Clinical trial results:
A Randomized, Multi-Center, Blinded, Placebo-Controlled Study of Mapatumumab ([HGS1012], a Fully Human Monoclonal Antibody to TRAIL-R1) in Combination with Sorafenib as a First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma

Summary

EudraCT number	2010-020798-17
Trial protocol	DE
Global end of trial date	29 November 2017

Results information

Result version number	v1 (current)
This version publication date	12 December 2018
First version publication date	12 December 2018

Trial information

Trial identification

Sponsor protocol code	200149

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.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 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.

Protection of trial subjects:

A suggested pre-medication regimen of diphenhydramine and acetaminophen administered within 1 hour prior to the start of the mapatumumab/placebo dose in order minimize infusion/hypersensitivity reactions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 February 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Romania: 38
Country: Number of subjects enrolled	Russian Federation: 20
Country: Number of subjects enrolled	Ukraine: 16
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	101
EEA total number of subjects	54

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)	61
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase 2, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mapatumumab in combination with sorafenib in participants with advanced hepatocellular carcinoma.

Pre-assignment

Screening details:

A total of 217 participants were screened of which 116 were screen failures and 101 participants were randomized in a ratio of 1:1 to any one of the 2 treatment arms. The study was conducted at 29 centers in 6 countries.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sorafenib+Placebo

Arm description:

Participants received sorafenib 400 milligrams (mg) orally twice daily continuously in each 21-day cycle. Placebo was administered via the intravenous route on Day 1 of each 21-day cycle. The treatments were administered until radiologic disease progression or unacceptable toxicity

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

Dosage and administration details:

Sorafenib was administered at a dose of 400 mg twice daily without food (at least 1 hour before or 2 hours after a meal).

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

Dosage and administration details:

Two hundred and fifty milliliters of normal saline was administered as intravenous infusion. Placebo was administered via the intravenous route on Day 1 of each 21-day cycle.

Arm title	Sorafenib+Mapatumumab 30 mg/kg

Arm description:

Participants received sorafenib 400 mg orally twice daily continuously in each 21-day cycle. Mapatumumab 30 milligrams per kilogram (mg/kg) was administered via the intravenous route on Day 1 of each 21-day cycle. The treatments were administered until radiologic disease progression or unacceptable toxicity.

Arm type	Experimental

Investigational medicinal product name	Mapatumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Mapatumumab was available as a lyophilized formulation in sterile, single-use 10 milliliter (mL) vials containing 100 mg mapatumumab. Mapatumumab was administered at a dose of 30 mg/kg via the intravenous route on Day 1 of each 21-day cycle.

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

Dosage and administration details:

Sorafenib was administered at a dose of 400 mg twice daily without food (at least 1 hour before or 2 hours after a meal).

Number of subjects in period 1	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg
Started	51	50
Completed	30	31
Not completed	21	19
Clinical progression	1	-
Adverse event, serious fatal	4	7
Metastatic Hepatocellular Carcinoma	1	-
Physician decision	6	1
Consent withdrawn by subject	6	5
Adverse event, non-fatal	2	3
Lack of compliance	1	-
Sponsor decision	-	1
Lost to follow-up	-	1
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Sorafenib+Placebo
Reporting group description:	
Participants received sorafenib 400 milligrams (mg) orally twice daily continuously in each 21-day cycle. Placebo was administered via the intravenous route on Day 1 of each 21-day cycle. The treatments were administered until radiologic disease progression or unacceptable toxicity	
Reporting group title	Sorafenib+Mapatumumab 30 mg/kg
Reporting group description:	
Participants received sorafenib 400 mg orally twice daily continuously in each 21-day cycle. Mapatumumab 30 milligrams per kilogram (mg/kg) was administered via the intravenous route on Day 1 of each 21-day cycle. The treatments were administered until radiologic disease progression or unacceptable toxicity.	

Reporting group values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg	Total
Number of subjects	51	50	101
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	28	33	61
From 65-84 years	23	17	40
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	60.8	60.0	
standard deviation	± 13.36	± 11.93	-
Sex: Female, Male Units: Subjects			
Female	12	24	36
Male	39	26	65
Race/Ethnicity, Customized Units: Subjects			
White/Caucasian – European Heritage	48	48	96
Asian–East Asian Heritage	1	0	1
Black or African American	2	2	4

End points

End points reporting groups

Reporting group title	Sorafenib+Placebo

Reporting group description:

Participants received sorafenib 400 milligrams (mg) orally twice daily continuously in each 21-day cycle. Placebo was administered via the intravenous route on Day 1 of each 21-day cycle. The treatments were administered until radiologic disease progression or unacceptable toxicity

Reporting group title	Sorafenib+Mapatumumab 30 mg/kg

Reporting group description:

Participants received sorafenib 400 mg orally twice daily continuously in each 21-day cycle. Mapatumumab 30 milligrams per kilogram (mg/kg) was administered via the intravenous route on Day 1 of each 21-day cycle. The treatments were administered until radiologic disease progression or unacceptable toxicity.

Primary: Time to progression-Blinded independent central review (BICR) assessment

End point title	Time to progression-Blinded independent central review (BICR) assessment

End point description:

Time to progression is defined as the time from randomization to radiologic disease progression based on blinded independent review (BICR) of imaging scans using modified Response Evaluation Criteria in Solid Tumors assessment (mRECIST) for hepatocellular carcinoma. The primary analysis was performed using Kaplan Meier methods. The median time to progression is reported with one-sided 90% confidence interval. Analysis was performed on the modified Intent to Treat (mITT) Population which comprised of all randomized participants who received at least part of 1 dose of study agent (mapatumumab/placebo and/or sorafenib) with participants analyzed according to the groups to which they were randomized. 99999 indicates upper limit was not measurable as one-sided confidence interval is presented. Only those participants who had their BICR scans read were included in the analysis.

End point type	Primary

End point timeframe:

Randomization to maximum of 24.1 months

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[1]	45[2]		
Units: Months				
median (confidence interval 90%)	5.6 (4.3 to 99999)	4.1 (2.8 to 99999)		

Notes:

[1] - mITT Population

[2] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio comparing mapatumumab to placebo obtained from Cox proportional hazards model with covariate adjustment for Barcelona Clinic Liver Cancer and ECOG performance status.

Comparison groups	Sorafenib+Placebo v Sorafenib+Mapatumumab 30 mg/kg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7382 [3]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.192
Confidence interval	
level	90 %
sides	1-sided
upper limit	1.737

Notes:

[3] - P-value for comparison of treatment groups obtained from stratified log-rank test-stratified by Barcelona Clinic Liver Cancer and Eastern Cooperative Oncology Group (ECOG) performance status.

Secondary: Time to progression-Investigator assessment

End point title	Time to progression-Investigator assessment

End point description:

Time to progression is defined as the time from randomization to radiologic disease progression. The primary analysis was performed using Kaplan Meier methods based on application of mRECIST for hepatocellular carcinoma to investigator assessments. The median time to progression is reported with one-sided 90% confidence interval. 99999 indicates upper limit was not measurable as one-sided confidence interval is presented.

End point type	Secondary

End point timeframe:

Randomization to maximum of 52.9 months

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[4]	50[5]		
Units: Months				
median (confidence interval 90%)	8.3 (5.4 to 99999)	6.4 (5.4 to 99999)		

Notes:

[4] - mITT Population

[5] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio comparing mapatumumab to placebo obtained from Cox proportional hazards model with covariate adjustment for Barcelona Clinic Liver Cancer and ECOG performance status.

Comparison groups	Sorafenib+Placebo v Sorafenib+Mapatumumab 30 mg/kg

Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3156 [6]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.922
Confidence interval	
level	90 %
sides	1-sided
upper limit	1.288

Notes:

[6] - P-value for comparison of treatment groups obtained from stratified log-rank test-stratified by Barcelona Clinic Liver Cancer and Eastern Cooperative Oncology Group (ECOG) performance status.

Secondary: Median overall survival

End point title	Median overall survival

End point description:

Overall survival is defined as time from randomization to death from any cause. The analysis was performed using Kaplan Meier methods. The median overall survival is reported with one-sided 90% confidence interval. 99999 indicates upper limit was not measurable as one-sided confidence interval is presented.

End point type	Secondary

End point timeframe:

Randomization to maximum of 52.9 months

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[7]	50[8]		
Units: Months				
median (confidence interval 90%)	10.1 (8.9 to 99999)	10.0 (7.3 to 99999)		

Notes:

[7] - mITT Population

[8] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio comparing mapatumumab to placebo obtained from Cox proportional hazards model with covariate adjustment for Barcelona Clinic Liver Cancer and ECOG performance status.

Comparison groups	Sorafenib+Placebo v Sorafenib+Mapatumumab 30 mg/kg
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6121 [9]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.007

Confidence interval	
level	90 %
sides	1-sided
upper limit	1.346

Notes:

[9] - P-value for comparison of treatment groups obtained from stratified log-rank test-stratified by Barcelona Clinic Liver Cancer and ECOG performance status.

Secondary: Progression free survival-BICR assessment

End point title	Progression free survival-BICR assessment

End point description:

Progression free survival is defined as time from randomization to radiologic disease progression or death from any cause. The analysis was performed using Kaplan Meier methods using BICR assessment of imaging scans. The median progression free survival is reported with one-sided 90% confidence interval. 99999 indicates upper limit was not measurable as one-sided confidence interval is presented. Only those participants who had their BICR scans read were included in the analysis.

End point type	Secondary

End point timeframe:

Randomization to maximum of 24.1 months

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[10]	45[11]		
Units: Months				
median (confidence interval 90%)	4.3 (3.1 to 99999)	3.2 (2.7 to 99999)		

Notes:

[10] - mITT Population

[11] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio comparing Mapatumumab to placebo obtained from Cox proportional hazards model with covariate adjustment for Barcelona Clinic Liver Cancer and ECOG performance status.

Comparison groups	Sorafenib+Placebo v Sorafenib+Mapatumumab 30 mg/kg
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6925 [12]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.066
Confidence interval	
level	90 %
sides	1-sided
upper limit	1.43

Notes:

[12] - P-value for comparison of treatment groups obtained from stratified log-rank test - stratified by Barcelona Clinic Liver Cancer and ECOG performance status.

Secondary: Progression free survival-Investigator assessment

End point title	Progression free survival-Investigator assessment

End point description:

Progression free survival is defined as time from randomization to radiologic disease progression or death from any cause. The analysis was performed using Kaplan Meier methods based on application of mRECIST for hepatocellular carcinoma to investigator assessments. The median progression free survival is reported with one-sided 90% confidence interval. 99999 indicates upper limit was not measurable as one-sided confidence interval is presented.

End point type	Secondary

End point timeframe:

Randomization to maximum of 52.9 months

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[13]	50[14]		
Units: Months				
median (confidence interval 90%)	5.4 (3.6 to 99999)	4.0 (3.4 to 99999)		

Notes:

[13] - mITT Population

[14] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio comparing Mapatumumab to placebo obtained from Cox proportional hazards model with covariate adjustment for Barcelona Clinic Liver Cancer and ECOG performance status.

Comparison groups	Sorafenib+Placebo v Sorafenib+Mapatumumab 30 mg/kg
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3088 [15]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.909
Confidence interval	
level	90 %
sides	1-sided
upper limit	1.191

Notes:

[15] - P-value for comparison of treatment groups obtained from stratified log-rank test - stratified by Barcelona Clinic Liver Cancer and ECOG performance status.

Secondary: Percentage of participants with objective response-BICR assessment

End point title	Percentage of participants with objective response-BICR assessment

End point description:

Objective response rate is defined as the percentage of participants with complete response+partial response according to mRECIST criteria for hepatocellular carcinoma using BICR assessment of imaging scans. The percentage of participants with objective response is reported along with 95% confidence interval. Only those participants who had their BICR scans read and having available assessment for best response were analyzed.

End point type	Secondary

End point timeframe:

Randomization to maximum of 24.1 months

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[16]	39[17]		
Units: Percentage of participants				
number (confidence interval 95%)	12.5 (4.2 to 26.8)	17.9 (7.5 to 33.5)		

Notes:

[16] - mITT Population

[17] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Sorafenib+Placebo v Sorafenib+Mapatumumab 30 mg/kg
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5458 [18]
Method	Fisher exact
Parameter estimate	Response rate difference
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.8
upper limit	26.6

Notes:

[18] - Nominal P-value for comparison of treatment groups obtained from Fisher's exact test.

Secondary: Percentage of participants with objective response-Investigator assessment

End point title	Percentage of participants with objective response-Investigator assessment

End point description:

Objective response rate is defined as the percentage of participants with complete response+partial response according to mRECIST criteria for hepatocellular carcinoma to investigator assessments. The percentage of participants with objective response is reported along with 95% confidence interval. Only those participants with available assessment for best response were analyzed.

End point type	Secondary

End point timeframe:

Randomization to maximum of 52.9 months

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[19]	48[20]		
Units: Percentage of participants				
number (confidence interval 95%)	7.8 (2.2 to 18.9)	14.6 (6.1 to 27.8)		

Notes:

[19] - mITT Population

[20] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Sorafenib+Placebo v Sorafenib+Mapatumumab 30 mg/kg
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3479 [21]
Method	Fisher exact
Parameter estimate	Response rate difference
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	26.2

Notes:

[21] - Nominal P-value for comparison of treatment groups obtained from Fisher's exact test.

Secondary: Percentage of participants with disease control-BICR assessment

End point title	Percentage of participants with disease control-BICR assessment

End point description:

Disease control rate is the percentage of participants with complete response+partial response+stable disease according to mRECIST criteria for hepatocellular carcinoma. The end point was based on BICR assessment of imaging scans. The percentage of participants with disease control is presented along with 95% confidence interval. Only those participants who had their BICR scans read and having available assessment for best response were analyzed.

End point type	Secondary

End point timeframe:

Randomization to maximum of 24.1 months

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[22]	39[23]		
Units: Percentage of participants				
number (confidence interval 95%)	92.5 (79.6 to 98.4)	71.8 (55.1 to 85.0)		

Notes:

[22] - mITT Population

[23] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Sorafenib+Placebo v Sorafenib+Mapatumumab 30 mg/kg
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0198 [24]
Method	Fisher exact
Parameter estimate	Disease control rate difference
Point estimate	-20.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.8
upper limit	1.8

Notes:

[24] - Nominal P-value for comparison of treatment groups obtained from Fisher's exact test.

Secondary: Percentage of participants with disease control-Investigator assessment

End point title	Percentage of participants with disease control-Investigator assessment

End point description:

Disease control rate is the percentage of participants with complete response+partial response+stable disease according to mRECIST criteria for hepatocellular carcinoma to investigator assessments. The percentage of participants with disease control is presented along with 95% confidence interval. Only those participants with available assessment for best response were analyzed.

End point type	Secondary

End point timeframe:

Randomization to maximum of 52.9 months

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[25]	48[26]		
Units: Percentage of participants				
number (confidence interval 95%)	74.5 (60.4 to 85.7)	68.8 (53.7 to 81.3)		

Notes:
[25] - mITT Population
[26] - mITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Sorafenib+Placebo v Sorafenib+Mapatumumab 30 mg/kg
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6558 [27]
Method	Fisher exact
Parameter estimate	Disease control rate difference
Point estimate	-5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.4
upper limit	13.8

Notes:
[27] - Nominal P-value for comparison of treatment groups obtained from Fisher's exact test.

Secondary: Time to response-BICR assessment

End point title	Time to response-BICR assessment

End point description:

Time to response is defined as time from randomization to first partial response or complete response in responders only. Complete Response (CR): Disappearance of intratumoral arterial enhancement in all target lesions. Partial Response (PR): At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions. Only responders were included in the analysis.

End point type	Secondary

End point timeframe:

Randomization to maximum of 24.1 months

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[28]	7[29]		
Units: Days				
median (full range (min-max))	44 (41 to 85)	48 (41 to 188)		

Notes:
[28] - mITT Population
[29] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response-BICR assessment

End point title	Duration of response-BICR assessment

End point description:

Duration of response is defined as time from first PR or CR to radiologic disease progression; in responders only. CR: Disappearance of intratumoral arterial enhancement in all target lesions. PR: At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the Baseline sum of the diameters of target lesions. Progressive disease (PD): An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started. Only responders were included in the analysis.

End point type	Secondary

End point timeframe:

Randomization to maximum of 24.1 months

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[30]	7[31]		
Units: Days				
median (full range (min-max))	123 (55 to 325)	127 (42 to 372)		

Notes:

[30] - mITT Population

[31] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with treatment-emergent non-serious adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of participants with treatment-emergent non-serious adverse events (AEs) and serious adverse events (SAEs)

End point description:

An AE is any unfavorable or unintended sign, symptom, or disease that is temporally associated with the use of a study agent but is not necessarily caused by the study agent. An SAE is an adverse event resulting in any of the following outcomes: death, life-threatening, inpatient hospitalization, prolongation of an existing hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect or other medically important events that may jeopardize the participant or may require intervention to prevent one of the other outcomes mentioned before. A treatment-emergent AE is an AE that emerged during treatment, having been absent pre-treatment, or worsened relative to the pre-treatment state. As-Treated Population comprised of participants who received at least part of 1 dose of study agent analyzed according to the treatment that they actually received.

End point type	Secondary

End point timeframe:

Start of study treatment to maximum of 52.9 months

End point values	Sorafenib+Placebo	Sorafenib+Map atumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[32]	50[33]		
Units: Participants				
Non-serious AEs|	47	49		
SAEs|	27	21		

Notes:

[32] - As-Treated Population

[33] - As-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with severe AEs

End point title	Number of participants with severe AEs

End point description:

An AE is any unfavorable or unintended sign, symptom, or disease that is temporally associated with the use of a study agent but is not necessarily caused by the study agent. Severity of AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0. Grade 1 represents mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 represents moderate; minimal, local or non-invasive intervention indicated. Grade 3 represents severe or medically significant but not immediately life -threatening; hospitalization or prolongation of hospitalization indicated; disabling. Grade 4 represents life –threatening consequences; urgent intervention indicated. Grade 5 represents death related to AE. Severe AE is defined as AEs classified by investigator as severe (causing inability to carry out usual activities), life threatening or fatal using NCI-CTCAE Version 4.0 grading.

End point type	Secondary

End point timeframe:

Start of study treatment to maximum of 52.9 months

End point values	Sorafenib+Placebo	Sorafenib+Map atumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[34]	50[35]		
Units: Participants	42	38		

Notes:

[34] - As-Treated Population

[35] - As-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with worst toxicity grade-chemistry parameters

End point title	Number of participants with worst toxicity grade-chemistry parameters

End point description:

Blood samples were collected for the evaluation of following chemistry parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), amylase, bilirubin, gamma glutamyl transferase (GGT), calcium, potassium, magnesium, albumin, sodium and

creatinine. Laboratory toxicities were graded based on NCI-CTCAE version 4.0. Grade 1 represents mild; asymptomatic or mild symptoms. Grade 2 represents moderate; minimal, local or non-invasive intervention indicated. Grade 3 represents severe or medically significant but not immediately life - threatening; hospitalization or prolongation of hospitalization indicated; disabling. Grade 4 represents life –threatening consequences; urgent intervention indicated. Number of participants with worst toxicity grades for any abnormalities observed in any chemistry parameters during study is presented. Only participants with data available at specified time points were analyzed (indicated by n=X in category titles).

End point type	Secondary
End point timeframe:	
Enrolment to maximum of 52.9 months	

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[36]	50[37]		
Units: Participants				
ALT increased; Grade 0, n=51, 50|	6	4		
ALT increased; Grade 1, n=51, 50|	30	28		
ALT increased; Grade 2, n=51, 50|	8	9		
ALT increased; Grade 3, n=51, 50|	7	9		
ALT increased; Grade 4, n=51, 50|	0	0		
AST increased; Grade 0, n=51, 50|	1	1		
AST increased; Grade 1, n=51, 50|	23	20		
AST increased; Grade 2, n=51, 50|	10	9		
AST increased; Grade 3, n=51, 50|	16	20		
AST increased; Grade 4, n=51, 50|	1	0		
ALP increased; Grade 0, n=51, 50|	4	8		
ALP increased; Grade 1, n=51, 50|	31	26		
ALP increased; Grade 2, n=51, 50|	11	11		
ALP increased; Grade 3, n=51, 50|	5	5		
ALP increased; Grade 4, n=51, 50|	0	0		
Amylase increased; Grade 0, n=51, 50|	30	22		
Amylase increased; Grade 1, n=51, 50|	9	17		
Amylase increased; Grade 2, n=51, 50|	5	8		
Amylase increased; Grade 3, n=51, 50|	6	3		
Amylase increased; Grade 4, n=51, 50|	1	0		
Bilirubin increased; Grade 0, n=51, 50|	12	9		
Bilirubin increased; Grade 1, n=51, 50|	15	10		
Bilirubin increased; Grade 2, n=51, 50|	17	16		
Bilirubin increased; Grade 3, n=51, 50|	7	13		
Bilirubin increased; Grade 4, n=51, 50|	0	2		
GGT increased; Grade 0, n=51, 50|	1	2		
GGT increased; Grade 1, n=51, 50|	10	13		
GGT increased; Grade 2, n=51, 50|	14	15		
GGT increased; Grade 3, n=51, 50|	23	18		
GGT increased; Grade 4, n=51, 50|	3	2		
Hypercalcemia; Grade 0, n=49, 47|	37	37		
Hypercalcemia; Grade 1, n=49, 47|	11	9		
Hypercalcemia; Grade 2, n=49, 47|	1	0		

Hypercalcemia; Grade 3, n=49, 47|	0	0		
Hypercalcemia; Grade 4, n=49, 47|	0	1		
Hyperkalemia; Grade 0; n=51, 50|	36	27		
Hyperkalemia; Grade 1; n=51, 50|	2	3		
Hyperkalemia; Grade 2; n=51, 50|	10	10		
Hyperkalemia; Grade 3; n=51, 50|	0	7		
Hyperkalemia; Grade 4; n=51, 50|	3	3		
Hypermagnesemia; Grade 0; n=51, 50|	29	28		
Hypermagnesemia; Grade 1; n=51, 50|	21	19		
Hypermagnesemia; Grade 2; n=51, 50|	0	0		
Hypermagnesemia; Grade 3; n=51, 50|	1	3		
Hypermagnesemia; Grade 4; n=51, 50|	0	0		
Hypernatremia; Grade 0, n=51, 50|	18	18		
Hypernatremia; Grade 1, n=51, 50|	16	14		
Hypernatremia; Grade 2, n=51, 50|	0	0		
Hypernatremia; Grade 3, n=51, 50|	16	15		
Hypernatremia; Grade 4, n=51, 50|	1	3		
Hypoalbuminemia; Grade 0, n=51, 50|	22	26		
Hypoalbuminemia; Grade 1, n=51, 50|	10	9		
Hypoalbuminemia; Grade 2, n=51, 50|	18	14		
Hypoalbuminemia; Grade 3, n=51, 50|	1	1		
Hypoalbuminemia; Grade 4, n=51, 50|	0	0		
Hypocalcemia; Grade 0, n=50, 50|	16	15		
Hypocalcemia; Grade 1, n=50, 50|	8	14		
Hypocalcemia; Grade 2, n=50, 50|	18	19		
Hypocalcemia; Grade 3, n=50, 50|	6	2		
Hypocalcemia; Grade 4, n=50, 50|	2	0		
Hypokalemia; Grade 0, n=51, 50|	37	41		
Hypokalemia; Grade 1, n=51, 50|	11	8		
Hypokalemia; Grade 2, n=51, 50|	0	0		
Hypokalemia; Grade 3, n=51, 50|	1	1		
Hypokalemia; Grade 4, n=51, 50|	2	0		
Hypomagnesemia; Grade 0, n=51, 50|	30	35		
Hypomagnesemia; Grade 1, n=51, 50|	19	13		
Hypomagnesemia; Grade 2, n=51, 50|	2	1		
Hypomagnesemia; Grade 3, n=51, 50|	0	0		
Hypomagnesemia; Grade 4, n=51, 50|	0	1		
Hyponatremia; Grade 0, n=49, 47|	40	32		
Hyponatremia; Grade 1, n=49, 47|	5	10		
Hyponatremia; Grade 2, n=49, 47|	2	3		
Hyponatremia; Grade 3, n=49, 47|	2	2		
Hyponatremia; Grade 4, n=49, 47|	0	0		
Lipase increased; Grade 0, n=51, 50|	19	13		
Lipase increased; Grade 1, n=51, 50|	5	6		
Lipase increased; Grade 2, n=51, 50|	8	8		
Lipase increased; Grade 3, n=51, 50|	16	17		
Lipase increased; Grade 4, n=51, 50|	3	6		
Renal: Creatinine increased; Grade 0, n=51, 50|	36	34		
Renal: Creatinine increased; Grade 1, n=51, 50|	7	12		
Renal: Creatinine increased; Grade 2, n=51, 50|	8	3		

Renal: Creatinine increased; Grade 3, n=51, 50|	0	1		
Renal: Creatinine increased; Grade 4, n=51, 50|	0	0		

Notes:

[36] - As-Treated Population

[37] - As-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with worst toxicity grade-hematology parameters

End point title	Number of participants with worst toxicity grade-hematology parameters

End point description:

Blood samples were collected for assessment of the following hematology parameters: activated partial thromboplastin time (APTT), hemoglobin, international normalized ratio (INR), lymphocytes, neutrophils, platelets and white blood cells (WBC). Laboratory toxicities were graded based on the NCI-CTCAE version 4.0. Grade 1 represents mild; asymptomatic or mild symptoms. Grade 2 represents moderate; minimal, local or non-invasive intervention indicated. Grade 3 represents severe or medically significant but not immediately life -threatening; hospitalization or prolongation of hospitalization indicated; disabling. Grade 4 represents life –threatening consequences; urgent intervention indicated. Number of participants with worst toxicity grades for any abnormalities observed in any hematology parameters during the study is presented. Only participants with data available at specified time points were analyzed (indicated by n=X in category titles).

End point type	Secondary

End point timeframe:

Enrolment to maximum of 52.9 months

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[38]	50[39]		
Units: Participants				
APTT prolonged; Grade 0, n=51, 50|	24	22		
APTT prolonged; Grade 1, n=51, 50|	19	24		
APTT prolonged; Grade 2, n=51, 50|	6	2		
APTT prolonged; Grade 3, n=51, 50|	2	2		
APTT prolonged; Grade 4, n=51, 50|	0	0		
Anemia; Grade 0, n=51, 50|	13	9		
Anemia; Grade 1, n=51, 50|	23	22		
Anemia; Grade 2, n=51, 50|	9	16		
Anemia; Grade 3, n=51, 50|	6	3		
Anemia; Grade 4, n=51, 50|	0	0		
Hemoglobin increased; Grade 0, n=46, 44|	46	44		
Hemoglobin increased; Grade 1, n=46, 44|	0	0		
Hemoglobin increased; Grade 2, n=46, 44|	0	0		
Hemoglobin increased; Grade 3, n=46, 44|	0	0		

Hemoglobin increased; Grade 4, n=46, 44|	0	0		
INR increased; Grade 0, n=51, 50|	2	3		
INR increased; Grade 1, n=51, 50|	35	30		
INR increased; Grade 2, n=51, 50|	12	14		
INR increased; Grade 3, n=51, 50|	2	3		
INR increased; Grade 4, n=51, 50|	0	0		
Lymphocytes decreased; Grade 0, n=51, 50|	24	23		
Lymphocytes decreased; Grade 1, n=51, 50|	3	0		
Lymphocytes decreased; Grade 2, n=51, 50|	16	18		
Lymphocytes decreased; Grade 3, n=51, 50|	8	8		
Lymphocytes decreased; Grade 4, n=51, 50|	0	1		
Lymphocytes increased; Grade 0, n=51, 49|	49	45		
Lymphocytes increased; Grade 1, n=51, 49|	0	0		
Lymphocytes increased; Grade 2, n=51, 49|	2	4		
Lymphocytes increased; Grade 3, n=51, 49|	0	0		
Lymphocytes increased; Grade 4, n=51, 49|	0	0		
Neutrophil count decreased; Grade 0, n=51, 50|	39	37		
Neutrophil count decreased; Grade 1, n=51, 50|	3	2		
Neutrophil count decreased; Grade 2, n=51, 50|	8	7		
Neutrophil count decreased; Grade 3, n=51, 50|	1	1		
Neutrophil count decreased; Grade 4, n=51, 50|	0	3		
Platelets decreased; Grade 0, n=51, 50|	21	21		
Platelets decreased; Grade 1, n=51, 50|	12	16		
Platelets decreased; Grade 2, n=51, 50|	10	6		
Platelets decreased; Grade 3, n=51, 50|	7	5		
Platelets decreased; Grade 4, n=51, 50|	1	2		
WBC decreased; Grade 0, n=51, 50|	33	30		
WBC decreased; Grade 1, n=51, 50|	10	12		
WBC decreased; Grade 2, n=51, 50|	8	5		
WBC decreased; Grade 3, n=51, 50|	0	3		
WBC decreased; Grade 4, n=51, 50|	0	0		

Notes:

[38] - As-Treated Population

[39] - As-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with anti-mapatumumab antibodies

End point title	Number of participants with anti-mapatumumab antibodies[40]

End point description:

Blood samples were collected for the assessment of serum antibodies. The presence of anti-mapatumumab antibodies was assessed using a validated electrochemiluminescent immunoassay. The assay incorporated a tiered testing approach which used screening and confirmation steps. The anti-drug antibody (ADA) confirmed positive participants were separated into transient or persistent antibody positives. Persistent positive refers to positive immunogenic response at 2 or more assessments or at the final assessment. Transient positive refers to positive immunogenic response at only 1 assessment and negative at the final assessment. Only participants with an available immunogenicity assay were analyzed.

End point type	Secondary

End point timeframe:

Randomization to maximum of 24.1 months

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Sorafenib+Mapatumumab 30 mg/kg was included in the analysis.

End point values	Sorafenib+Mapatumumab 30 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	49[41]			
Units: Participants				
Transient positive|	6			
Persistent positive|	7			
Negative|	36			

Notes:

[41] - As-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP)

End point title	Change from Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP)

End point description:

SBP and DBP were obtained on Day 1 of each cycle. Baseline is the last assessment prior to first dose. Change from Baseline is the value at indicated time point minus the value at Baseline. 99999 indicates data was not available due to insufficient number of participants. Only those participants with data available at specified time points were analyzed (indicated by n=X in category titles).

End point type	Secondary

End point timeframe:

Baseline and Day 1 of Cycles 2 to 75 (each cycle of 21 days)

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[42]	50[43]		
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
SBP; Cycle 2 Day 1, n=46, 44|	2.3 (± 14.13)	2.2 (± 18.64)		
SBP; CYCLE 3 DAY 1, n=39, 35|	6.0 (± 16.81)	4.1 (± 13.66)		
SBP; CYCLE 4; DAY 1; n=33, 32|	2.1 (± 15.57)	5.3 (± 13.52)		
SBP; CYCLE 5 DAY 1; n=27, 26|	1.7 (± 13.05)	4.9 (± 16.42)		
SBP; CYCLE 6 DAY 1; n=24, 22|	1.3 (± 12.14)	5.1 (± 13.40)		
SBP; CYCLE 7 DAY 1; n=24, 22|	-0.8 (± 11.02)	5.0 (± 12.78)		
SBP; CYCLE 8 DAY 1; n=22, 21|	-1.6 (± 11.48)	5.2 (± 14.83)		
SBP; CYCLE 9 DAY 1; n=19, 16|	1.2 (± 16.37)	7.8 (± 13.98)		
SBP; CYCLE 10 DAY 1; n=18, 16|	1.4 (± 16.57)	4.5 (± 16.19)		
SBP; CYCLE 11 DAY 1; n=16, 15|	2.4 (± 18.82)	5.2 (± 18.32)		
SBP; CYCLE 12 DAY 1; n=15, 13|	2.7 (± 12.34)	5.2 (± 14.73)		
SBP; CYCLE 13 DAY 1; n=13, 12|	2.3 (± 12.26)	3.0 (± 14.91)		
SBP; CYCLE 14 DAY 1; n=12, 12|	-1.0 (± 10.13)	4.0 (± 14.63)		
SBP; CYCLE 15 DAY 1; n=10, 9|	1.4 (± 8.21)	6.7 (± 21.05)		
SBP; CYCLE 16 DAY 1; n=10, 9|	1.8 (± 5.79)	7.9 (± 15.28)		
SBP; CYCLE 17 DAY 1; n=8, 8|	1.3 (± 11.95)	10.1 (± 17.70)		
SBP; CYCLE 18 DAY 1; n=8, 8|	-2.0 (± 9.26)	9.5 (± 19.41)		
SBP; CYCLE 19 DAY 1; n=6, 8|	-4.8 (± 14.93)	8.4 (± 20.68)		
SBP; CYCLE 20 DAY 1; n=6, 8|	1.2 (± 9.13)	5.8 (± 19.33)		
SBP; CYCLE 21 DAY 1; n=4, 8|	2.5 (± 8.23)	10.0 (± 21.23)		
SBP; CYCLE 22 DAY 1; n=4, 8|	6.0 (± 10.55)	5.5 (± 14.11)		
SBP; CYCLE 23 DAY 1; n=4, 8|	-1.0 (± 10.80)	12.9 (± 20.15)		
SBP; CYCLE 24 DAY 1; n=4, 8|	-3.0 (± 6.38)	5.6 (± 19.86)		
SBP; CYCLE 25 DAY 1; n=4, 8|	1.3 (± 12.20)	11.3 (± 20.08)		
SBP; CYCLE 26 DAY 1; n=4, 7|	6.0 (± 11.89)	9.3 (± 22.92)		
SBP; CYCLE 27 DAY 1; n=4, 5|	3.3 (± 10.44)	8.4 (± 18.04)		
SBP; CYCLE 28 DAY 1; n=4, 5|	3.3 (± 7.41)	5.2 (± 20.19)		
SBP; CYCLE 29 DAY 1; n=3, 4|	-0.7 (± 14.29)	3.3 (± 24.27)		
SBP; CYCLE 30 DAY 1; n=3, 4|	2.7 (± 6.43)	-2.3 (± 13.43)		
SBP; CYCLE 31 DAY 1; n=3, 4|	-3.0 (± 11.79)	2.0 (± 23.15)		
SBP; CYCLE 32 DAY 1; n=3, 4|	5.0 (± 4.58)	3.3 (± 16.40)		
SBP; CYCLE 33 DAY 1; n=2, 4|	0.0 (± 14.14)	-5.3 (± 19.96)		
SBP; CYCLE 34 DAY 1; n=1, 4|	13.0 (± 99999)	-5.3 (± 10.66)		
SBP; CYCLE 35 DAY 1; n=0, 4|	99999 (± 99999)	-5.0 (± 15.81)		
SBP; CYCLE 36 DAY 1; n=0, 4|	99999 (± 99999)	-1.5 (± 13.00)		
SBP; CYCLE 37 DAY 1; n=0, 3|	99999 (± 99999)	-6.0 (± 23.52)		
SBP; CYCLE 38 DAY 1; n=0, 3|	99999 (± 99999)	-1.3 (± 18.04)		
SBP; CYCLE 39 DAY 1; n=0, 3|	99999 (± 99999)	-4.3 (± 21.01)		
SBP; CYCLE 40 DAY 1; n=0, 2|	99999 (± 99999)	-12.5 (± 10.61)		
SBP; CYCLE 41 DAY 1; n=0, 2|	99999 (± 99999)	-15.0 (± 21.21)		

SBP; CYCLE 42 DAY 1; n=0, 2|	99999 (± 99999)	-7.5 (± 17.68)		
SBP; CYCLE 43 DAY 1; n=0, 2|	99999 (± 99999)	-17.5 (± 17.68)		
SBP; CYCLE 44 DAY 1; n=0, 2|	99999 (± 99999)	-10.0 (± 14.14)		
SBP; CYCLE 45 DAY 1; n=0, 2|	99999 (± 99999)	-17.5 (± 17.68)		
SBP; CYCLE 46 DAY 1; n=0, 2|	99999 (± 99999)	-5.0 (± 21.21)		
SBP; CYCLE 47 DAY 1; n=0, 2|	99999 (± 99999)	-17.5 (± 17.68)		
SBP; CYCLE 48 DAY 1; n=0, 2|	99999 (± 99999)	-5.0 (± 21.21)		
SBP; CYCLE 49 DAY 1; n=0, 2|	99999 (± 99999)	-17.5 (± 17.68)		
SBP; CYCLE 50 DAY 1; n=0, 2|	99999 (± 99999)	-15.0 (± 21.21)		
SBP; CYCLE 51 DAY 1; n=0, 2|	99999 (± 99999)	-10.0 (± 21.21)		
SBP; CYCLE 52 DAY 1; n=0, 2|	99999 (± 99999)	-17.5 (± 17.68)		
SBP; CYCLE 53 DAY 1; n=0, 2|	99999 (± 99999)	-20.0 (± 14.14)		
SBP; CYCLE 54 DAY 1; n=0, 2|	99999 (± 99999)	-10.0 (± 14.14)		
SBP; CYCLE 55 DAY 1; n=0, 1|	99999 (± 99999)	-30.0 (± 99999)		
SBP; CYCLE 56 DAY 1; n=0, 1|	99999 (± 99999)	-30.0 (± 99999)		
SBP; CYCLE 57 DAY 1; n=0, 1|	99999 (± 99999)	-30.0 (± 99999)		
SBP; CYCLE 58 DAY 1; n=0, 1|	99999 (± 99999)	-25.0 (± 99999)		
SBP; CYCLE 59 DAY 1; n=0, 1|	99999 (± 99999)	-20.0 (± 99999)		
SBP; CYCLE 60 DAY 1; n=0, 1|	99999 (± 99999)	-30.0 (± 99999)		
SBP; CYCLE 61 DAY 1; n=0, 1|	99999 (± 99999)	-25.0 (± 99999)		
SBP; CYCLE 62 DAY 1; n=0, 1|	99999 (± 99999)	-23.0 (± 99999)		
SBP; CYCLE 63 DAY 1; n=0, 1|	99999 (± 99999)	-28.0 (± 99999)		
SBP; CYCLE 64 DAY 1; n=0, 1|	99999 (± 99999)	-25.0 (± 99999)		
SBP; CYCLE 65 DAY 1; n=0, 1|	99999 (± 99999)	-26.0 (± 99999)		
SBP; CYCLE 66 DAY 1; n=0, 1|	99999 (± 99999)	-32.0 (± 99999)		
SBP; CYCLE 67 DAY 1; n=0, 1|	99999 (± 99999)	-33.0 (± 99999)		
SBP; CYCLE 68 DAY 1; n=0, 1|	99999 (± 99999)	-32.0 (± 99999)		
SBP; CYCLE 69 DAY 1; n=0, 1|	99999 (± 99999)	-31.0 (± 99999)		
SBP; CYCLE 70 DAY 1; n=0, 1|	99999 (± 99999)	-25.0 (± 99999)		
SBP; CYCLE 71 DAY 1; n=0, 1|	99999 (± 99999)	-28.0 (± 99999)		
SBP; CYCLE 72 DAY 1; n=0, 1|	99999 (± 99999)	-30.0 (± 99999)		

SBP; CYCLE 73 DAY 1; n=0, 1|	99999 (± 99999)	-27.0 (± 99999)		
SBP; CYCLE 74 DAY 1; n=0, 1|	99999 (± 99999)	-30.0 (± 99999)		
SBP; CYCLE 75 DAY 1; n=0, 1|	99999 (± 99999)	-28.0 (± 99999)		
DBP; Cycle 2 Day 1, n=46, 44|	-0.6 (± 8.51)	0.7 (± 9.82)		
DBP; CYCLE 3 DAY 1, n=39, 35|	2.1 (± 7.20)	1.4 (± 8.90)		
DBP; CYCLE 4; DAY 1; n=33, 32|	1.8 (± 10.52)	2.4 (± 8.22)		
DBP; CYCLE 5 DAY 1; n=27, 26|	0.9 (± 10.00)	3.0 (± 15.49)		
DBP; CYCLE 6 DAY 1; n=24, 22|	3.5 (± 8.32)	1.2 (± 10.21)		
DBP; CYCLE 7 DAY 1; n=24, 22|	0.5 (± 8.57)	2.0 (± 7.42)		
DBP; CYCLE 8 DAY 1; n=22, 21|	0.5 (± 7.37)	2.3 (± 8.27)		
DBP; CYCLE 9 DAY 1; n=19, 16|	2.7 (± 8.67)	4.1 (± 9.15)		
DBP; CYCLE 10 DAY 1; n=18, 16|	2.7 (± 9.81)	2.4 (± 7.50)		
DBP; CYCLE 11 DAY 1; n=16, 15|	-0.1 (± 10.25)	0.9 (± 9.49)		
DBP; CYCLE 12 DAY 1; n=15, 13|	0.6 (± 7.80)	2.1 (± 8.65)		
DBP; CYCLE 13 DAY 1; n=13, 12|	-2.2 (± 6.07)	-2.7 (± 7.64)		
DBP; CYCLE 14 DAY 1; n=12, 12|	0.7 (± 6.87)	3.3 (± 11.78)		
DBP; CYCLE 15 DAY 1; n=10, 9|	2.1 (± 8.49)	1.1 (± 12.97)		
DBP; CYCLE 16 DAY 1; n=10, 9|	0.1 (± 7.68)	0.1 (± 11.88)		
DBP; CYCLE 17 DAY 1; n=8, 8|	-1.5 (± 8.23)	5.0 (± 7.15)		
DBP; CYCLE 18 DAY 1; n=8, 8|	0.1 (± 6.47)	3.4 (± 11.15)		
DBP; CYCLE 19 DAY 1; n=6, 8|	-2.5 (± 5.82)	5.5 (± 12.17)		
DBP; CYCLE 20 DAY 1; n=6, 8|	2.3 (± 3.83)	3.5 (± 10.09)		
DBP; CYCLE 21 DAY 1; n=4, 8|	0.8 (± 2.99)	2.8 (± 11.96)		
DBP; CYCLE 22 DAY 1; n=4, 8|	-1.8 (± 3.95)	3.8 (± 7.63)		
DBP; CYCLE 23 DAY 1; n=4, 8|	2.5 (± 4.20)	5.1 (± 12.12)		
DBP; CYCLE 24 DAY 1; n=4, 8|	-3.0 (± 11.17)	2.5 (± 12.99)		
DBP; CYCLE 25 DAY 1; n=4, 8|	3.5 (± 3.11)	2.5 (± 15.80)		
DBP; CYCLE 26 DAY 1; n=4, 7|	0.0 (± 3.27)	4.0 (± 14.57)		
DBP; CYCLE 27 DAY 1; n=4, 5|	-3.3 (± 4.72)	3.6 (± 11.67)		
DBP; CYCLE 28 DAY 1; n=4, 5|	2.0 (± 1.63)	4.0 (± 14.21)		
DBP; CYCLE 29 DAY 1; n=3, 4|	1.7 (± 10.41)	-2.0 (± 7.26)		
DBP; CYCLE 30 DAY 1; n=3, 4|	-0.3 (± 4.04)	-2.3 (± 6.60)		
DBP; CYCLE 31 DAY 1; n=3, 4|	6.7 (± 7.64)	0.5 (± 11.45)		
DBP; CYCLE 32 DAY 1; n=3, 4|	2.7 (± 7.51)	-0.3 (± 7.76)		
DBP; CYCLE 33 DAY 1; n=2, 4|	0.5 (± 7.78)	-2.5 (± 8.50)		
DBP; CYCLE 34 DAY 1; n=1, 4|	-15.0 (± 99999)	-1.8 (± 6.99)		
DBP; CYCLE 35 DAY 1; n=0, 4|	99999 (± 99999)	-3.0 (± 8.12)		
DBP; CYCLE 36 DAY 1; n=0, 4|	99999 (± 99999)	1.5 (± 3.00)		
DBP; CYCLE 37 DAY 1; n=0, 3|	99999 (± 99999)	1.7 (± 12.58)		
DBP; CYCLE 38 DAY 1; n=0, 3|	99999 (± 99999)	-2.3 (± 6.81)		
DBP; CYCLE 39 DAY 1; n=0, 3|	99999 (± 99999)	0.3 (± 10.50)		
DBP; CYCLE 40 DAY 1; n=0, 2|	99999 (± 99999)	0.0 (± 0.00)		
DBP; CYCLE 41 DAY 1; n=0, 2|	99999 (± 99999)	-7.5 (± 3.54)		
DBP; CYCLE 42 DAY 1; n=0, 2|	99999 (± 99999)	0.0 (± 0.00)		

DBP; CYCLE 43 DAY 1; n=0, 2|	99999 (± 99999)	-7.5 (± 3.54)		
DBP; CYCLE 44 DAY 1; n=0, 2|	99999 (± 99999)	-2.5 (± 3.54)		
DBP; CYCLE 45 DAY 1; n=0, 2|	99999 (± 99999)	-7.5 (± 3.54)		
DBP; CYCLE 46 DAY 1; n=0, 2|	99999 (± 99999)	-5.0 (± 7.07)		
DBP; CYCLE 47 DAY 1; n=0, 2|	99999 (± 99999)	-3.0 (± 24.04)		
DBP; CYCLE 48 DAY 1; n=0, 2|	99999 (± 99999)	-5.0 (± 7.07)		
DBP; CYCLE 49 DAY 1; n=0, 2|	99999 (± 99999)	-12.5 (± 3.54)		
DBP; CYCLE 50 DAY 1; n=0, 2|	99999 (± 99999)	-5.0 (± 7.07)		
DBP; CYCLE 51 DAY 1; n=0, 2|	99999 (± 99999)	-5.0 (± 7.07)		
DBP; CYCLE 52 DAY 1; n=0, 2|	99999 (± 99999)	-10.0 (± 7.07)		
DBP; CYCLE 53 DAY 1; n=0, 2|	99999 (± 99999)	-7.5 (± 3.54)		
DBP; CYCLE 54 DAY 1; n=0, 2|	99999 (± 99999)	-5.0 (± 7.07)		
DBP; CYCLE 55 DAY 1; n=0, 1|	99999 (± 99999)	-15.0 (± 99999)		
DBP; CYCLE 56 DAY 1; n=0, 1|	99999 (± 99999)	-10.0 (± 99999)		
DBP; CYCLE 57 DAY 1; n=0, 1|	99999 (± 99999)	-15.0 (± 99999)		
DBP; CYCLE 58 DAY 1; n=0, 1|	99999 (± 99999)	-10.0 (± 99999)		
DBP; CYCLE 59 DAY 1; n=0, 1|	99999 (± 99999)	-10.0 (± 99999)		
DBP; CYCLE 60 DAY 1; n=0, 1|	99999 (± 99999)	-15.0 (± 99999)		
DBP; CYCLE 61 DAY 1; n=0, 1|	99999 (± 99999)	-15.0 (± 99999)		
DBP; CYCLE 62 DAY 1; n=0, 1|	99999 (± 99999)	-13.0 (± 99999)		
DBP; CYCLE 63 DAY 1; n=0, 1|	99999 (± 99999)	-15.0 (± 99999)		
DBP; CYCLE 64 DAY 1; n=0, 1|	99999 (± 99999)	-14.0 (± 99999)		
DBP; CYCLE 65 DAY 1; n=0, 1|	99999 (± 99999)	-15.0 (± 99999)		
DBP; CYCLE 66 DAY 1; n=0, 1|	99999 (± 99999)	-17.0 (± 99999)		
DBP; CYCLE 67 DAY 1; n=0, 1|	99999 (± 99999)	-14.0 (± 99999)		
DBP; CYCLE 68 DAY 1; n=0, 1|	99999 (± 99999)	-15.0 (± 99999)		
DBP; CYCLE 69 DAY 1; n=0, 1|	99999 (± 99999)	-17.0 (± 999999)		
DBP; CYCLE 70 DAY 1; n=0, 1|	99999 (± 99999)	-16.0 (± 99999)		
DBP; CYCLE 71 DAY 1; n=0, 1|	99999 (± 99999)	-15.0 (± 99999)		
DBP; CYCLE 72 DAY 1; n=0, 1|	99999 (± 99999)	-19.0 (± 99999)		
DBP; CYCLE 73 DAY 1; n=0, 1|	99999 (± 99999)	-15.0 (± 99999)		

DBP; CYCLE 74 DAY 1; n=0, 1|	99999 (± 99999)	-14.0 (± 99999)		
DBP; CYCLE 75 DAY 1; n=0, 1|	99999 (± 99999)	-17.0 (± 99999)		

Notes:

[42] - As-Treated Population

[43] - As-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate

End point title	Change from Baseline in heart rate

End point description:

Heart rate was obtained on Day 1 of each cycle. Baseline is the last assessment prior to first dose. Change from Baseline is the value at indicated time point minus the value at Baseline. 99999 indicates data was not available due to insufficient number of participants. Only those participants with data available at specified time points were analyzed (indicated by n=X in category titles).

End point type	Secondary

End point timeframe:

Baseline and Day 1 of Cycles 2 to 75 (each cycle of 21 days)

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[44]	50[45]		
Units: Beats per minute				
arithmetic mean (standard deviation)				
Cycle 2 Day 1, n=46, 44|	0.7 (± 8.32)	-1.8 (± 9.42)		
CYCLE 3 DAY 1, n=39, 35|	1.7 (± 7.69)	-1.6 (± 6.78)		
CYCLE 4; DAY 1; n=33, 32|	1.0 (± 10.09)	1.9 (± 7.61)		
CYCLE 5 DAY 1; n=27, 26|	1.3 (± 9.45)	0.2 (± 10.65)		
CYCLE 6 DAY 1; n=24, 22|	0.2 (± 10.37)	0.3 (± 8.31)		
CYCLE 7 DAY 1; n=24, 22|	2.0 (± 8.40)	-1.8 (± 8.80)		
CYCLE 8 DAY 1; n=22, 21|	0.5 (± 7.70)	-0.4 (± 7.30)		
CYCLE 9 DAY 1; n=19, 16|	2.1 (± 8.04)	0.3 (± 7.10)		
CYCLE 10 DAY 1; n=18, 16|	2.3 (± 8.62)	0.5 (± 13.54)		
CYCLE 11 DAY 1; n=16, 15|	-0.8 (± 6.51)	-2.0 (± 9.88)		
CYCLE 12 DAY 1; n=15, 13|	-0.7 (± 4.28)	0.2 (± 9.92)		
CYCLE 13 DAY 1; n=13, 12|	0.9 (± 5.47)	0.9 (± 9.77)		
CYCLE 14 DAY 1; n=12, 12|	1.6 (± 7.03)	3.1 (± 10.25)		
CYCLE 15 DAY 1; n=10, 9|	5.6 (± 12.39)	2.2 (± 8.51)		
CYCLE 16 DAY 1; n=10, 9|	3.3 (± 7.06)	0.7 (± 9.12)		
CYCLE 17 DAY 1; n=8, 8|	3.1 (± 7.20)	1.6 (± 10.23)		
CYCLE 18 DAY 1; n=8, 8|	6.4 (± 8.68)	-0.5 (± 6.12)		
CYCLE 19 DAY 1; n=6, 8|	-2.5 (± 10.54)	0.5 (± 9.78)		
CYCLE 20 DAY 1; n=6, 8|	0.3 (± 6.38)	0.9 (± 7.36)		
CYCLE 21 DAY 1; n=4, 8|	0.5 (± 1.91)	-1.4 (± 10.28)		
CYCLE 22 DAY 1; n=4, 8|	0.5 (± 1.91)	3.0 (± 13.41)		

CYCLE 23 DAY 1; n=4, 8|	-3.8 (± 6.02)	2.9 (± 9.76)		
CYCLE 24 DAY 1; n=4, 8|	-2.5 (± 5.97)	2.9 (± 10.92)		
CYCLE 25 DAY 1; n=4, 8|	-1.8 (± 2.06)	0.3 (± 11.13)		
CYCLE 26 DAY 1; n=4, 7|	-0.5 (± 1.91)	1.6 (± 11.43)		
CYCLE 27 DAY 1; n=4, 5|	-2.0 (± 2.31)	2.4 (± 11.70)		
CYCLE 28 DAY 1; n=4, 5|	-1.8 (± 5.56)	-0.2 (± 13.68)		
CYCLE 29 DAY 1; n=3, 4|	0.0 (± 4.00)	-3.8 (± 6.45)		
CYCLE 30 DAY 1; n=3, 4|	0.3 (± 2.08)	-9.3 (± 5.25)		
CYCLE 31 DAY 1; n=3, 4|	-2.7 (± 6.43)	-0.8 (± 8.77)		
CYCLE 32 DAY 1; n=3, 4|	2.0 (± 4.00)	-3.8 (± 6.65)		
CYCLE 33 DAY 1; n=2, 4|	-2.0 (± 0.00)	-5.5 (± 7.55)		
CYCLE 34 DAY 1; n=1, 4|	0.0 (± 99999)	-3.5 (± 4.43)		
CYCLE 35 DAY 1; n=0, 4|	99999 (± 99999)	-4.8 (± 4.99)		
CYCLE 36 DAY 1; n=0, 4|	99999 (± 99999)	-8.0 (± 8.37)		
CYCLE 37 DAY 1; n=0, 3|	99999 (± 99999)	-9.3 (± 6.11)		
CYCLE 38 DAY 1; n=0, 3|	99999 (± 99999)	-2.0 (± 6.93)		
CYCLE 39 DAY 1; n=0, 3|	99999 (± 99999)	-4.7 (± 6.43)		
CYCLE 40 DAY 1; n=0, 2|	99999 (± 99999)	-4.0 (± 8.49)		
CYCLE 41 DAY 1; n=0, 2|	99999 (± 99999)	-7.0 (± 9.90)		
CYCLE 42 DAY 1; n=0, 2|	99999 (± 99999)	-2.0 (± 8.49)		
CYCLE 43 DAY 1; n=0, 2|	99999 (± 99999)	-6.0 (± 14.14)		
CYCLE 44 DAY 1; n=0, 2|	99999 (± 99999)	-2.0 (± 14.14)		
CYCLE 45 DAY 1; n=0, 2|	99999 (± 99999)	-4.0 (± 14.14)		
CYCLE 46 DAY 1; n=0, 2|	99999 (± 99999)	-3.0 (± 18.38)		
CYCLE 47 DAY 1; n=0, 2|	99999 (± 99999)	-2.0 (± 14.14)		
CYCLE 48 DAY 1; n=0, 2|	99999 (± 99999)	-3.0 (± 15.56)		
CYCLE 49 DAY 1; n=0, 2|	99999 (± 99999)	-9.0 (± 9.90)		
CYCLE 50 DAY 1; n=0, 2|	99999 (± 99999)	-5.0 (± 9.90)		
CYCLE 51 DAY 1; n=0, 2|	99999 (± 99999)	-5.0 (± 12.73)		
CYCLE 52 DAY 1; n=0, 2|	99999 (± 99999)	-8.0 (± 11.31)		
CYCLE 53 DAY 1; n=0, 2|	99999 (± 99999)	-10.0 (± 2.83)		
CYCLE 54 DAY 1; n=0, 2|	99999 (± 99999)	-2.0 (± 8.49)		
CYCLE 55 DAY 1; n=0, 1|	99999 (± 99999)	-10.0 (± 99999)		
CYCLE 56 DAY 1; n=0, 1|	99999 (± 99999)	-12.0 (± 99999)		
CYCLE 57 DAY 1; n=0, 1|	99999 (± 99999)	-10.0 (± 99999)		
CYCLE 58 DAY 1; n=0, 1|	99999 (± 99999)	-8.0 (± 99999)		

CYCLE 59 DAY 1; n=0, 1|	99999 (± 99999)	-12.0 (± 99999)		
CYCLE 60 DAY 1; n=0, 1|	99999 (± 99999)	-10.0 (± 99999)		
CYCLE 61 DAY 1; n=0, 1|	99999 (± 99999)	-12.0 (± 99999)		
CYCLE 62 DAY 1; n=0, 1|	99999 (± 99999)	-14.0 (± 99999)		
CYCLE 63 DAY 1; n=0, 1|	99999 (± 99999)	-15.0 (± 99999)		
CYCLE 64 DAY 1; n=0, 1|	99999 (± 99999)	-10.0 (± 99999)		
CYCLE 65 DAY 1; n=0, 1|	99999 (± 99999)	-11.0 (± 99999)		
CYCLE 66 DAY 1; n=0, 1|	99999 (± 99999)	-12.0 (± 99999)		
CYCLE 67 DAY 1; n=0, 1|	99999 (± 99999)	-9.0 (± 99999)		
CYCLE 68 DAY 1; n=0, 1|	99999 (± 99999)	-10.0 (± 99999)		
CYCLE 69 DAY 1; n=0, 1|	99999 (± 99999)	-12.0 (± 99999)		
CYCLE 70 DAY 1; n=0, 1|	99999 (± 99999)	-9.0 (± 99999)		
CYCLE 71 DAY 1; n=0, 1|	99999 (± 99999)	-7.0 (± 99999)		
CYCLE 72 DAY 1; n=0, 1|	99999 (± 99999)	-10.0 (± 99999)		
CYCLE 73 DAY 1; n=0, 1|	99999 (± 99999)	-9.0 (± 99999)		
CYCLE 74 DAY 1; n=0, 1|	99999 (± 99999)	-8.0 (± 99999)		
CYCLE 75 DAY 1; n=0, 1|	99999 (± 99999)	-9.0 (± 99999)		

Notes:

[44] - As-Treated Population

[45] - As-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in temperature

End point title	Change from Baseline in temperature

End point description:

Temperature was obtained on Day 1 of each cycle. Baseline is the last assessment prior to first dose. Change from Baseline is the value at indicated time point minus the value at Baseline. 99999 indicates data was not available due to insufficient number of participants. Only those participants with data available at specified time points were analyzed (indicated by n=X in category titles).

End point type	Secondary

End point timeframe:

Baseline and Day 1 of Cycles 2 to 75 (each cycle of 21 days)

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[46]	50[47]		
Units: Celsius				
arithmetic mean (standard deviation)				
Cycle 2 Day 1, n=46, 43|	0.02 (± 0.288)	-0.02 (± 0.242)		
CYCLE 3 DAY 1, n=39, 35|	-0.01 (± 0.374)	-0.11 (± 0.340)		
CYCLE 4; DAY 1; n=33, 32|	0.02 (± 0.354)	-0.05 (± 0.298)		
CYCLE 5 DAY 1; n=27, 26|	0.05 (± 0.374)	-0.04 (± 0.218)		
CYCLE 6 DAY 1; n=23, 22|	-0.05 (± 0.374)	-0.07 (± 0.223)		
CYCLE 7 DAY 1; n=24, 22|	0.03 (± 0.334)	-0.10 (± 0.408)		
CYCLE 8 DAY 1; n=21, 21|	0.01 (± 0.460)	0.02 (± 0.161)		
CYCLE 9 DAY 1; n=19, 16|	0.04 (± 0.493)	0.00 (± 0.171)		
CYCLE 10 DAY 1; n=18, 16|	0.05 (± 0.539)	0.04 (± 0.200)		
CYCLE 11 DAY 1; n=16, 15|	-0.02 (± 0.468)	-0.09 (± 0.181)		
CYCLE 12 DAY 1; n=15, 13|	0.00 (± 0.270)	0.02 (± 0.245)		
CYCLE 13 DAY 1; n=13, 12|	0.00 (± 0.354)	0.03 (± 0.176)		
CYCLE 14 DAY 1; n=12, 12|	0.13 (± 0.380)	-0.04 (± 0.219)		
CYCLE 15 DAY 1; n=10, 9|	0.11 (± 0.420)	-0.13 (± 0.269)		
CYCLE 16 DAY 1; n=10, 9|	0.01 (± 0.318)	-0.04 (± 0.174)		
CYCLE 17 DAY 1; n=8, 8|	0.00 (± 0.227)	0.05 (± 0.076)		
CYCLE 18 DAY 1; n=8, 8|	-0.14 (± 0.346)	-0.09 (± 0.189)		
CYCLE 19 DAY 1; n=6, 8|	-0.10 (± 0.456)	0.10 (± 0.207)		
CYCLE 20 DAY 1; n=6, 8|	-0.02 (± 0.397)	0.01 (± 0.146)		
CYCLE 21 DAY 1; n=4, 8|	0.13 (± 0.411)	-0.01 (± 0.304)		
CYCLE 22 DAY 1; n=4, 8|	0.17 (± 0.206)	0.00 (± 0.193)		
CYCLE 23 DAY 1; n=4, 8|	0.03 (± 0.299)	0.13 (± 0.231)		
CYCLE 24 DAY 1; n=4, 8|	0.18 (± 0.171)	0.06 (± 0.119)		
CYCLE 25 DAY 1; n=4, 8|	0.20 (± 0.432)	0.00 (± 0.185)		
CYCLE 26 DAY 1; n=4, 7|	0.15 (± 0.129)	-0.01 (± 0.308)		
CYCLE 27 DAY 1; n=4, 5|	0.18 (± 0.171)	0.10 (± 0.173)		
CYCLE 28 DAY 1; n=4, 5|	0.15 (± 0.208)	-0.02 (± 0.179)		
CYCLE 29 DAY 1; n=3, 4|	0.13 (± 0.153)	-0.02 (± 0.275)		
CYCLE 30 DAY 1; n=3, 4|	0.10 (± 0.173)	0.00 (± 0.082)		
CYCLE 31 DAY 1; n=3, 4|	-0.07 (± 0.351)	0.05 (± 0.265)		
CYCLE 32 DAY 1; n=3, 4|	0.10 (± 0.173)	-0.05 (± 0.265)		
CYCLE 33 DAY 1; n=2, 4|	0.30 (± 0.424)	-0.07 (± 0.222)		

CYCLE 34 DAY 1; n=1, 4|	0.30 (± 99999)	-0.20 (± 0.283)		
CYCLE 35 DAY 1; n=0, 4|	99999 (± 99999)	-0.05 (± 0.058)		
CYCLE 36 DAY 1; n=0, 4|	99999 (± 99999)	-0.07 (± 0.150)		
CYCLE 37 DAY 1; n=0, 3|	99999 (± 99999)	-0.30 (± 0.458)		
CYCLE 38 DAY 1; n=0, 3|	99999 (± 99999)	0.00 (± 0.100)		
CYCLE 39 DAY 1; n=0, 3|	99999 (± 99999)	-0.07 (± 0.058)		
CYCLE 40 DAY 1; n=0, 2|	99999 (± 99999)	0.00 (± 0.00)		
CYCLE 41 DAY 1; n=0, 2|	99999 (± 99999)	-0.10 (± 0.141)		
CYCLE 42 DAY 1; n=0, 2|	99999 (± 99999)	0.05 (± 0.071)		
CYCLE 43 DAY 1; n=0, 2|	99999 (± 99999)	-0.05 (± 0.212)		
CYCLE 44 DAY 1; n=0, 2|	99999 (± 99999)	0.00 (± 0.141)		
CYCLE 45 DAY 1; n=0, 2|	99999 (± 99999)	0.00 (± 0.283)		
CYCLE 46 DAY 1; n=0, 2|	99999 (± 99999)	-0.05 (± 0.071)		
CYCLE 47 DAY 1; n=0, 2|	99999 (± 99999)	0.05 (± 0.212)		
CYCLE 48 DAY 1; n=0, 2|	99999 (± 99999)	0.00 (± 0.000)		
CYCLE 49 DAY 1; n=0, 2|	99999 (± 99999)	-0.05 (± 0.212)		
CYCLE 50 DAY 1; n=0, 2|	99999 (± 99999)	0.00 (± 0.141)		
CYCLE 51 DAY 1; n=0, 2|	99999 (± 99999)	-0.05 (± 0.071)		
CYCLE 52 DAY 1; n=0, 2|	99999 (± 99999)	-0.10 (± 0.141)		
CYCLE 53 DAY 1; n=0, 2|	99999 (± 99999)	0.05 (± 0.071)		
CYCLE 54 DAY 1; n=0, 2|	99999 (± 99999)	-0.05 (± 0.071)		
CYCLE 55 DAY 1; n=0, 1|	99999 (± 99999)	-0.20 (± 99999)		
CYCLE 56 DAY 1; n=0, 1|	99999 (± 99999)	-0.10 (± 99999)		
CYCLE 57 DAY 1; n=0, 1|	99999 (± 99999)	0.00 (± 99999)		
CYCLE 58 DAY 1; n=0, 1|	99999 (± 99999)	-0.10 (± 99999)		
CYCLE 59 DAY 1; n=0, 1|	99999 (± 99999)	0.00 (± 99999)		
CYCLE 60 DAY 1; n=0, 1|	99999 (± 99999)	-0.10 (± 99999)		
CYCLE 61 DAY 1; n=0, 1|	99999 (± 99999)	-0.10 (± 99999)		
CYCLE 62 DAY 1; n=0, 1|	99999 (± 99999)	0.00 (± 99999)		
CYCLE 63 DAY 1; n=0, 1|	99999 (± 99999)	-0.10 (± 99999)		
CYCLE 64 DAY 1; n=0, 1|	99999 (± 99999)	-0.10 (± 99999)		

CYCLE 65 DAY 1; n=0, 1|	99999 (± 99999)	0.00 (± 99999)		
CYCLE 66 DAY 1; n=0, 1|	99999 (± 99999)	-0.20 (± 99999)		
CYCLE 67 DAY 1; n=0, 1|	99999 (± 99999)	-0.10 (± 99999)		
CYCLE 68 DAY 1; n=0, 1|	99999 (± 99999)	0.00 (± 99999)		
CYCLE 69 DAY 1; n=0, 1|	99999 (± 99999)	-0.20 (± 99999)		
CYCLE 70 DAY 1; n=0, 1|	99999 (± 99999)	0.00 (± 99999)		
CYCLE 71 DAY 1; n=0, 1|	99999 (± 99999)	-0.10 (± 99999)		
CYCLE 72 DAY 1; n=0, 1|	99999 (± 99999)	-0.20 (± 99999)		
CYCLE 73 DAY 1; n=0, 1|	99999 (± 99999)	-0.10 (± 99999)		
CYCLE 74 DAY 1; n=0, 1|	99999 (± 99999)	-0.20 (± 99999)		
CYCLE 75 DAY 1; n=0, 1|	99999 (± 99999)	-0.10 (± 99999)		

Notes:

[46] - As-Treated Population

[47] - As-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in respiratory rate

End point title	Change from Baseline in respiratory rate

End point description:

Respiratory rate was obtained on Day 1 of each cycle. Baseline is the last assessment prior to first dose. Change from Baseline is the value at indicated time point minus the value at Baseline. 99999 indicates data was not available due to insufficient number of participants. Only those participants with data available at specified time points were analyzed (indicated by n=X in category titles).

End point type	Secondary

End point timeframe:

Baseline and Day 1 of Cycles 2 to 75 (each cycle of 21 days)

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[48]	50[49]		
Units: Breaths per minute				
arithmetic mean (standard deviation)				
CYCLE 2 Day 1, n=46, 44|	-0.1 (± 1.62)	0.1 (± 1.31)		
CYCLE 3 DAY 1, n=39, 35|	0.2 (± 2.34)	-0.2 (± 1.71)		
CYCLE 4; DAY 1; n=32, 32|	0.2 (± 1.79)	-0.3 (± 1.45)		
CYCLE 5 DAY 1; n=26, 26|	-0.1 (± 1.86)	-0.3 (± 1.50)		
CYCLE 6 DAY 1; n=24, 22|	0.5 (± 2.15)	-0.3 (± 1.88)		
CYCLE 7 DAY 1; n=24, 22|	-0.1 (± 2.09)	-0.2 (± 1.74)		

CYCLE 8 DAY 1; n=21, 21|	0.6 (± 1.78)	-0.1 (± 1.59)		
CYCLE 9 DAY 1; n=19, 16|	-0.5 (± 1.98)	-0.2 (± 2.04)		
CYCLE 10 DAY 1; n=18, 16|	-1.7 (± 2.95)	-0.4 (± 2.03)		
CYCLE 11 DAY 1; n=16, 15|	-0.8 (± 1.97)	-0.8 (± 2.21)		
CYCLE 12 DAY 1; n=15, 13|	0.0 (± 2.48)	-1.0 (± 2.45)		
CYCLE 13 DAY 1; n=13, 12|	-0.2 (± 1.69)	-0.7 (± 2.67)		
CYCLE 14 DAY 1; n=12, 12|	0.4 (± 2.43)	-1.0 (± 2.52)		
CYCLE 15 DAY 1; n=10, 9|	-0.5 (± 1.65)	-0.9 (± 3.06)		
CYCLE 16 DAY 1; n=10, 9|	-0.5 (± 1.72)	-0.9 (± 2.76)		
CYCLE 17 DAY 1; n=8, 8|	0.0 (± 2.20)	0.1 (± 1.81)		
CYCLE 18 DAY 1; n=8, 8|	-0.4 (± 2.07)	0.4 (± 1.60)		
CYCLE 19 DAY 1; n=6, 8|	0.7 (± 1.37)	0.0 (± 1.51)		
CYCLE 20 DAY 1; n=6, 8|	0.2 (± 0.75)	0.0 (± 1.60)		
CYCLE 21 DAY 1; n=4, 8|	0.8 (± 0.96)	-0.1 (± 1.64)		
CYCLE 22 DAY 1; n=4, 8|	0.0 (± 0.00)	-0.1 (± 1.36)		
CYCLE 23 DAY 1; n=4, 8|	0.5 (± 1.00)	0.4 (± 1.60)		
CYCLE 24 DAY 1; n=4, 8|	-0.3 (± 1.26)	0.0 (± 1.20)		
CYCLE 25 DAY 1; n=4, 8|	-0.3 (± 0.50)	-0.3 (± 1.49)		
CYCLE 26 DAY 1; n=4, 7|	-0.5 (± 1.00)	0.0 (± 1.63)		
CYCLE 27 DAY 1; n=4, 5|	0.0 (± 1.41)	0.0 (± 1.00)		
CYCLE 28 DAY 1; n=4, 5|	-0.3 (± 0.50)	0.2 (± 2.17)		
CYCLE 29 DAY 1; n=3, 4|	-0.7 (± 1.53)	-0.3 (± 2.22)		
CYCLE 30 DAY 1; n=3, 4|	0.0 (± 0.00)	-0.3 (± 2.06)		
CYCLE 31 DAY 1; n=3, 4|	0.7 (± 0.58)	0.3 (± 2.36)		
CYCLE 32 DAY 1; n=3, 4|	-0.7 (± 1.53)	0.0 (± 2.16)		
CYCLE 33 DAY 1; n=2, 4|	-2.0 (± 0.00)	-0.8 (± 1.50)		
CYCLE 34 DAY 1; n=1, 4|	0.0 (± 99999)	0.8 (± 1.50)		
CYCLE 35 DAY 1; n=0, 4|	99999 (± 99999)	0.0 (± 1.83)		
CYCLE 36 DAY 1; n=0, 4|	99999 (± 99999)	0.3 (± 1.71)		
CYCLE 37 DAY 1; n=0, 3|	99999 (± 99999)	-1.0 (± 1.73)		
CYCLE 38 DAY 1; n=0, 3|	99999 (± 99999)	-0.3 (± 2.52)		
CYCLE 39 DAY 1; n=0, 3|	99999 (± 99999)	-1.0 (± 1.73)		
CYCLE 40 DAY 1; n=0, 2|	99999 (± 99999)	0.0 (± 0.00)		
CYCLE 41 DAY 1; n=0, 2|	99999 (± 99999)	0.0 (± 0.00)		
CYCLE 42 DAY 1; n=0, 2|	99999 (± 99999)	0.0 (± 0.00)		
CYCLE 43 DAY 1; n=0, 2|	99999 (± 99999)	0.0 (± 0.00)		
CYCLE 44 DAY 1; n=0, 2|	99999 (± 99999)	0.0 (± 0.00)		
CYCLE 45 DAY 1; n=0, 2|	99999 (± 99999)	-1.5 (± 0.71)		
CYCLE 46 DAY 1; n=0, 2|	99999 (± 99999)	0.0 (± 0.00)		
CYCLE 47 DAY 1; n=0, 2|	99999 (± 99999)	-0.5 (± 0.71)		
CYCLE 48 DAY 1; n=0, 2|	99999 (± 99999)	1.0 (± 1.41)		
CYCLE 49 DAY 1; n=0, 2|	99999 (± 99999)	-1.0 (± 1.41)		

CYCLE 50 DAY 1; n=0, 2|	99999 (± 99999)	0.0 (± 0.00)		
CYCLE 51 DAY 1; n=0, 2|	99999 (± 99999)	0.0 (± 0.00)		
CYCLE 52 DAY 1; n=0, 2|	99999 (± 99999)	0.0 (± 0.00)		
CYCLE 53 DAY 1; n=0, 2|	99999 (± 99999)	-1.0 (± 1.41)		
CYCLE 54 DAY 1; n=0, 2|	99999 (± 99999)	0.0 (± 0.00)		
CYCLE 55 DAY 1; n=0, 1|	99999 (± 99999)	0.0 (± 99999)		
CYCLE 56 DAY 1; n=0, 1|	99999 (± 99999)	0.0 (± 99999)		
CYCLE 57 DAY 1; n=0, 1|	99999 (± 99999)	0.0 (± 99999)		
CYCLE 58 DAY 1; n=0, 1|	99999 (± 99999)	0.0 (± 99999)		
CYCLE 59 DAY 1; n=0, 1|	99999 (± 99999)	0.0 (± 99999)		
CYCLE 60 DAY 1; n=0, 1|	99999 (± 99999)	0.0 (± 99999)		
CYCLE 61 DAY 1; n=0, 1|	99999 (± 99999)	0.0 (± 99999)		
CYCLE 62 DAY 1; n=0, 1|	99999 (± 99999)	-1.0 (± 99999)		
CYCLE 63 DAY 1; n=0, 1|	99999 (± 99999)	-1.0 (± 99999)		
CYCLE 64 DAY 1; n=0, 1|	99999 (± 99999)	-2.0 (± 99999)		
CYCLE 65 DAY 1; n=0, 1|	99999 (± 99999)	-2.0 (± 99999)		
CYCLE 66 DAY 1; n=0, 1|	99999 (± 99999)	-1.0 (± 99999)		
CYCLE 67 DAY 1; n=0, 1|	99999 (± 99999)	-2.0 (± 99999)		
CYCLE 68 DAY 1; n=0, 1|	99999 (± 99999)	-2.0 (± 99999)		
CYCLE 69 DAY 1; n=0, 1|	99999 (± 99999)	-1.0 (± 99999)		
CYCLE 70 DAY 1; n=0, 1|	99999 (± 99999)	-2.0 (± 99999)		
CYCLE 71 DAY 1; n=0, 1|	99999 (± 99999)	-2.0 (± 99999)		
CYCLE 72 DAY 1; n=0, 1|	99999 (± 99999)	-2.0 (± 99999)		
CYCLE 73 DAY 1; n=0, 1|	99999 (± 99999)	-2.0 (± 99999)		
CYCLE 74 DAY 1; n=0, 1|	99999 (± 99999)	-2.0 (± 99999)		
CYCLE 75 DAY 1; n=0, 1|	99999 (± 99999)	-2.0 (± 99999)		

Notes:

[48] - As-Treated Population

[49] - As-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in weight

End point title	Change from Baseline in weight

End point description:

Weight was obtained on Day 1 of each cycle. Baseline is the last assessment prior to first dose. Change from Baseline is the value at indicated time point minus the value at Baseline. 99999 indicates data was not available due to insufficient number of participants. Only those participants with data available at specified time points were analyzed (indicated by n=X in category titles).

End point type	Secondary

End point timeframe:

Baseline and Day 1 of Cycles 2 to 75 (each cycle of 21 days)

End point values	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[50]	50[51]		
Units: Kilograms				
arithmetic mean (standard deviation)				
Cycle 2 Day 1, n=46, 44|	-1.51 (± 2.192)	-1.55 (± 2.405)		
CYCLE 3 DAY 1, n=39, 35|	-2.54 (± 2.734)	-1.88 (± 2.710)		
CYCLE 4; DAY 1; n=33, 32|	-3.02 (± 2.451)	-1.86 (± 3.305)		
CYCLE 5 DAY 1; n=27, 26|	-3.31 (± 2.521)	-2.01 (± 3.301)		
CYCLE 6 DAY 1; n=24, 22|	-3.25 (± 3.078)	-2.61 (± 4.200)		
CYCLE 7 DAY 1; n=24, 22|	-3.75 (± 4.172)	-2.14 (± 5.877)		
CYCLE 8 DAY 1; n=22, 21|	-3.89 (± 4.384)	-2.61 (± 5.016)		
CYCLE 9 DAY 1; n=19, 16|	-4.14 (± 5.151)	-2.14 (± 4.998)		
CYCLE 10 DAY 1; n=18, 16|	-5.50 (± 6.983)	-1.99 (± 5.478)		
CYCLE 11 DAY 1; n=16, 15|	-5.70 (± 6.045)	-1.67 (± 4.681)		
CYCLE 12 DAY 1; n=15, 13|	-5.85 (± 5.206)	-1.72 (± 4.260)		
CYCLE 13 DAY 1; n=13, 12|	-6.54 (± 5.795)	-1.11 (± 4.483)		
CYCLE 14 DAY 1; n=12, 12|	-7.03 (± 6.500)	-1.23 (± 3.899)		
CYCLE 15 DAY 1; n=10, 9|	-7.21 (± 7.449)	-1.09 (± 4.705)		
CYCLE 16 DAY 1; n=10, 9|	-7.59 (± 6.970)	-0.93 (± 4.519)		
CYCLE 17 DAY 1; n=8, 8|	-8.49 (± 8.606)	-1.24 (± 5.205)		
CYCLE 18 DAY 1; n=8, 8|	-8.25 (± 9.002)	-0.80 (± 4.888)		
CYCLE 19 DAY 1; n=6, 8|	-8.78 (± 9.953)	-0.19 (± 5.044)		
CYCLE 20 DAY 1; n=6, 8|	-9.22 (± 10.752)	-0.40 (± 5.986)		

CYCLE 21 DAY 1; n=4, 8|	-3.03 (± 7.950)	-0.29 (± 6.354)		
CYCLE 22 DAY 1; n=4, 8|	-3.50 (± 7.735)	-0.32 (± 5.370)		
CYCLE 23 DAY 1; n=4, 8|	-4.13 (± 8.189)	-0.16 (± 5.297)		
CYCLE 24 DAY 1; n=4, 7|	-3.38 (± 7.273)	-1.93 (± 1.511)		
CYCLE 25 DAY 1; n=4, 8|	-3.88 (± 8.250)	0.04 (± 5.789)		
CYCLE 26 DAY 1; n=4, 7|	-3.88 (± 6.981)	0.54 (± 6.484)		
CYCLE 27 DAY 1; n=4, 5|	-4.88 (± 6.408)	-2.04 (± 2.308)		
CYCLE 28 DAY 1; n=4, 5|	-5.13 (± 6.115)	-2.20 (± 1.989)		
CYCLE 29 DAY 1; n=3, 4|	-5.50 (± 7.697)	-2.18 (± 1.786)		
CYCLE 30 DAY 1; n=3, 4|	-5.83 (± 7.286)	-3.25 (± 0.379)		
CYCLE 31 DAY 1; n=3, 4|	-5.50 (± 7.467)	-3.38 (± 0.435)		
CYCLE 32 DAY 1; n=3, 4|	-5.50 (± 7.467)	-3.05 (± 0.100)		
CYCLE 33 DAY 1; n=2, 4|	-1.75 (± 1.061)	-3.13 (± 0.150)		
CYCLE 34 DAY 1; n=1, 4|	-2.50 (± 99999)	-3.18 (± 0.350)		
CYCLE 35 DAY 1; n=0, 4|	99999 (± 99999)	-3.25 (± 0.379)		
CYCLE 36 DAY 1; n=0, 4|	99999 (± 99999)	-3.38 (± 0.624)		
CYCLE 37 DAY 1; n=0, 3|	99999 (± 99999)	-3.17 (± 0.961)		
CYCLE 38 DAY 1; n=0, 3|	99999 (± 99999)	-2.63 (± 0.814)		
CYCLE 39 DAY 1; n=0, 3|	99999 (± 99999)	-3.00 (± 0.200)		
CYCLE 40 DAY 1; n=0, 2|	99999 (± 99999)	-3.40 (± 0.566)		
CYCLE 41 DAY 1; n=0, 2|	99999 (± 99999)	-2.90 (± 0.141)		
CYCLE 42 DAY 1; n=0, 2|	99999 (± 99999)	-3.00 (± 0.000)		
CYCLE 43 DAY 1; n=0, 2|	99999 (± 99999)	-2.90 (± 0.141)		
CYCLE 44 DAY 1; n=0, 2|	99999 (± 99999)	-3.90 (± 1.273)		
CYCLE 45 DAY 1; n=0, 2|	99999 (± 99999)	-4.40 (± 1.980)		
CYCLE 46 DAY 1; n=0, 2|	99999 (± 99999)	-3.90 (± 1.273)		
CYCLE 47 DAY 1; n=0, 2|	99999 (± 99999)	-3.40 (± 0.566)		
CYCLE 48 DAY 1; n=0, 2|	99999 (± 99999)	-3.65 (± 0.919)		
CYCLE 49 DAY 1; n=0, 2|	99999 (± 99999)	-4.40 (± 1.980)		
CYCLE 50 DAY 1; n=0, 2|	99999 (± 99999)	-4.15 (± 1.626)		
CYCLE 51 DAY 1; n=0, 2|	99999 (± 99999)	-3.65 (± 0.919)		

CYCLE 52 DAY 1; n=0, 2|	99999 (± 99999)	-2.90 (± 0.141)		
CYCLE 53 DAY 1; n=0, 2|	99999 (± 99999)	-4.40 (± 1.980)		
CYCLE 54 DAY 1; n=0, 2|	99999 (± 99999)	-3.65 (± 0.919)		
CYCLE 55 DAY 1; n=0, 1|	99999 (± 99999)	-2.80 (± 99999)		
CYCLE 56 DAY 1; n=0, 1|	99999 (± 99999)	-1.80 (± 99999)		
CYCLE 57 DAY 1; n=0, 1|	99999 (± 99999)	-0.80 (± 99999)		
CYCLE 58 DAY 1; n=0, 1|	99999 (± 99999)	-1.30 (± 99999)		
CYCLE 59 DAY 1; n=0, 1|	99999 (± 99999)	-0.30 (± 99999)		
CYCLE 60 DAY 1; n=0, 1|	99999 (± 99999)	-0.30 (± 99999)		
CYCLE 61 DAY 1; n=0, 1|	99999 (± 99999)	0.00 (± 99999)		
CYCLE 62 DAY 1; n=0, 1|	99999 (± 99999)	-0.30 (± 99999)		
CYCLE 63 DAY 1; n=0, 1|	99999 (± 99999)	-0.80 (± 99999)		
CYCLE 64 DAY 1; n=0, 1|	99999 (± 99999)	-0.60 (± 99999)		
CYCLE 65 DAY 1; n=0, 1|	99999 (± 99999)	-2.80 (± 99999)		
CYCLE 66 DAY 1; n=0, 1|	99999 (± 99999)	-3.30 (± 99999)		
CYCLE 67 DAY 1; n=0, 1|	99999 (± 99999)	-3.80 (± 99999)		
CYCLE 68 DAY 1; n=0, 1|	99999 (± 99999)	-1.30 (± 99999)		
CYCLE 69 DAY 1; n=0, 1|	99999 (± 99999)	-1.80 (± 99999)		
CYCLE 70 DAY 1; n=0, 1|	99999 (± 99999)	0.20 (± 99999)		
CYCLE 71 DAY 1; n=0, 1|	99999 (± 99999)	-0.80 (± 99999)		
CYCLE 72 DAY 1; n=0, 1|	99999 (± 99999)	-0.80 (± 99999)		
CYCLE 73 DAY 1; n=0, 1|	99999 (± 99999)	-1.30 (± 99999)		
CYCLE 74 DAY 1; n=0, 1|	99999 (± 99999)	-0.80 (± 99999)		
CYCLE 75 DAY 1; n=0, 1|	99999 (± 99999)	-0.30 (± 99999)		

Notes:

[50] - As-Treated Population

[51] - As-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentration of mapatumumab

End point title	Serum concentration of mapatumumab[52]

End point description:

Blood samples were collected for determination of serum mapatumumab concentration at the indicated

time points. 99999 indicates standard deviation could not be calculated as only one participant was analyzed at the specified time points. Only those participants with data available at the specified time points were analyzed (indicated by n=X in category titles).

End point type	Secondary

End point timeframe:

Day1 pre-dose(Cycle 1,2,4,5,6,8,9,10,12,14,16,17,18,20,22,24,26,28,30,32,34);end of infusion (Cycle 1);Day8 pre-dose(Cycle 1);Day15 pre-dose (Cycle 1,2);Day21(Cycle 2,4,6,8,9,12,14,16,18,20,22,24,26,28,30,32,34);Cycle 99(end of treatment) (21-day cycles)

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Sorafenib+Mapatumumab 30 mg/kg was included in the analysis.

End point values	Sorafenib+Mapatumumab 30 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	50[53]			
Units: Nanograms per milliliter				
arithmetic mean (standard deviation)				
CYCLE 1 Day 1, pre-dose, n=46|	638.4 (± 2668.01)			
CYCLE 1 DAY 1,end of infusion, n=46|	555157.6 (± 260848.85)			
CYCLE 1; DAY 8, pre-dose; n=40|	250229.9 (± 89714.76)			
CYCLE 1 DAY 15, pre-dose; n=1|	121556.0 (± 99999)			
CYCLE 2 DAY 1, pre-dose; n=40|	126588.4 (± 149231.45)			
CYCLE 2 DAY 15, pre-dose; n=3|	128839.0 (± 153667.78)			
CYCLE 2 DAY 21; n=28|	180606.6 (± 109893.28)			
CYCLE 4 DAY 1, pre-dose; n=31|	194936.8 (± 142242.80)			
CYCLE 4, DAY 21; n=23|	183754.3 (± 93584.71)			
CYCLE 5, DAY 1, pre-dose; n=1|	223681.0 (± 99999)			
CYCLE 6, DAY 1, pre-dose; n=21|	160741.5 (± 64893.03)			
CYCLE 6, DAY 21; n=20|	201237.7 (± 75352.54)			
CYCLE 8, DAY 1, pre-dose; n=21|	246616.5 (± 204363.04)			
CYCLE 8, DAY 21; n=17|	187927.6 (± 104803.16)			
CYCLE 9, DAY 1, pre-dose; n=1|	136122.0 (± 99999)			
CYCLE 10, DAY 1, pre-dose; n=16|	204147.1 (± 103243.21)			
CYCLE 10, DAY 21; n=15|	219503.0 (± 105968.15)			
CYCLE 12, DAY 1, pre-dose; n=12|	200141.1 (± 93093.68)			
CYCLE 12, DAY 21; n=11|	256924.5 (± 111904.82)			
CYCLE 14, DAY 1, pre-dose; n=9|	207930.6 (± 84247.04)			

CYCLE 14, DAY 21 n=9|	256779.4 (± 127463.67)			
CYCLE 16, DAY 1, pre-dose; n=9|	196074.3 (± 100377.45)			
CYCLE 16, DAY 21; n=8|	253521.0 (± 87675.77)			
CYCLE 17, DAY 1, pre-dose; n=1|	156161.0 (± 99999)			
CYCLE 18, DAY 1, pre-dose; n=8|	199379.4 (± 61011.54)			
CYCLE 18, DAY 21; n=7|	229539.1 (± 86440.46)			
CYCLE 20 DAY 1, pre-dose; n=8|	189486.6 (± 54097.82)			
CYCLE 20, DAY 21; n=7|	222443.7 (± 86046.38)			
CYCLE 22 DAY 1, pre-dose; n=8|	208485.4 (± 80252.29)			
CYCLE 22, DAY 21; n=7|	212481.1 (± 110103.79)			
CYCLE 24 DAY 1, pre-dose; n=8|	219439.8 (± 71740.01)			
CYCLE 24, DAY 21; n=7|	221249.1 (± 73317.41)			
CYCLE 26 DAY 1, pre-dose; n=4|	223427.3 (± 67101.56)			
CYCLE 26, DAY 21; n=4|	295941.5 (± 100208.45)			
CYCLE 28 DAY 1, pre-dose; n=3|	219802.7 (± 115484.98)			
CYCLE 28, DAY 21; n=2|	173018.5 (± 54870.78)			
CYCLE 30 DAY 1, pre-dose; n=2|	173200.5 (± 13447.05)			
CYCLE 30, DAY 21; n=2|	180484.5 (± 14783.48)			
CYCLE 32 DAY 1, pre-dose; n=1|	178275.0 (± 99999)			
CYCLE 32, DAY 21; n=1|	177496.0 (± 99999)			
CYCLE 34 DAY 1, pre-dose; n=1|	150553.0 (± 99999)			
CYCLE 34, DAY 21; n=1|	134781.0 (± 99999)			
CYCLE 99, end of treatment; n=14|	86640.1 (± 64981.14)			

Notes:

[53] - As-Treated Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Start of study treatment up to maximum of 52.9 months

Adverse event reporting additional description:

Treatment-emergent non-serious AEs and SAEs were collected in the As-Treated Population which comprised of participants who received at least part of 1 dose of study agent analyzed according to the treatment that they actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Sorafenib+Placebo

Reporting group description:

Participants received sorafenib 400 milligrams (mg) orally twice daily continuously in each 21-day cycle. Placebo was administered via the intravenous route on Day 1 of each 21-day cycle. The treatments were administered until radiologic disease progression or unacceptable toxicity

Reporting group title	Sorafenib+Mapatumumab 30 mg/kg

Reporting group description:

Participants received sorafenib 400 mg orally twice daily continuously in each 21-day cycle. Mapatumumab 30 milligrams per kilogram (mg/kg) was administered via the intravenous route on Day 1 of each 21-day cycle. The treatments were administered until radiologic disease progression or unacceptable toxicity

Serious adverse events	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 51 (52.94%)	21 / 50 (42.00%)	
number of deaths (all causes)	40	39	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	9 / 51 (17.65%)	4 / 50 (8.00%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 9	0 / 4	
Hepatic cancer metastatic			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			

General physical health deterioration			
subjects affected / exposed	2 / 51 (3.92%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Disease progression			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 51 (1.96%)	2 / 50 (4.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			

subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
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 / 51 (0.00%)	2 / 50 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial flutter			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Gastric haemorrhage			
subjects affected / exposed	2 / 51 (3.92%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	2 / 51 (3.92%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ascites			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 51 (1.96%)	2 / 50 (4.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sorafenib+Placebo	Sorafenib+Mapatumumab 30 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 51 (92.16%)	49 / 50 (98.00%)	
Investigations			
Weight decreased			
subjects affected / exposed	22 / 51 (43.14%)	19 / 50 (38.00%)	
occurrences (all)	41	34	
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 51 (21.57%)	9 / 50 (18.00%)	
occurrences (all)	37	25	
Lipase increased			
subjects affected / exposed	12 / 51 (23.53%)	17 / 50 (34.00%)	
occurrences (all)	37	46	
Gamma-glutamyltransferase increased			

subjects affected / exposed	11 / 51 (21.57%)	8 / 50 (16.00%)	
occurrences (all)	17	12	
Blood bilirubin increased			
subjects affected / exposed	9 / 51 (17.65%)	5 / 50 (10.00%)	
occurrences (all)	36	14	
Alanine aminotransferase increased			
subjects affected / exposed	8 / 51 (15.69%)	7 / 50 (14.00%)	
occurrences (all)	18	11	
Amylase increased			
subjects affected / exposed	8 / 51 (15.69%)	7 / 50 (14.00%)	
occurrences (all)	12	29	
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 51 (9.80%)	0 / 50 (0.00%)	
occurrences (all)	11	0	
Platelet count decreased			
subjects affected / exposed	6 / 51 (11.76%)	0 / 50 (0.00%)	
occurrences (all)	34	0	
Transaminases increased			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Weight increased			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	4	
White blood cell count decreased			
subjects affected / exposed	3 / 51 (5.88%)	3 / 50 (6.00%)	
occurrences (all)	34	9	
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 51 (23.53%)	16 / 50 (32.00%)	
occurrences (all)	16	25	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 51 (7.84%)	3 / 50 (6.00%)	
occurrences (all)	5	3	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	10 / 51 (19.61%)	8 / 50 (16.00%)	
occurrences (all)	15	13	
Thrombocytopenia			
subjects affected / exposed	5 / 51 (9.80%)	7 / 50 (14.00%)	
occurrences (all)	9	13	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 51 (15.69%)	11 / 50 (22.00%)	
occurrences (all)	12	26	
Fatigue			
subjects affected / exposed	15 / 51 (29.41%)	6 / 50 (12.00%)	
occurrences (all)	24	10	
Oedema peripheral			
subjects affected / exposed	9 / 51 (17.65%)	6 / 50 (12.00%)	
occurrences (all)	12	7	
Pyrexia			
subjects affected / exposed	3 / 51 (5.88%)	5 / 50 (10.00%)	
occurrences (all)	3	8	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	19 / 51 (37.25%)	16 / 50 (32.00%)	
occurrences (all)	46	29	
Abdominal pain			
subjects affected / exposed	9 / 51 (17.65%)	8 / 50 (16.00%)	
occurrences (all)	22	11	
Nausea			
subjects affected / exposed	8 / 51 (15.69%)	8 / 50 (16.00%)	
occurrences (all)	11	10	
Vomiting			
subjects affected / exposed	7 / 51 (13.73%)	5 / 50 (10.00%)	
occurrences (all)	23	7	
Ascites			
subjects affected / exposed	6 / 51 (11.76%)	0 / 50 (0.00%)	
occurrences (all)	11	0	
Abdominal pain upper			

subjects affected / exposed	0 / 51 (0.00%)	4 / 50 (8.00%)	
occurrences (all)	0	5	
Haemorrhoids			
subjects affected / exposed	4 / 51 (7.84%)	0 / 50 (0.00%)	
occurrences (all)	5	0	
Stomatitis			
subjects affected / exposed	4 / 51 (7.84%)	3 / 50 (6.00%)	
occurrences (all)	4	4	
Constipation			
subjects affected / exposed	3 / 51 (5.88%)	3 / 50 (6.00%)	
occurrences (all)	4	5	
Dyspepsia			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	3 / 51 (5.88%)	5 / 50 (10.00%)	
occurrences (all)	3	7	
Hepatic pain			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	6	
Jaundice hepatocellular			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 51 (11.76%)	0 / 50 (0.00%)	
occurrences (all)	8	0	
Dysphonia			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
Rash papular			
subjects affected / exposed	0 / 51 (0.00%)	9 / 50 (18.00%)	
occurrences (all)	0	13	
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	18 / 51 (35.29%)	19 / 50 (38.00%)	
occurrences (all)	29	28	
Hyperkeratosis			
subjects affected / exposed	0 / 51 (0.00%)	6 / 50 (12.00%)	
occurrences (all)	0	7	
Rash			
subjects affected / exposed	4 / 51 (7.84%)	6 / 50 (12.00%)	
occurrences (all)	5	6	
Alopecia			
subjects affected / exposed	3 / 51 (5.88%)	4 / 50 (8.00%)	
occurrences (all)	3	4	
Pruritus			
subjects affected / exposed	3 / 51 (5.88%)	4 / 50 (8.00%)	
occurrences (all)	3	4	
Erythema			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	6	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	3 / 51 (5.88%)	6 / 50 (12.00%)	
occurrences (all)	3	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 51 (23.53%)	9 / 50 (18.00%)	
occurrences (all)	17	15	
Hypocalcaemia			
subjects affected / exposed	9 / 51 (17.65%)	4 / 50 (8.00%)	
occurrences (all)	32	15	
Hyponatraemia			
subjects affected / exposed	7 / 51 (13.73%)	7 / 50 (14.00%)	
occurrences (all)	9	9	
Hypokalaemia			

subjects affected / exposed	6 / 51 (11.76%)	3 / 50 (6.00%)	
occurrences (all)	20	6	
Hypoalbuminaemia			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	7	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2010	Amendment 01 - Inclusion criteria: adjusted serum albumin levels to ≥2.8 grams per deciliter (g/dL) or ≥28 grams per liter (g/L) – modified in order to be consistent with criteria for Child Pugh A. - Mapatumumab/placebo will be discontinued for Grade 4 transaminase elevations of any duration if they are considered related to mapatumumab. - Participants requiring a delay of >21 days for hypertension,will discontinue sorafenib, unless in the study investigator's opinion, the participant may benefit from continued treatment. - Concomitant medications – allowable regimens. - Statistical analysis for primary endpoint – includes testing the hazard ratio for time to progression (TTP) at a 1-sided significance level of 0.01 with a Cox proportional hazards model controlling for the factors stratifying randomization as covariates. - Criteria for protocol specified events revised for transaminases (Grade 4 elevations), lipase or amylase (Grade 4 elevations; Grade 3 elevations associated with clinical/imaging findings of pancreatitis, resulting in chronic damage to the pancreas). - Modified Response Evaluation Criteria in Hepatocellular Carcinoma (mRECIST for HCC) adapted from Lencioni, 2010 for use in this study.
23 February 2011	Amendment 02 - Exclusion criteria added: History of organ allograft - Prohibited medications– clarified to include any locoregional therapy including embolization, radiofrequency ablation (RFA) or percutaneous ethanol injection.
15 July 2015	Amendment 03 - The protocol amendment number and version date have been added to the cover page. - A revision chronology page has been added. - The protocol has been modified to allow participants to receive extended access to study drug while receiving the local standard of care for hepatocellular carcinoma (HCC). A new section has been added to clarify assessments required for participants receiving extended access to study drug. - The long term follow up phase of the study has been removed as there is no longer a requirement to follow participants for long term survival since at least 90% of participants have met the survival endpoint. - The protocol has been updated to comply, where applicable, with the GlaxoSmithKline Standard Operating Procedure (GSK SOP), associated guidance and protocol template. - Reference to contacting Human Genome Science to report Adverse Events has been updated to GSK Case Management Group (CMG).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported