Clinical trial results:
Sorafenib Long Term Extension Program (STEP)

Summary

EudraCT number	2007-002604-17
Trial protocol	FR DE ES IT PL GB BE BG
Global end of trial date	24 September 2021

Results information

Result version number	v2 (current)
This version publication date	16 July 2022
First version publication date	30 March 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	12311

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00625378
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	24 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of the program was to enable patients, currently receiving sorafenib (Nexavar) in a Bayer/Onyx sponsored clinical trial, to continue sorafenib treatment after their respective study had met its primary endpoint and/or had reached the end as defined in the original protocol. An additional objective was the assessment of the safety of Nexavar or Nexavar combination treatment.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects/ /legal representatives. Participating subjects/ /legal representatives signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	26 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	China: 10
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Italy: 31

Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Poland: 70
Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	Ukraine: 1
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	204
EEA total number of subjects	126

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)	109
From 65 to 84 years	93
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at multiple centers in 19 countries between 21-Dec-2007 (first subject first visit) and 24-Sep-2021 (last subject last visit).

Pre-assignment

Screening details:

Overall, 206 subjects were transferred from the feeder studies and have signed informed consent for STEP. Of these 206 subjects, 2 subjects were never treated and 204 subjects received the study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sorafenib monotherapy

Arm description:

Subjects received single-agent sorafenib at the same dose and schedule as in their original Clinical Trial.

Arm type	Experimental
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	Nexavar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

At the same dose and schedule as in the subjects' original Clinical Trial

Arm title	Sorafenib+Erlotinib

Arm description:

Subjects received sorafenib and erlotinib combination at the same dose and schedule as in their original Clinical Trial.

Arm type	Experimental
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	Nexavar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

At the same dose and schedule as in the subjects' original Clinical Trial

Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

At the same dose and schedule as in the subjects' original Clinical Trial

Number of subjects in period 1	Sorafenib monotherapy	Sorafenib+Erlotinib
Started	203	1
Completed	0	0
Not completed	203	1
Disease progression, recurrence or relapse	88	-
Non-compliant with study medication	3	-
Adverse event	22	-
Sponsor decision	1	-
Missing	2	-
Multiple toxicities	1	-
New cancer	1	-
PTA program	2	-
Consent withdrawn by subject	16	-
Investigator's decision	1	-
Sponsor's decision to stop the trial	1	-
End of treatment not available	2	-
Death	38	-
Switch to commercial drug	6	1
Medical decision	1	-
Lost to follow-up	17	-
Recurrent rise in amylase and lipase	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Sorafenib monotherapy
Reporting group description:	
Subjects received single-agent sorafenib at the same dose and schedule as in their original Clinical Trial.	
Reporting group title	Sorafenib+Erlotinib
Reporting group description:	
Subjects received sorafenib and erlotinib combination at the same dose and schedule as in their original Clinical Trial.	

Reporting group values	Sorafenib monotherapy	Sorafenib+Erlotinib	Total
Number of subjects	203	1	204
Age Categorical Units: Subjects			
Age Continuous			
"99999" denotes that value was not calculated due to the only 1 subject in the group.			
Units: years			
arithmetic mean	63.5	20.0	
standard deviation	± 9.6	± 99999	-
Gender Categorical Units: Subjects			
Female	63	0	63
Male	140	1	141
Race Units: Subjects			
Asian	39	1	40
Hispanic	2	0	2
Japanese/American	1	0	1
White	161	0	161
ECOG performance status			
Eastern cooperative oncology group (ECOG) performance status: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work; 2 = Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours			
Units: Subjects			
ECOG 0	25	1	26
ECOG 1	16	0	16
ECOG 2	1	0	1
Missing	161	0	161

End points

End points reporting groups

Reporting group title	Sorafenib monotherapy
Reporting group description:	
Subjects received single-agent sorafenib at the same dose and schedule as in their original Clinical Trial.	
Reporting group title	Sorafenib+Erlotinib
Reporting group description:	
Subjects received sorafenib and erlotinib combination at the same dose and schedule as in their original Clinical Trial.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
SAF included all subjects who received at least one dose of study medication.	

Primary: Sorafenib treatment duration within STEP

End point title	Sorafenib treatment duration within STEP[1]
End point description:	
Treatment duration was calculated in days as the date of the last dose of any study treatment minus date of the first dose of any study treatment plus one day.	
End point type	Primary
End point timeframe:	
From the date of the first sorafenib dose until the date of the last sorafenib dose, with a mean duration of 25 months and max duration of 153.8 months	

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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

End point values	Sorafenib monotherapy	Sorafenib+Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[2]	1[3]		
Units: Months				
median (inter-quartile range (Q1-Q3))	15.69 (6.41 to 33.19)	40.13 (40.13 to 40.13)		

Notes:

[2] - SAF

[3] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with new treatment-emergent adverse events (TEAEs)

End point title	Number of subjects with new treatment-emergent adverse events (TEAEs)[4]
End point description:	

An adverse event (AE) was any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The adverse event did not necessarily have to have a causal relationship with this treatment. A serious adverse event (SAE) was any untoward medical occurrence that at any dose: resulted in death; was life-threatening; required in-patient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability or incapacity; was a congenital anomaly or birth defect; was an important medical event. A new treatment-emergent

adverse event (TEAE) was any AE that had a start date on or after ICF date in STEP and up to 30 days after the last sorafenib dose. A drug-related new TEAE was any new TEAE that had a causal relationship with the study treatment as assessed by the investigator. disc. = discontinuation

End point type	Primary

End point timeframe:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Notes:

[4] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

End point values	Sorafenib monotherapy	Sorafenib+Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[5]	1[6]		
Units: Subjects				
Any AE	166	1		
Serious AE (SAE)	113	1		
AE leading to dose modification	64	0		
AE leading to study drug discontinuation	56	0		
AE leading to death	37	0		
Sorafenib-related AE	117	1		
Sorafenib-related SAE	25	1		
Sorafenib-related AE leading to dose modification	42	0		
Sorafenib-related AE leading to study drug disc.	21	0		
Sorafenib-related AE leading to death	2	0		

Notes:

[5] - SAF

[6] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with new TEAEs of CTCAE grades 3 or higher by worst CTCAE grade

End point title	Number of subjects with new TEAEs of CTCAE grades 3 or higher by worst CTCAE grade[7]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The AE did not necessarily have to have a causal relationship with this treatment. A new treatment-emergent adverse event (TEAE) was any AE that had a start date on or after ICF date in STEP and up to 30 days after the last sorafenib dose. CTCAE: Common Terminology Criteria Adverse Event.

End point type	Primary

End point timeframe:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Notes:

[7] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

End point values	Sorafenib monotherapy	Sorafenib+Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[8]	1[9]		
Units: Subjects				
Grade 3	71	1		
Grade 4	17	1		
Grade 5	37	0		

Notes:

[8] - SAF

[9] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with study drug-related new TEAEs of CTCAE grades 3 or higher by worst CTCAE grade

End point title	Number of subjects with study drug-related new TEAEs of CTCAE grades 3 or higher by worst CTCAE grade[10]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The AE did not necessarily have to have a causal relationship with this treatment. A new treatment-emergent adverse event (TEAE) was any AE that had a start date on or after ICF date in STEP and up to 30 days after the last sorafenib dose. A drug-related new TEAE was a new TEAE that had a causal relationship with the study treatment as assessed by the investigator. CTCAE: Common Terminology Criteria Adverse Event.

End point type	Primary

End point timeframe:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Notes:

[10] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

End point values	Sorafenib monotherapy	Sorafenib+Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[11]	1[12]		
Units: Subjects				
Grade 3	49	1		
Grade 4	6	0		
Grade 5	2	0		

Notes:

[11] - SAF

[12] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with all adverse events

End point title	Number of subjects with all adverse events[13]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The AE did not necessarily have to have a causal relationship with this treatment. A drug-related AE was any AE that had a causal relationship with the study treatment as assessed by the investigator. All AEs in STEP were the combination of AEs ongoing from feeder studies and new TEAEs. disc. = discontinuation

End point type	Primary

End point timeframe:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Notes:

[13] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

End point values	Sorafenib monotherapy	Sorafenib+Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[14]	1[15]		
Units: Subjects				
Any AE	184	1		
Serious AE (SAE)	114	1		
AE leading to dose modification	72	0		
AE leading to study drug discontinuation	56	0		
AE leading to death	37	0		
Sorafenib-related AE	159	1		
Sorafenib-related SAE	26	1		
Sorafenib-related AE leading to dose modification	53	0		
Sorafenib-related AE leading to study drug disc.	21	0		
Sorafenib-related AE leading to death	2	0		

Notes:

[14] - SAF

[15] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with all adverse events of CTCAE grades 3 or higher by worst CTCAE grade

End point title	Number of subjects with all adverse events of CTCAE grades 3 or higher by worst CTCAE grade[16]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The AE did not necessarily have to have a causal relationship with this treatment. All AEs in STEP were the combination of AEs ongoing from feeder studies and new TEAEs.

End point type	Primary

End point timeframe:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Notes:

[16] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

End point values	Sorafenib monotherapy	Sorafenib+Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[17]	1[18]		
Units: Subjects				
Grade 3	81	1		
Grade 4	17	1		
Grade 5	37	0		

Notes:

[17] - SAF

[18] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with study drug-related all adverse events of CTCAE grades 3 or higher by worst CTCAE

End point title	Number of subjects with study drug-related all adverse events of CTCAE grades 3 or higher by worst CTCAE[19]

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The AE did not necessarily have to have a causal relationship with this treatment. A drug-related AE was any AE that had a causal relationship with the study treatment as assessed by the investigator. All AEs in STEP was a combination of AEs ongoing from feeder studies and new TEAEs.

End point type	Primary

End point timeframe:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Notes:

[19] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

End point values	Sorafenib monotherapy	Sorafenib+Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[20]	1[21]		
Units: Subjects				
Grade 3	65	1		
Grade 4	6	0		
Grade 5	2	0		

Notes:

[20] - SAF

[21] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of deaths with primary cause of death

End point title	Number of deaths with primary cause of death[22]

End point description:

Primary cause of death included: any cause; progressive disease; toxicity due to study treatment (with at least one AE with outcome death); other (unspecified) or missing cause.

End point type	Primary

End point timeframe:

From signing the ICF in STEP until completion or discontinuation of the study, with a mean duration of 26 months

Notes:

[22] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

End point values	Sorafenib monotherapy	Sorafenib+Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[23]	1[24]		
Units: Subjects				
Any cause	62	0		
Progressive disease	34	0		
Toxicity due to study treatment	3	0		
Other	21	0		
Missing	4	0		

Notes:

[23] - SAF

[24] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with abnormal hematological and biochemical laboratory values by worst CTCAE grade

End point title	Number of subjects with abnormal hematological and biochemical laboratory values by worst CTCAE grade[25]

End point description:

Subjects with a specific laboratory value that were "not graded" are not included in the table. CTCAE grade was set to “not graded” if the reference ranges or other information necessary to derive grades were unavailable or result had a special character (such as > or <) then the grade. "99999" denotes that value was not countable due to no evaluable data for the subject.

End point type	Primary

End point timeframe:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Notes:

[25] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

End point values	Sorafenib monotherapy	Sorafenib+Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[26]	1[27]		
Units: Subjects				
Neutrophils (n=165;0) - Grade 1	19	99999		
Neutrophils (n=165;0) - Grade 2	7	99999		
Neutrophils (n=165;0) - Grade 3	0	99999		
Neutrophils (n=165;0) - Grade 4	2	99999		
Hemoglobin (n=191;1) - Grade 1	67	1		
Hemoglobin (n=191;1) - Grade 2	40	0		
Hemoglobin (n=191;1) - Grade 3	13	0		
Hemoglobin (n=191;1) - Grade 4	8	0		
Lymphopenia (n=187;1) - Grade 1	37	0		
Lymphopenia (n=187) - Grade 2	37	0		
Lymphopenia (n=187;1) - Grade 3	20	0		
Lymphopenia (n=187;1) - Grade 4	4	1		
Platelets (n=189;1) - Grade 1	48	0		
Platelets (n=189;1) - Grade 2	7	0		
Platelets (n=189;1) - Grade 3	7	0		
Platelets (n=189;1) - Grade 4	17	1		
Leukocytes (n=192;1) - Grade 1	40	1		
Leukocytes (n=192;1) - Grade 2	12	0		
Leukocytes (n=19;1) - Grade 3	2	0		
Leukocytes (n=192;1) - Grade 4	1	0		
INR (n=82;0) - Grade 1	17	99999		
INR (n=82;0) - Grade 2	1	99999		
INR (n=82;0) - Grade 3	11	99999		
INR (n=82;0) - Grade 4	0	99999		
ALT (n=174;1) - Grade 1	66	1		
ALT (n=174;1) - Grade 2	13	0		
ALT (n=174;1) - Grade 3	7	0		
ALT (n=174;1) - Grade 4	0	0		
Amylase (n=178;1) - Grade 1	39	1		
Amylase (n=178;1) - Grade 2	12	0		
Amylase (n=178;1) - Grade 3	8	0		
Amylase (n=178;1) - Grade 4	0	0		
AST (n=183;1) - Grade 1	88	1		
AST (n=183;1) - Grade 2	19	0		
AST (n=183;1) - Grade 3	6	0		
AST (n=183;1) - Grade 4	0	0		
Lipase (n=165;1) - Grade 1	32	0		
Lipase (n=165;1) - Grade 2	11	1		
Lipase (n=165;1) - Grade 3	28	0		
Lipase (n=165;1) - Grade 4	7	0		

Notes:

[26] - SAF

[27] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with ECOG performance status by 6-months time intervals

End point title	Number of subjects with ECOG performance status by 6-months time intervals[28]

End point description:

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

End point type	Primary

End point timeframe:

Up to 156 months

Notes:

[28] - 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: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified.

End point values	Sorafenib monotherapy	Sorafenib+Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[29]	1[30]		
Units: Subjects				
Months 1-6 (n=42;1) - Missing	2	0		
Months 1-6 (n=42;1) - ECOG 0	28	1		
Months 1-6 (n=42;1) - ECOG 1	11	0		
Months 1-6 (n=42;1) - ECOG 2	1	0		
Months 7-12 (n=38;1) - Missing	3	0		
Months 7-12 (n=38;1) - ECOG 0	29	1		
Months 7-12 (n=38;1) - ECOG 1	6	0		
Months 13-18 (n=33;1) - Missing	2	0		
Months 13-18 (n=33;1) - ECOG 0	22	1		
Months 13-18 (n=33;1) - ECOG 1	7	0		
Months 13-18 (n=33;1) - ECOG 2	1	0		
Months 13-18 (n=33;1) - ECOG 3	1	0		
Months 19-24 (n=28;1) - Missing	2	0		
Months 19-24 (n=28;1) - ECOG 0	15	1		
Months 19-24 (n=28;1) - ECOG 1	9	0		
Months 19-24 (n=28;1) - ECOG 2	1	0		
Months 19-24 (N=28;1) - ECOG 5	1	0		
Months 25-30 (n=23;1) - Missing	2	0		
Months 25-30 (n=23;1) - ECOG 0	13	1		
Months 25-30 (n=23;1) - ECOG 1	7	0		
Months 25-30 (n=23;1) - ECOG 5	1	0		
Months 31-36 (n=19;1) - Missing	1	0		
Months 31-36 (n=19;1) - ECOG 0	9	1		
Months 31-36 (n=19;1) - ECOG 1	8	0		
Months 31-36 (n=19;1) - ECOG 5	1	0		
Months 37-42 (n=19;1) - ECOG 0	10	1		
Months 37-42 (n=19;1) - ECOG 1	8	0		
Months 37-42 (n=19;1) - ECOG 5	1	0		
Months 43-48 (n=16;1) - ECOG 0	9	0		

Months 43-48 (n=16;1) - ECOG 1	6	0		
Months 43-48 (n=16;1) - ECOG 5	1	0		
Months 49-54 (n=13;1) - ECOG 0	7	0		
Months 49-54 (n=13;1) - ECOG 1	6	0		
Months 55-60 (n=19;1) - Missing	2	0		
Months 55-60 (n=19;1) - ECOG 0	11	0		
Months 55-60 (n=19;1) - ECOG 1	6	0		
Months 61-66 (n=15;1) - Missing	1	0		
Months 61-66 (n=15;1) - ECOG 0	8	0		
Months 61-66 (n=15;1) - ECOG 1	6	0		
Months 67-72 (n=14;1) - ECOG 0	8	0		
Months 67-72 (n=14;1) - ECOG 1	6	0		
Months 73-78 (n=13;1) - ECOG 0	7	0		
Months 73-78 (n=13;1) - ECOG 1	5	0		
Months 73-78 (n=13;1) - ECOG 2	1	0		
Months 79-84 (n=10;1) - ECOG 0	6	0		
Months 79-84 (n=10;1) - ECOG 1	4	0		
Months 85-90 (n=10;1) - ECOG 0	4	0		
Months 85-90 (n=10;1) - ECOG 1	5	0		
Months 85-90 (n=10;1) - ECOG 2	1	0		
Months 91-96 (n=9;1) - ECOG 0	5	0		
Months 91-96 (n=9;1) - ECOG 1	4	0		
Months 97-102 (n=8;1) - Missing	2	0		
Months 97-102 (n=8;1) - ECOG 0	4	0		
Months 97-102 (n=8;1) - ECOG 1	2	0		
Months 103-108 (n=5;1) - Missing	1	0		
Months 103-108 (n=5;1) - ECOG 0	1	0		
Months 103-108 (n=5;1) - ECOG 1	3	0		
Months 109-114 (n=3;1) - ECOG 0	1	0		
Months 109-114 (n=3;1) - ECOG 1	2	0		
Months 115-120 (n=3;1) - ECOG 0	2	0		
Months 115-120 (n=3;1) - ECOG 2	1	0		
Months 121-126 (n=3;1) - ECOG 0	1	0		
Months 121-126 (n=3;1) - ECOG 1	1	0		
Months 121-126 (n=3;1) - ECOG 2	1	0		
Months 127-132 (n=3;1) - ECOG 0	1	0		
Months 127-132 (n=3;1) - ECOG 1	2	0		
Months 133-138 (n=3;1) - ECOG 0	1	0		
Months 133-138 (n=3;1) - ECOG 1	2	0		
Months 139-144 (n=3;1) - ECOG 0	1	0		
Months 139-144 (n=3;1) - ECOG 1	1	0		
Months 139-144 (n=3;1) - ECOG 2	1	0		
Months 145-150 (n=3;1) - ECOG 0	1	0		
Months 145-150 (n=3;1) - ECOG 1	1	0		
Months 145-150 (n=3;1) - ECOG 2	1	0		
Months 151-156 (n=3;1) - ECOG 0	1	0		
Months 151-156 (n=3;1) - ECOG 1	1	0		
Months 151-156 (n=3;1) - ECOG 2	1	0		
Last available value (n=64;1) - Missing	9	0		
Last available value (n=64;1) - ECOG 0	20	1		
Last available value (n=64;1) - ECOG 1	25	0		
Last available value (n=64;1) - ECOG 2	4	0		

Last available value (n=64;1) - ECOG 3	1	0		
Last available value (n=64;1) - ECOG 5	5	0		

Notes:

[29] - SAF

[30] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing the ICF in STEP until 30 days after the last sorafenib dose, with a mean duration of 26 months

Adverse event reporting additional description:

Adverse event reporting for the numbers of deaths (all causes) considers all deaths that occurred at any time during the study until the end of the follow up (with a mean duration of 26 months); deaths resulting from adverse events considers both adverse events with CTCAE grade 5 and/or adverse events with outcome 'Fatal'.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Sorafenib+Erlotinib

Reporting group description:

Subjects received sorafenib and erlotinib combination at the same dose and schedule as in their original Clinical Trial.

Reporting group title	Sorafenib monotherapy

Reporting group description:

Subjects received single-agent sorafenib at the same dose and schedule as in their original Clinical Trial.

Serious adverse events	Sorafenib+Erlotinib	Sorafenib monotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	114 / 203 (56.16%)	
number of deaths (all causes)	0	62	
number of deaths resulting from adverse events	0	39	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone cancer metastatic			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			

subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	0 / 1 (0.00%)	4 / 203 (1.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemangioma			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver carcinoma ruptured			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of ampulla of Vater			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm recurrence			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine tumour of the lung metastatic			

subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 1 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 1 (100.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			

subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Stent placement			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 1 (0.00%)	6 / 203 (2.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 6	
Disease progression			
subjects affected / exposed	1 / 1 (100.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Impaired healing			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 1 (0.00%)	5 / 203 (2.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 5	
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 3	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)	4 / 203 (1.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			

subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 1 (0.00%)	4 / 203 (1.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	1 / 4	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Personality change			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Angiocardiogram			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological procedural complication			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac arrest			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 1 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 1 (100.00%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery stenosis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	0 / 1 (0.00%)	5 / 203 (2.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Basal ganglia infarction			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 1 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			

subjects affected / exposed	0 / 1 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Migraine			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	8 / 203 (3.94%)	
occurrences causally related to treatment / all	0 / 0	3 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 1 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)	4 / 203 (1.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 1 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 1 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 1 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 1 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			

subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoperitoneum			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1 (100.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			

subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hepatic function abnormal			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic lesion			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute kidney injury			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck mass			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
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 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 1 (100.00%)	0 / 203 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			

subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 1 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 1 (0.00%)	9 / 203 (4.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 3	
Perirectal abscess			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	0 / 1 (0.00%)	6 / 203 (2.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 3	
Staphylococcal infection			

subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spontaneous bacterial peritonitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 1 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 1 (0.00%)	2 / 203 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cachexia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypercalcaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 203 (0.49%)	
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: 1 %

Non-serious adverse events	Sorafenib+Erlotinib	Sorafenib monotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	151 / 203 (74.38%)	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences (all)	0	7	
Hypertension			
subjects affected / exposed	1 / 1 (100.00%)	26 / 203 (12.81%)	
occurrences (all)	2	26	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 1 (0.00%)	33 / 203 (16.26%)	
occurrences (all)	0	41	
Asthenia			
subjects affected / exposed	0 / 1 (0.00%)	6 / 203 (2.96%)	
occurrences (all)	0	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences (all)	0	3	
Dysphonia			
subjects affected / exposed	0 / 1 (0.00%)	4 / 203 (1.97%)	
occurrences (all)	0	4	
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)	5 / 203 (2.46%)	
occurrences (all)	0	5	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 1 (0.00%)	4 / 203 (1.97%)	
occurrences (all)	0	4	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	8 / 203 (3.94%)	
occurrences (all)	0	9	
Lipase increased			

subjects affected / exposed	0 / 1 (0.00%)	13 / 203 (6.40%)	
occurrences (all)	0	15	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	8 / 203 (3.94%)	
occurrences (all)	0	10	
Haemoglobin decreased			
subjects affected / exposed	0 / 1 (0.00%)	7 / 203 (3.45%)	
occurrences (all)	0	9	
Amylase increased			
subjects affected / exposed	0 / 1 (0.00%)	9 / 203 (4.43%)	
occurrences (all)	0	13	
Platelet count decreased			
subjects affected / exposed	0 / 1 (0.00%)	6 / 203 (2.96%)	
occurrences (all)	0	6	
Weight decreased			
subjects affected / exposed	0 / 1 (0.00%)	10 / 203 (4.93%)	
occurrences (all)	0	10	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences (all)	0	3	
Headache			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences (all)	0	3	
Lethargy			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences (all)	0	3	
Neuropathy peripheral			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 1 (0.00%)	5 / 203 (2.46%)	
occurrences (all)	0	5	
Thrombocytopenia			

subjects affected / exposed	0 / 1 (0.00%)	4 / 203 (1.97%)	
occurrences (all)	0	5	
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	15 / 203 (7.39%)	
occurrences (all)	0	16	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 1 (0.00%)	5 / 203 (2.46%)	
occurrences (all)	0	6	
Abdominal pain upper			
subjects affected / exposed	0 / 1 (0.00%)	5 / 203 (2.46%)	
occurrences (all)	0	13	
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)	8 / 203 (3.94%)	
occurrences (all)	0	18	
Ascites			
subjects affected / exposed	0 / 1 (0.00%)	4 / 203 (1.97%)	
occurrences (all)	0	4	
Diarrhoea			
subjects affected / exposed	0 / 1 (0.00%)	100 / 203 (49.26%)	
occurrences (all)	0	147	
Nausea			
subjects affected / exposed	0 / 1 (0.00%)	11 / 203 (5.42%)	
occurrences (all)	0	14	
Stomatitis			
subjects affected / exposed	0 / 1 (0.00%)	12 / 203 (5.91%)	
occurrences (all)	0	15	
Constipation			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences (all)	0	3	
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	6 / 203 (2.96%)	
occurrences (all)	0	10	
Skin and subcutaneous tissue disorders			
Acne			

subjects affected / exposed	1 / 1 (100.00%)	2 / 203 (0.99%)	
occurrences (all)	1	3	
Alopecia			
subjects affected / exposed	0 / 1 (0.00%)	11 / 203 (5.42%)	
occurrences (all)	0	12	
Dry skin			
subjects affected / exposed	0 / 1 (0.00%)	6 / 203 (2.96%)	
occurrences (all)	0	6	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 1 (100.00%)	82 / 203 (40.39%)	
occurrences (all)	1	96	
Pruritus			
subjects affected / exposed	0 / 1 (0.00%)	4 / 203 (1.97%)	
occurrences (all)	0	4	
Rash			
subjects affected / exposed	0 / 1 (0.00%)	16 / 203 (7.88%)	
occurrences (all)	0	19	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 1 (0.00%)	5 / 203 (2.46%)	
occurrences (all)	0	6	
Proteinuria			
subjects affected / exposed	0 / 1 (0.00%)	5 / 203 (2.46%)	
occurrences (all)	0	5	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences (all)	0	3	
Arthralgia			
subjects affected / exposed	0 / 1 (0.00%)	6 / 203 (2.96%)	
occurrences (all)	0	10	
Muscle spasms			

subjects affected / exposed	0 / 1 (0.00%)	5 / 203 (2.46%)	
occurrences (all)	0	7	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 1 (0.00%)	16 / 203 (7.88%)	
occurrences (all)	0	16	
Hypocalcaemia			
subjects affected / exposed	0 / 1 (0.00%)	5 / 203 (2.46%)	
occurrences (all)	0	8	
Hypophosphataemia			
subjects affected / exposed	0 / 1 (0.00%)	3 / 203 (1.48%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2011	Global amendment 02 forming integrated protocol Version 3.0 introduced the following changes: An inclusion criterion was added to allow subjects who received combination treatment with sorafenib (Nexavar) and TACE (transarterial chemoembolization) in their originating study to be eligible for this extension study. The exclusion criterion regarding concurrent anti-cancer chemotherapy was, therefore, modified to clarify that the exclusion did not apply to subjects being treated with sorafenib in combination with TACE.
30 March 2012	Global amendment 03 forming integrated protocol Version 4.0 introduced the following changes: 1. Inclusion of an Evaluation of Overall Survival. 2. Inclusion of safety as a stated objective with the main objective of this program remained unchanged.
25 March 2014	Global amendment 04 forming integrated protocol Version 5.0 introduced the following changes: 1. Removal of all references to erlotinib. 2. Removal of references to placebo in association with sorafenib administration. 3. Addition of TACE to the permissible anticancer chemotherapies and addition of guidance on Sorafenib dose modification in combination with TACE. 4.Clarification of which CTC version was used for the grading of liver function abnormalities.
15 May 2018	Global amendment 07 forming integrated protocol Version 6.0 introduced the following changes: 1. Overall survival (OS) evaluation removed from the study objectives. 2. Safety visits were modified. 3. Laboratory evaluations were modified. 4. Follow-up period was changed.
26 May 2020	Global amendment 08 forming integrated protocol Version 7.0 introduced the following changes: 1. Added Post-Trial Access Program. 2. Removal of the instructions for dose modifications for the combination of sorafenib with capecitabine and TACE. 3. Added clarification for continuation on study drug. 4. Added clarification for ending the study. 5. Added clarification on last patient last visit date. 6. The timepoint of the performance of the analyses was corrected, last patient last visit was changed to “after the end of the study”.

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.

No primary endpoints were defined specifically for study STEP as the primary purpose of this study was to enable patients to continue sorafenib treatment. The 26-month long-term follow-up duration was the mean follow-up duration for the subjects.

Notes: