020
First version publication date	09 February 2020

Trial information

Trial identification

Sponsor protocol code	FKB238-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02810457
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 122990

Notes:

Sponsors

Sponsor organisation name	Centus Biotherapeutics Limited
Sponsor organisation address	1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, United Kingdom, CB2 0AA
Public contact	Clinical Trial Information, Centus Biotherapeutics Limited, Clinical-Trial@centusbio.com
Scientific contact	Clinical Trial Information, Centus Biotherapeutics Limited, Clinical-Trial@centusbio.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	Interim
Date of interim/final analysis	07 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 January 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the efficacy equivalence of FKB238 and EU-Avastin when used in combination with paclitaxel/carboplatin as measured by overall response rate (ORR).

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), and applicable regulatory and data protection requirements.
The investigator explained the benefits and risks of participation in the study to each subject or the subject's legally acceptable representative and obtained written informed consent. Written informed consent was required to be obtained prior to the subject entering the study and before initiation of any study-related procedure.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belarus: 50
Country: Number of subjects enrolled	Bosnia and Herzegovina: 23
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Croatia: 8
Country: Number of subjects enrolled	Georgia: 27
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Hungary: 52
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	Peru: 13
Country: Number of subjects enrolled	Philippines: 13
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Russian Federation: 184
Country: Number of subjects enrolled	Serbia: 59
Country: Number of subjects enrolled	Spain: 19

Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	Thailand: 36
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	Ukraine: 120
Country: Number of subjects enrolled	United States: 16
Country: Number of subjects enrolled	Vietnam: 9
Worldwide total number of subjects	731
EEA total number of subjects	150

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)	462
From 65 to 84 years	269
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were screened at 146 centres in 24 countries (136 centres in 24 countries randomised patients) in Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Georgia, Germany, Greece, Hungary, Italy, Japan, Republic of Korea, Peru, Philippines, Poland, Romania, Russia, Serbia, Spain, Taiwan, Thailand, Turkey, Ukraine, United States, and Vietnam.

Pre-assignment

Screening details:

Of a total of 1023 patients who signed informed consent and were screened, 292 patients were not randomised (i.e., screen failures), with a total of 731 patients randomised to treatment. Of these patients, 728 received study treatment.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	FKB238

Arm description:

FKB238 was administered on Day 1 of each 21-day cycle until objective progressive disease (PD) or other criteria for treatment discontinuation were met. Paclitaxel and carboplatin (combination drugs) were administered on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. The number of cycles was to be determined based on the patients' need and the investigator's assessment. All three drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle in the order of paclitaxel followed by carboplatin, then FKB238.

Arm type	Experimental
Investigational medicinal product name	FKB238
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg on Day 1 of each 21-day cycle until objective PD or other criteria for treatment discontinuation were met. The initial dose of FKB238 was to be delivered over 90 minutes as an IV infusion. If the first infusion was well tolerated, the second infusion could be administered over 60 minutes. If the 60-minute infusion was well tolerated, all subsequent infusions could be administered over 30 minutes.

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

Dosage and administration details:

200 mg/m2, administered by IV infusion over 3 hours on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. The number of cycles was to be determined based on the patients' need and the investigator's assessment.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

AUC 6.0, administered by IV infusion over 15 to 60 minutes on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. The number of cycles was to be determined based on the patients' need and the investigator's assessment.

Arm title	Avastin

Arm description:

Avastin was administered on Day 1 of each 21-day cycle until objective progressive disease (PD) or other criteria for treatment discontinuation were met. Paclitaxel and carboplatin (combination drugs) were administered on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. The number of cycles was to be determined based on the patients' need and the investigator's assessment. All three drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle in the order of paclitaxel followed by carboplatin, then Avastin.

Arm type	Active comparator
Investigational medicinal product name	Avastin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg on Day 1 of each 21-day cycle until objective PD or other criteria for treatment discontinuation were met. The initial dose of Avastin was to be delivered over 90 minutes as an IV infusion. If the first infusion was well tolerated, the second infusion could be administered over 60 minutes. If the 60-minute infusion was well tolerated, all subsequent infusions could be administered over 30 minutes.

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

Dosage and administration details:

200 mg/m2, administered by IV infusion over 3 hours on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. The number of cycles was to be determined based on the patients' need and the investigator's assessment.

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

Dosage and administration details:

AUC 6.0, administered by IV infusion over 15 to 60 minutes on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. The number of cycles was to be determined based on the patients' need and the investigator's assessment.

Number of subjects in period 1	FKB238	Avastin
Started	364	367
Received study treatment	362	366
Completed	37	38
Not completed	327	329
Patient decision	31	35

Objective PD assessed by RECIST v1.1	191	199
Other	64	49
Adverse event	37	43
Lost to follow-up	2	2
Did not receive study treatment	2	1

Baseline characteristics

Reporting groups	
Reporting group title	FKB238

Reporting group description:

FKB238 was administered on Day 1 of each 21-day cycle until objective progressive disease (PD) or other criteria for treatment discontinuation were met. Paclitaxel and carboplatin (combination drugs) were administered on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. The number of cycles was to be determined based on the patients' need and the investigator's assessment. All three drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle in the order of paclitaxel followed by carboplatin, then FKB238.

Reporting group title	Avastin

Reporting group description:

Avastin was administered on Day 1 of each 21-day cycle until objective progressive disease (PD) or other criteria for treatment discontinuation were met. Paclitaxel and carboplatin (combination drugs) were administered on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. The number of cycles was to be determined based on the patients' need and the investigator's assessment. All three drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle in the order of paclitaxel followed by carboplatin, then Avastin.

Reporting group values	FKB238	Avastin	Total
Number of subjects	364	367	731
Age categorical Units: Subjects			
Adults (18-64 years)	238	224	462
From 65-84 years	126	143	269
Gender categorical Units: Subjects			
Female	119	129	248
Male	245	238	483
Race Units: Subjects			
White	316	320	636
Black and African American	1	0	1
Asian, other than Japanese	37	37	74
Japanese	2	3	5
American Indian or Alaska Native	1	4	5
Other	7	3	10

End points

End points reporting groups

Reporting group title	FKB238

Reporting group description:

FKB238 was administered on Day 1 of each 21-day cycle until objective progressive disease (PD) or other criteria for treatment discontinuation were met. Paclitaxel and carboplatin (combination drugs) were administered on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. The number of cycles was to be determined based on the patients' need and the investigator's assessment. All three drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle in the order of paclitaxel followed by carboplatin, then FKB238.

Reporting group title	Avastin

Reporting group description:

Avastin was administered on Day 1 of each 21-day cycle until objective progressive disease (PD) or other criteria for treatment discontinuation were met. Paclitaxel and carboplatin (combination drugs) were administered on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. The number of cycles was to be determined based on the patients' need and the investigator's assessment. All three drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle in the order of paclitaxel followed by carboplatin, then Avastin.

Subject analysis set title	ITT Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients randomised to treatment. Patients were included in the treatment group according to the randomisation assigned, regardless of the treatment actually given. All efficacy analyses were performed on the ITT population.

Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

All patients randomised to treatment who received at least 1 dose of IP with no important protocol deviations. Patients were included in the treatment group according to the treatment actually given. All efficacy analyses were performed on the PPS.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients randomised to treatment who received at least 1 dose of Investigational Product (IP). Patients were included in the treatment group according to the treatment actually given. All safety analyses were performed on the Safety Population. Treatment groups were analysed according to the first IP actually received.

Subject analysis set title	Pharmacokinetics Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All Per Protocol Set patients who have at least one serum drug concentration data, which is defined in the study protocol, after IP administration. Patients were included in the treatment group according to the treatment actually given.

Subject analysis set title	ADA Evaluable Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All Per Protocol Set patients who have at least one anti-drug antibody (ADA) assessment prior to and after baseline data. Patients were included in the treatment group according to the treatment actually given.

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

The primary variable in this study was ORR, defined as the proportion of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) (by RECIST v1.1). A BOR is defined as the best response (in the order of CR, PR, stable disease (SD), progressive disease (PD), and not

evaluable (NE)) among all post-baseline disease assessments that occur until progression, or last evaluable assessment in the absence of progression prior to the initiation of subsequent anti-cancer therapy, irrespective of whether or not subjects discontinued the study treatment. This assessment was performed using the Per Protocol Set (PPS) and the independent central radiological assessments.

End point type	Primary

End point timeframe:

Until data cut-off, which occured 12 months after randomisation of the last patient enrolled

End point values	FKB238	Avastin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	352	354		
Units: percentage of subjects				
number (confidence interval 95%)	51.7 (46.35 to 57.03)	53.4 (48.04 to 58.68)		

Statistical analyses

Statistical analysis title	Difference in BICR ORR
Comparison groups	FKB238 v Avastin
Number of subjects included in analysis	706
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Risk difference (RD)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0905
upper limit	0.0568

Notes:

[1] - In order to compare the ORRs in the two treatment arms, the difference in ORRs will be calculated and a 95% Wald asymptotic confidence interval (CI) given. If the 95% CI is within the interval [± 0.1221], an equivalence between FKB238 and EU- Avastin, with respect to the ORR, is confirmed. BICR = Blinded independent central review.

Secondary: Overall Response Rate (ORR) at Week 19

End point title	Overall Response Rate (ORR) at Week 19

End point description:

ORR (by RECIST v1.1) at Week 19 will be defined as the proportion of subjects with a BOR of CR or PR assessed at Week 19. Only tumour assessment performed up until 19 weeks (i.e., week 18 assessment + 7 day assessment window) from randomisation are considered in this analysis. This assessment was performed using the Per Protocol Set (PPS) and the independent central radiological assessments.

End point type	Secondary

End point timeframe:

Until Week 19

End point values	FKB238	Avastin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	352	354		
Units: percentage of subjects				
number (confidence interval 95%)	47.7 (42.41 to 53.09)	50.8 (45.51 to 56.17)		

Statistical analyses

Statistical analysis title	Risk difference in BICR ORR at Week 19
Comparison groups	FKB238 v Avastin
Number of subjects included in analysis	706
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Risk difference (RD)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1049
upper limit	0.0425

Notes:

[2] - Comparison between groups: Risk difference in ORR at week 19. BICR = Blinded independent central review.

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

The event of interest for progression-free survival (PFS) is defined as first documented disease progression or death from any cause, whichever occurs first. Disease progression will be based on tumour assessments according to RECIST v1.1 criteria. The items of the overall response CR, PR, SD and NE will be taken as progression-free whereas PD will denote disease progression. PFS is defined as the interval from the date of randomisation until the earlier date of the first documentation of disease progression or death due to any reason. This assessment was performed using the ITT Population and the independent central radiological assessments.

End point type	Secondary

End point timeframe:

Until data cut-off, which occurred 12 months after randomisation of the last patient enrolled

End point values	FKB238	Avastin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	364	367		
Units: Months				
median (confidence interval 95%)	7.72 (7.46 to 7.98)	7.62 (6.90 to 7.82)		

Statistical analyses

Statistical analysis title	Hazard ratio analysis

Statistical analysis description:

Hazard ratio and its 95% confidence interval are calculated using the cox regression model adjusting for the listed baseline characteristics with ties handled by the Efron method. Treatment hazard ratio < 1 favours FKB238.

Comparison groups	FKB238 v Avastin
Number of subjects included in analysis	731
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.16

Notes:

[3] - Hazard ratio of FKB238 versus Avastin

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

The event of interest is defined as death from any cause. OS is defined as the interval from date of randomisation until the date of death due to any cause. This assessment was performed using the ITT Population.

End point type	Secondary

End point timeframe:

Until data cut-off, which occurred 12 months after randomisation of the last patient enrolled

End point values	FKB238	Avastin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	364	367		
Units: Months				
median (confidence interval 95%)	14.13 (12.52 to 16.56)	16.95 (14.65 to 19.02)		

Statistical analyses

Statistical analysis title	Hazard ratio analysis

Statistical analysis description:

Hazard ratio and its 95% confidence interval are calculated using the cox regression model adjusting for the listed baseline characteristics with ties handled by the Efron method. Treatment hazard ratio < 1 favours FKB238.

Comparison groups	FKB238 v Avastin
Number of subjects included in analysis	731
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.45

Notes:

[4] - Hazard ratio of FKB238 versus Avastin

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was evaluated in this study as a secondary efficacy endpoint. Only the patients defined as responders in the primary analysis of ORR were taken into account for the analysis of DOR. The event of interest is defined as first documented disease progression or death due to any reason, whichever occurs first. DOR is defined as the interval from the first documented response (as defined per RECIST v1.1) until the earlier date of the first documented disease progression or death due to any reason. The date of first documented response will be taken as the date of the first tumour assessment with an overall visit response of CR or PR. DOR will be calculated in units of months. This assessment was performed using the ITT Population and the independent central radiological assessments.

End point type	Secondary

End point timeframe:

Until data cut-off, which occurred 12 months after randomisation of the last patient enrolled

End point values	FKB238	Avastin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	197		
Units: duration of response (months)				
median (confidence interval 95%)	6.47 (5.39 to 7.69)	6.31 (4.93 to 7.29)		

Statistical analyses

Statistical analysis title	Hazard ratio analysis

Statistical analysis description:

Hazard ratio and its 95% confidence interval are calculated using the cox regression model adjusting for the listed baseline characteristics with ties handled by the Efron method. Treatment hazard ratio < 1 favours FKB238.

Comparison groups	FKB238 v Avastin
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.23

Notes:

[5] - Hazard ratio of FKB238 versus Avastin

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

The Disease Control Rate (DCR) is defined as the proportion of patients defined as responders. The number and percentage of responders and non-responders and the 95% Pearson-Clopper CI of DCR for each treatment arm is provided. The odds ratio for treatment (Arm2 versus Arm1) and the corresponding 95% Wald CI will be produced based on a logistic regression analysis of DCR. This assessment of DCR was based on the ITT population using the independent central radiological assessments.

End point type	Secondary

End point timeframe:

Until data cut-off, which occurred 12 months after randomisation of the last patient enrolled

End point values	FKB238	Avastin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	364	367		
Units: percentage of subjects with response				
number (confidence interval 95%)	87.6 (83.81 to 90.84)	87.5 (83.64 to 90.68)		

Statistical analyses

Statistical analysis title	Comparison between arms: Odds ratio

Statistical analysis description:

The DCR is compared between treatment arms using logistic regression adjusting for the listed baseline characteristics. Odds ratio > 1 favours FKB238.

Comparison groups	FKB238 v Avastin
Number of subjects included in analysis	731
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Odds ratio (OR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.58

Notes:

[6] - Comparison between arms: Odds ratio

Other pre-specified: Serum trough concentrations

End point title	Serum trough concentrations

End point description:

Serum trough concentration (Ctrough) and serum maximum concentration (Cmax; at completion of infusion) were compared between treatment arms and descriptive statistics provided. Ctrough and Cmax concentrations were summarised using the pharmacokinetics (PK) population for each visit at which samples were taken. The zero values provided for both treatment arms at Cycle 1, Day 1 pre-infusion are equivalent to a Not Calculable result.

End point type	Other pre-specified

End point timeframe:

From pre-infusion Cycle 1, Day 1 through to pre-infusion Cycle 6, Day1

End point values	FKB238	Avastin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	351		
Units: ug/ml				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 pre-infusion	0 (± 0)	0 (± 0)		
Cycle 1, Day 1 post-infusion	255.15 (± 184.3)	245.11 (± 206.8)		
Cycle 2, Day 1 pre-infusion	42.74 (± 91.9)	48.48 (± 77.3)		
Cycle 4, Day 1 pre-infusion	77.16 (± 69.4)	83.26 (± 85.5)		

Cycle 4, Day 1 post-infusion	339.91 (± 91.3)	373.92 (± 51.6)		
Cycle 6, Day 1 pre-infusion	87.25 (± 124.5)	108.22 (± 69.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Anti-Drug Antibody (ADA)

End point title	Anti-Drug Antibody (ADA)

End point description:

The ADA levels were summarised at baseline and post-baseline time points using descriptive statistics. This assessment was performed using the ADA Evaluable Population.

End point type	Other pre-specified

End point timeframe:

Until data cut-off, which occurred 12 months after randomisation of the last patient enrolled

End point values	FKB238	Avastin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305	305		
Units: Number of subjects				
number (not applicable)				
ADA prevalence (ADA positive, baseline or post)	9	9		
Treatment-emergent ADA positive (ADA incidence)	7	7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From time of informed consent, throughout the treatment period and up to and including the 30-days after the last dose of study treatment. All ongoing and any new AEs/SAEs identified during the 30 days after last dose were followed to resolution.

Adverse event reporting additional description:

All safety summaries and analyses were based on the Safety Population. Adverse Events (AEs) were coded using the latest MedDRA version. AEs are categorised as treatment-emergent AEs. Intensity of AEs were assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4 grading system.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	FKB238

Reporting group description:

FKB238 was administered on Day 1 of each 21-day cycle until objective progressive disease (PD) or other criteria for treatment discontinuation were met. Paclitaxel and carboplatin (combination drugs) were administered on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. The number of cycles was to be determined based on the patients' need and the investigator's assessment. All three drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle in the order of paclitaxel followed by carboplatin, then FKB238.

Reporting group title	Avastin

Reporting group description:

Avastin was administered on Day 1 of each 21-day cycle until objective progressive disease (PD) or other criteria for treatment discontinuation were met. Paclitaxel and carboplatin (combination drugs) were administered on Day 1 of each 21-day cycle for at least 4, and no more than 6 cycles. The number of cycles was to be determined based on the patients' need and the investigator's assessment. All three drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle in the order of paclitaxel followed by carboplatin, then Avastin.

Serious adverse events	FKB238	Avastin	
Total subjects affected by serious adverse events			
subjects affected / exposed	91 / 362 (25.14%)	95 / 366 (25.96%)	
number of deaths (all causes)	195	177	
number of deaths resulting from adverse events	30	23	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to bone			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			

subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 362 (0.55%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 362 (0.00%)	2 / 366 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	5 / 362 (1.38%)	3 / 366 (0.82%)	
occurrences causally related to treatment / all	0 / 5	1 / 3	
deaths causally related to treatment / all	0 / 5	1 / 3	
Fatigue			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 362 (0.28%)	2 / 366 (0.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	

Mucosal inflammation			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden death			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 362 (0.55%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 362 (0.55%)	3 / 366 (0.82%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	

Haemoptysis			
subjects affected / exposed	2 / 362 (0.55%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Oesophagobronchial fistula			
subjects affected / exposed	2 / 362 (0.55%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 362 (0.55%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 362 (0.00%)	4 / 366 (1.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	6 / 362 (1.66%)	5 / 366 (1.37%)	
occurrences causally related to treatment / all	2 / 6	1 / 5	
deaths causally related to treatment / all	1 / 2	0 / 3	
Pulmonary fibrosis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	3 / 362 (0.83%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	1 / 3	0 / 1	
Pulmonary mass			

subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 362 (0.55%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 362 (0.28%)	3 / 366 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	3 / 362 (0.83%)	2 / 366 (0.55%)	
occurrences causally related to treatment / all	3 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 362 (0.28%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	2 / 362 (0.55%)	2 / 366 (0.55%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal fracture			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	3 / 362 (0.83%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Acute myocardial infarction			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 362 (0.55%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Cor pulmonale			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral arteriosclerosis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral atrophy			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 362 (0.55%)	3 / 366 (0.82%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 2	1 / 3	
Dizziness			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	2 / 362 (0.55%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Facial paresis			

subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 362 (0.28%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Ischaemic stroke			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Polyneuropathy			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	1 / 362 (0.28%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uraemic encephalopathy			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 362 (1.38%)	9 / 366 (2.46%)	
occurrences causally related to treatment / all	5 / 5	6 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	7 / 362 (1.93%)	5 / 366 (1.37%)	
occurrences causally related to treatment / all	7 / 7	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	7 / 362 (1.93%)	18 / 366 (4.92%)	
occurrences causally related to treatment / all	8 / 8	19 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 362 (0.00%)	2 / 366 (0.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 362 (0.55%)	2 / 366 (0.55%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 362 (0.28%)	3 / 366 (0.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			

subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 362 (0.83%)	2 / 366 (0.55%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholelithiasis			
subjects affected / exposed	0 / 362 (0.00%)	2 / 366 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 362 (0.28%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 362 (0.28%)	2 / 366 (0.55%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 362 (0.00%)	2 / 366 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 362 (0.00%)	2 / 366 (0.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 362 (0.28%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	2 / 362 (0.55%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 362 (0.28%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia			
subjects affected / exposed	10 / 362 (2.76%)	9 / 366 (2.46%)	
occurrences causally related to treatment / all	5 / 12	4 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 362 (0.00%)	2 / 366 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypocalcaemia			

subjects affected / exposed	1 / 362 (0.28%)	0 / 366 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 362 (0.00%)	1 / 366 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	FKB238	Avastin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	341 / 362 (94.20%)	348 / 366 (95.08%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	38 / 362 (10.50%)	35 / 366 (9.56%)	
occurrences (all)	53	45	
Aspartate aminotransferase increased			
subjects affected / exposed	32 / 362 (8.84%)	35 / 366 (9.56%)	
occurrences (all)	43	45	
Blood alkaline phosphatase increased			
subjects affected / exposed	19 / 362 (5.25%)	27 / 366 (7.38%)	
occurrences (all)	24	39	
Gamma-glutamyltransferase increased			
subjects affected / exposed	38 / 362 (10.50%)	31 / 366 (8.47%)	
occurrences (all)	48	46	
Neutrophil count decreased			
subjects affected / exposed	24 / 362 (6.63%)	25 / 366 (6.83%)	
occurrences (all)	32	30	
Platelet count decreased			
subjects affected / exposed	30 / 362 (8.29%)	25 / 366 (6.83%)	
occurrences (all)	48	38	
Weight decreased			

subjects affected / exposed	41 / 362 (11.33%)	56 / 366 (15.30%)	
occurrences (all)	48	62	
White blood cell count decreased			
subjects affected / exposed	24 / 362 (6.63%)	26 / 366 (7.10%)	
occurrences (all)	36	36	
Vascular disorders			
Hypertension			
subjects affected / exposed	42 / 362 (11.60%)	44 / 366 (12.02%)	
occurrences (all)	47	54	
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 362 (4.97%)	23 / 366 (6.28%)	
occurrences (all)	21	24	
Neuropathy peripheral			
subjects affected / exposed	58 / 362 (16.02%)	52 / 366 (14.21%)	
occurrences (all)	63	60	
Paraesthesia			
subjects affected / exposed	24 / 362 (6.63%)	22 / 366 (6.01%)	
occurrences (all)	26	22	
Peripheral sensory neuropathy			
subjects affected / exposed	28 / 362 (7.73%)	25 / 366 (6.83%)	
occurrences (all)	28	25	
Polyneuropathy			
subjects affected / exposed	16 / 362 (4.42%)	23 / 366 (6.28%)	
occurrences (all)	18	31	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	105 / 362 (29.01%)	119 / 366 (32.51%)	
occurrences (all)	135	146	
Leukopenia			
subjects affected / exposed	43 / 362 (11.88%)	50 / 366 (13.66%)	
occurrences (all)	58	89	
Neutropenia			
subjects affected / exposed	109 / 362 (30.11%)	145 / 366 (39.62%)	
occurrences (all)	163	212	
Thrombocytopenia			

subjects affected / exposed	44 / 362 (12.15%)	66 / 366 (18.03%)	
occurrences (all)	78	102	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	37 / 362 (10.22%)	59 / 366 (16.12%)	
occurrences (all)	45	71	
Fatigue			
subjects affected / exposed	41 / 362 (11.33%)	45 / 366 (12.30%)	
occurrences (all)	55	48	
Non-cardiac chest pain			
subjects affected / exposed	18 / 362 (4.97%)	11 / 366 (3.01%)	
occurrences (all)	18	15	
Pyrexia			
subjects affected / exposed	15 / 362 (4.14%)	21 / 366 (5.74%)	
occurrences (all)	17	24	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	19 / 362 (5.25%)	21 / 366 (5.74%)	
occurrences (all)	23	23	
Diarrhoea			
subjects affected / exposed	35 / 362 (9.67%)	35 / 366 (9.56%)	
occurrences (all)	44	41	
Nausea			
subjects affected / exposed	52 / 362 (14.36%)	45 / 366 (12.30%)	
occurrences (all)	72	57	
Vomiting			
subjects affected / exposed	24 / 362 (6.63%)	18 / 366 (4.92%)	
occurrences (all)	29	24	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 362 (4.70%)	25 / 366 (6.83%)	
occurrences (all)	20	26	
Dyspnoea			
subjects affected / exposed	17 / 362 (4.70%)	29 / 366 (7.92%)	
occurrences (all)	17	29	
Epistaxis			

subjects affected / exposed	16 / 362 (4.42%)	23 / 366 (6.28%)	
occurrences (all)	20	36	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	154 / 362 (42.54%)	159 / 366 (43.44%)	
occurrences (all)	157	162	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	24 / 362 (6.63%)	41 / 366 (11.20%)	
occurrences (all)	31	52	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	32 / 362 (8.84%)	36 / 366 (9.84%)	
occurrences (all)	49	48	
Back pain			
subjects affected / exposed	22 / 362 (6.08%)	14 / 366 (3.83%)	
occurrences (all)	25	14	
Myalgia			
subjects affected / exposed	29 / 362 (8.01%)	32 / 366 (8.74%)	
occurrences (all)	61	73	
Infections and infestations			
Pneumonia			
subjects affected / exposed	18 / 362 (4.97%)	20 / 366 (5.46%)	
occurrences (all)	20	24	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	43 / 362 (11.88%)	42 / 366 (11.48%)	
occurrences (all)	56	48	
Hyperglycaemia			
subjects affected / exposed	14 / 362 (3.87%)	22 / 366 (6.01%)	
occurrences (all)	18	29	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2016	Amendment 1: The purpose of this amendment was to give more detailed clarification on the study procedure for EGFR mutation and ALK gene arrangement status, brain CT/MRI at screening, blood pressure measurement, dose modifications for non-haematologic toxicity, other concomitant medications, primary efficacy assessment, and the type of palliative radiotherapy allowed. In addition, urine pregnancy test was added as an alternative to serum pregnancy test and there was a clarification of visit allowance for radiological tumour assessments and assessments for survival.
20 April 2016	Amendment 2: The purpose of this amendment was to give more detailed clarification on the study procedure for brain CT/MRI at screening and the definition for prior weight loss.
12 April 2017	Amendment 3: The purpose of this amendment was to add details to the study procedure for urinalysis and urine dipstick, secondary objectives and secondary endpoints, treatments administered, re-start of study treatment, stop and re-initiation of IP prior to/after surgery, haematologic toxicities of the IP, study populations, screening procedures and screening failures, recording of AEs, and safety laboratory determinations. Additionally, the exclusion criterion of hypersensitivity was updated to include active ingredients of the IP or combination drugs; a clarification was added that patients who discontinue breastfeeding may be included in the study; the exclusion criterion of treatment with any other investigational agent for any reason within 28 days before the first dose of IP was updated to clarify that this treatment may be for any reason, and the Coordinating Investigator and his role as a signatory to the clinical study report was introduced.
22 May 2018	Amendment 4: The main purpose of this amendment was to clarify procedures to be completed during the Extended Treatment Period and to update the Sponsor’s signature page.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported