



Clinical trial results:

Sorafenib alone or in combination with everolimus in patients with unresectable hepatocellular carcinoma. A randomized multicenter phase II trial.

Summary

EudraCT number	2009-011884-35
Trial protocol	HU AT
Global end of trial date	18 March 2016

Results information

Result version number	v1 (current)
This version publication date	06 January 2023
First version publication date	06 January 2023

Trial information

Trial identification

Sponsor protocol code	SAKK 77/08 and SASL 29
-----------------------	------------------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01005199
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Swiss Group for Clinical Cancer Research (SAKK)
Sponsor organisation address	Effingerstrasse 33, Bern, Switzerland, 3008
Public contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer, +41 31389 91 91, sakkkc@sakk.ch
Scientific contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer, +41 31389 91 91, sakkkc@sakk.ch

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	21 February 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Investigate if the combination of sorafenib plus everolimus can stop tumor progression, with a sorafenib monotherapy group used to control selection bias. No formal comparison is planned.

Protection of trial subjects:

Protection of trial subjects was ensured by Safety Monitoring, i.e. assessment of adverse events, serious adverse events, adverse drug reactions, and the continuous assessment of laboratory values and vital signs.

Background therapy:

None

Evidence for comparator:

Sorafenib tosylate is a multitargeted tyrosine kinase inhibitor, is the standard of care for first-line systemic treatment of advanced hepatocellular carcinoma (HCC). Everolimus is a potent inhibitor of mTOR-pathway which is frequently activated in HCC. Preclinical data suggested that the combination of both drugs has additive effects compared to monotherapy and may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth and by blocking blood flow to the tumor.

Actual start date of recruitment	30 December 2009
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	Austria: 3
Country: Number of subjects enrolled	Hungary: 45
Country: Number of subjects enrolled	Switzerland: 57
Worldwide total number of subjects	105
EEA total number of subjects	48

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)	42
From 65 to 84 years	63
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between December 30th, 2009 and February 11th, 2013, 106 eligible patients were registered. One patient did not receive any study treatment and was not considered for analysis.

Pre-assignment

Screening details:

Eligibility criteria of a patient were checked by the investigator. Once a patient fulfils all inclusion criteria and not any of the exclusion criteria, he/she was enrolled.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm SE: Sorafenib and everolimus

Arm description:

Patients receiving sorafenib (S) and everolimus (E)

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

Dosage and administration details:

2 x 400 mg o.i.d.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	Afinitor®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 5 mg o.i.d.

Arm title	Arm S: Sorafenib
------------------	------------------

Arm description:

Patients receiving sorafenib (S)

Arm type	Active comparator
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	Nexavar®
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 x 400 mg o.i.d.

Number of subjects in period 1	Arm SE: Sorafenib and everolimus	Arm S: Sorafenib
Started	59	46
Completed	59	46

Period 2

Period 2 title	Treatment phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm SE: Sorafenib and everolimus

Arm description:

Patients receiving sorafenib (S) and everolimus (E)

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

Dosage and administration details:

2 x 400 mg o.i.d.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	Afinitor®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 5 mg o.i.d.

Arm title	Arm S: Sorafenib
------------------	------------------

Arm description:

Patients receiving sorafenib (S)

Arm type	Active comparator
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	Nexavar®
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 x 400 mg o.i.d.

Number of subjects in period 2	Arm SE: Sorafenib and everolimus	Arm S: Sorafenib
Started	59	46
Completed	59	46

Period 3

Period 3 title	Follow-up Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm SE: Sorafenib and everolimus

Arm description:

Patients receiving sorafenib (S) and everolimus (E)

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

Dosage and administration details:

2 x 400 mg o.i.d.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	Afinitor®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 5 mg o.i.d.

Arm title	Arm S: Sorafenib
------------------	------------------

Arm description:

Patients receiving sorafenib (S)

Arm type	Active comparator
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	Nexavar®
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 x 400 mg o.i.d.

Number of subjects in period 3	Arm SE: Sorafenib and everolimus	Arm S: Sorafenib
Started	59	46
Completed	0	0
Not completed	59	46
Consent withdrawn by subject	2	3
Death	3	2
Other	7	2
Unacceptable toxicity	17	9
Progressive disease	30	30

Baseline characteristics

Reporting groups

Reporting group title	Arm SE: Sorafenib and everolimus
-----------------------	----------------------------------

Reporting group description:

Patients receiving sorafenib (S) and everolimus (E)

Reporting group title	Arm S: Sorafenib
-----------------------	------------------

Reporting group description:

Patients receiving sorafenib (S)

Reporting group values	Arm SE: Sorafenib and everolimus	Arm S: Sorafenib	Total
Number of subjects	59	46	105
Age categorical			
Units: Subjects			
Adults (18-64 years)	24	18	42
From 65-84 years	35	28	63
Gender categorical			
Units: Subjects			
Female	11	6	17
Male	48	40	88

End points

End points reporting groups

Reporting group title	Arm SE: Sorafenib and everolimus
Reporting group description: Patients receiving sorafenib (S) and everolimus (E)	
Reporting group title	Arm S: Sorafenib
Reporting group description: Patients receiving sorafenib (S)	
Reporting group title	Arm SE: Sorafenib and everolimus
Reporting group description: Patients receiving sorafenib (S) and everolimus (E)	
Reporting group title	Arm S: Sorafenib
Reporting group description: Patients receiving sorafenib (S)	
Reporting group title	Arm SE: Sorafenib and everolimus
Reporting group description: Patients receiving sorafenib (S) and everolimus (E)	
Reporting group title	Arm S: Sorafenib
Reporting group description: Patients receiving sorafenib (S)	
Subject analysis set title	Arm SE: Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description: Patients in Arm SE who received at least one dose of trial medication and have a documented tumor assessment at 12 weeks 7 days (or documented progression any time before or a tumor assessment any time after).	
Subject analysis set title	Arm S: Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description: Patients in Arm S who received at least one dose of trial medication and have a documented tumor assessment at 12 weeks +/-7 days (or documented progression any time before or no missing assessment any time after).	

Primary: PE | Progression free survival (PFS) at 12 weeks

End point title	PE Progression free survival (PFS) at 12 weeks ^[1]
End point description: For the primary endpoint, progression was strictly defined according to RECIST (version 1.1). In other words, clinical progression was not counted as "Progression".	
End point type	Primary
End point timeframe: From trial registration until week 12.	

Notes:

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

Justification: Statistical analyses for the primary endpoint were conducted rather against the comparator (Arm S) than historical data.

For treatment Arm SE, 33 out of 50 (66.0%) patients were progression free. The null hypothesis for this treatment arm was that the true proportion of PFS at 12 weeks is less than or equal to 55%. Having a p-value of 0.059, which was larger than 0.05, the null hypothesis could not be rejected at the 5% significance level.

End point values	Arm SE: Per Protocol Set	Arm S: Per Protocol Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	43		
Units: Patients (%)				
number (confidence interval 95%)	66 (53.5 to 100)	69.8 (56.3 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Objective Response (OR)

End point title	SE Objective Response (OR)
-----------------	------------------------------

End point description:

OR was defined as having complete response (CR) or partial response (PR) as best response. For this endpoint, patients in the safety population having at least one tumor assessment were considered as evaluable.

Best responses in Arm SE were CR = 0.0% patients, PR = 10.2% patients, stable disease (SD) = 67.8% patients; progressive disease (PD) = 15.3% patients and missing data for 6.8% patients; in Arm S best responses were CR = 0.0% patients, PR = 0.0% patients, SD = 80.4% patients, PD = 19.6% patients and missing data for 0.0% patients.

End point type	Secondary
----------------	-----------

End point timeframe:

From registration until end of treatment

End point values	Arm SE: Sorafenib and everolimus	Arm S: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55 ^[2]	46		
Units: Patients with OR (%)				
number (confidence interval 95%)	10.9 (4.1 to 22.2)	0.0 (0.0 to 7.7)		

Notes:

[2] - 55 patients in the safety population had at least one tumor assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Disease stabilization (DS)

End point title	SE Disease stabilization (DS)
-----------------	---------------------------------

End point description:

DS was defined as having CR, PR or SD as best response.

End point type	Secondary
----------------	-----------

End point timeframe:

From registration until end of study.

End point values	Arm SE: Sorafenib and everolimus	Arm S: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55 ^[3]	46		
Units: Patients with DS (%)				
number (confidence interval 95%)	83.6 (71.2 to 92.2)	80.4 (66.1 to 90.6)		

Notes:

[3] - 55 patients in the safety population had at least one tumor assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Duration of DS

End point title	SE Duration of DS
-----------------	---------------------

End point description:

Duration of DS was calculated from the time that measurement criteria (CR, PR or SD) were met for the first time until documented tumor progression or death due to tumor. The duration of DS was censored if a second line treatment was started, the patient was lost to follow up or tumor assessments were outstanding or the patient died without documented tumor progression (and no tumor progression reported before). Patients without a tumor progression were censored at the time of the last tumor assessment.

In Arm SE there were 46 evaluable patients with 39 events and seven patients being censored. In Arm S there were 37 evaluable patients with 30 events and seven patients being censored.

End point type	Secondary
----------------	-----------

End point timeframe:

From the time that measurement criteria (CR, PR or SD) were met for the first time until documented tumor progression or death due to tumor.

End point values	Arm SE: Sorafenib and everolimus	Arm S: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46 ^[4]	37 ^[5]		
Units: Duration of DS (months)				
median (confidence interval 95%)	6.7 (4.1 to 9.4)	6.7 (3.5 to 8.8)		

Notes:

[4] - 46 patients with DS (i.e. CR, PR or SD).

[5] - 37 patients with DS (i.e. CR, PR or SD).

Statistical analyses

Statistical analysis title	Kaplan-Meier Analysis / Cox regression
----------------------------	--

Statistical analysis description:

Hazard ratio for duration of DS [Arm SE vs. Arm S]

Comparison groups	Arm SE: Sorafenib and everolimus v Arm S: Sorafenib
-------------------	---

Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.4

Secondary: SE | Progression free survival (PFS)

End point title	SE Progression free survival (PFS)
End point description:	
PFS was calculated from randomization until first documented tumor progression or death, whichever occurred first. PFS was censored if a second line treatment was started, the patient was lost to follow up or tumor assessments were outstanding (and no tumor progression had been reported before). Patients without a tumor progression were censored at the time of the last tumor assessment. In Arm SE, 55 out of 59 evaluable patients had progression or died, while four patients had not experienced progression or death. In Arm S, 44 out of 46 evaluable patients had progression or died, while two patients had not experienced progression or death.	
End point type	Secondary
End point timeframe:	
From randomization until first documented tumor progression or death, whichever occurred first.	

End point values	Arm SE: Sorafenib and everolimus	Arm S: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	46		
Units: PFS (months)				
median (confidence interval 95%)	5.2 (4 to 6.8)	6.6 (4.5 to 8.2)		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analysis / Cox regression
Statistical analysis description:	
HR for PFS (Arm SE vs. Arm S)	
Comparison groups	Arm SE: Sorafenib and everolimus v Arm S: Sorafenib
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.4

Secondary: SE | Time to tumor progression (TTP)

End point title	SE Time to tumor progression (TTP)
-----------------	--------------------------------------

End point description:

TTP was calculated from randomization until first documented tumor progression or tumor-related death. TTP was censored if a second line treatment was started, the patient was lost to follow up or died without documented tumor progression or tumor assessments were outstanding (and no tumor progression reported before). Patients without a tumor progression were censored at the time of the last tumor assessment.

In Arm SE, progression or death due to tumor occurred in 50 (out of 59) patients, while nine patients had not experienced progression or death due to tumor. In Arm S, progression or death due to tumor occurred in 39 (out of 46) patients, while seven patients have not experienced progression or death due to tumor.

End point type	Secondary
----------------	-----------

End point timeframe:

From randomization until first documented tumor progression or tumor related death.

End point values	Arm SE: Sorafenib and everolimus	Arm S: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	46		
Units: Time to TTP (months)				
median (confidence interval 95%)	6.2 (4.6 to 8.3)	7.6 (4.5 to 8.3)		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analysis / Cox regression
----------------------------	--

Statistical analysis description:

HR for TTP (Arm SE vs Arm S)

Comparison groups	Arm SE: Sorafenib and everolimus v Arm S: Sorafenib
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.4

Secondary: SE | Overall Survival (OS)

End point title	SE Overall Survival (OS)
-----------------	----------------------------

End point description:

OS was calculated from randomization until death. If the patient was lost to follow up or still alive, then OS was censored at the time the patient was last known to be alive.

Using the reverse KM estimator, the median follow up time are 39.6 and 48.3 months in treatment arm SE and S, respectively.

In Arm SE, death occurred in 46 (out of 59) patients. Eight patients were lost to follow up and five patients were still alive by their third year follow up. In Arm S, death occurred in 42 (out of 46) patients. Since the follow up after treatment termination for each patient was maximum three years, two patients were lost to follow up and two patients were still alive by their third year follow up.

End point type	Secondary
----------------	-----------

End point timeframe:

From randomization until death

End point values	Arm SE: Sorafenib and everolimus	Arm S: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	46		
Units: OS (months)				
median (confidence interval 95%)	13 (9.9 to 19.2)	10 (7.9 to 14.3)		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analysis / Cox regression (OS)
----------------------------	---

Statistical analysis description:

HR for OS (Arm SE vs Arm S)

Comparison groups	Arm SE: Sorafenib and everolimus v Arm S: Sorafenib
-------------------	---

Number of subjects included in analysis	105
---	-----

Analysis specification	Pre-specified
------------------------	---------------

Analysis type	other
---------------	-------

P-value	= 0.2695
---------	----------

Method	Regression, Cox
--------	-----------------

Parameter estimate	Cox proportional hazard
--------------------	-------------------------

Point estimate	0.8
----------------	-----

Confidence interval

level	95 %
-------	------

sides	2-sided
-------	---------

lower limit	0.5
-------------	-----

upper limit	1.2
-------------	-----

Statistical analysis title	Kaplan-Meier Analysis / Cox regression (Vit. B12)
Statistical analysis description:	
HR for OS between Vitamin B12 ≥ 600 and < 600 ng/l using a Cox model adjusted for treatment arm (Arm SE vs Arm S), WHO performance status (1 vs 0) and Extrahepatic spread (No vs Yes) HR (95% CI) Treatment arm: 0.8 [0.5; 1.2] p = 0.2695; HR (95% CI) WHO performance status: 0.7 [0.4; 1.0] p = 0.0691; HR (95% CI) Extrahepatic spread: 0.9 [0.6; 1.4] p = 0.7066	
Comparison groups	Arm SE: Sorafenib and everolimus v Arm S: Sorafenib
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6924
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.8

Secondary: SE | Serum alpha fetoprotein (AFP) level

End point title	SE Serum alpha fetoprotein (AFP) level
End point description:	
For this endpoint, patients in the safety population having baseline (non missing) AFP $\geq 1.5 \times$ ULN were considered as evaluable. For each cycle, number of patients having (non missing) AFP, median, minimum and maximum AFP levels were summarized stratified by treatment arm.	
End point type	Secondary
End point timeframe:	
At each cycle.	

End point values	Arm SE: Sorafenib and everolimus	Arm S: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25 ^[6]	28 ^[7]		
Units: Serum AFP (ng/ml)				
median (full range (min-max))				
Cycle 1	350 (8 to 76764)	99 (6 to 440729)		
Cycle 2	642 (8 to 526474)	72 (39 to 179813)		
Cycle 3	283 (7 to 294700)	229 (7 to 432563)		
Cycle 4	432 (6 to 137309)	82 (37 to 608910)		
Cycle 5	224 (6 to 243365)	144 (23 to 579998)		
Cycle 6	339 (26 to 53293)	112 (30 to 378186)		

Cycle 7	462 (183 to 79196)	96 (52 to 490421)		
Cycle 8	591 (43 to 73246)	98 (43 to 433950)		
Cycle 9	324 (43 to 99010)	102 (81 to 283844)		
Cycle 10	483 (44 to 128176)	339 (88 to 361161)		
Cycle 11	545 (3 to 2017)	386 (94 to 400836)		
Cycle 12	616 (71 to 212700)	2138 (123 to 426065)		
Cycle 13	355 (109 to 966)	135 (113 to 3553)		
Cycle 14	1095 (96 to 2000)	2919 (146 to 5961)		
Cycle 15	1810 (90 to 2000)	5662 (5662 to 5662)		
Cycle 16	1953 (350 to 2000)	0 (0 to 0)		
Cycle 17	350 (350 to 350)	0 (0 to 0)		
Cycle 18	2455 (2000 to 2909)	0 (0 to 0)		
Cycle 19	3603 (2000 to 5206)	0 (0 to 0)		
Cycle 20	1122 (1122 to 1122)	0 (0 to 0)		
Cycle 21	8613 (8613 to 8613)	0 (0 to 0)		
Cycle 22	10572 (10572 to 10572)	0 (0 to 0)		
Cycle 23	12496 (12496 to 12496)	0 (0 to 0)		
Cycle 24	0 (0 to 0)	0 (0 to 0)		
Cycle 25	22780 (22780 to 22780)	0 (0 to 0)		
Cycle 26	0 (0 to 0)	0 (0 to 0)		
Cycle 27	31832 (31832 to 31832)	0 (0 to 0)		
Cycle 28	0 (0 to 0)	0 (0 to 0)		
Cycle 29	0 (0 to 0)	0 (0 to 0)		
Cycle 30	77429 (77429 to 77429)	0 (0 to 0)		

Notes:

[6] - N for cycles 1 to 30: 25,15,19,12,15,11,9,8,5,8,5,4,4,3,3,3,1,2,2,1,1,1,1,0,1,0,1,0,0,1

[7] - N for cycle 1 to 15: 28,14,22,13,17,9,10,7,8,5,6,3,4,2,1

Attachments (see zip file)	SAKK 7708_AFP levels/SAKK 7708_AFP.png
-----------------------------------	--

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Viral (re)-activation in patients with chronic hepatitis B/C virus infection

End point title	SE Viral (re)-activation in patients with chronic hepatitis B/C virus infection
-----------------	---

End point description:

HBV/HCV (re)-activation was defined as:

HBV reactivation: at least 1 log increase in HBV DNA or new appearance of measurable HBV DNA AND LFT (liver function test [ALT]) elevation of 5 x ULN or 3 x baseline LFT value

HCV activation: 5 x ULN or 3 x baseline LFT value in the presence of HCV RNA or new appearance of measurable HCV PCR RNA

"At least 1 log increase" means that present HBV DNA / previous HBV DNA ≥ 10 .

End point type	Secondary
----------------	-----------

End point timeframe:

At various time points.

End point values	Arm SE: Sorafenib and everolimus	Arm S: Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	46		
Units: Patients (%)				
number (not applicable)				
(Re)-activation of HBV Missing	5.1	0.0		
(Re)-activation of HBV No	94.9	100.0		
Activation of HCV No	94.9	93.5		
Activation of HCV Yes	5.1	6.5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From registration until end of study.

Adverse event reporting additional description:

All enrolled patients receiving at least one dose of any of the study drugs.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	25.0
--------------------	------

Reporting groups

Reporting group title	Arm SE: Sorafenib and everolimus
-----------------------	----------------------------------

Reporting group description:

Patients receiving sorafenib (S) and everolimus (E)

Reporting group title	Arm S: Sorafenib
-----------------------	------------------

Reporting group description:

Patients receiving sorafenib (S)

Serious adverse events	Arm SE: Sorafenib and everolimus	Arm S: Sorafenib	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 59 (49.15%)	14 / 46 (30.43%)	
number of deaths (all causes)	46	42	
number of deaths resulting from adverse events	13	8	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression	Additional description: Arm SE-[1]: Abdom. pain in context of tumor progression (TP); [2]: Worse. of general condition in context of TP leading to death; [3]: Death due to hepat. failure in context of TP Arm S-[1]: Decomp. liver cirrhosis. in context of TP leading to death		
subjects affected / exposed	3 / 59 (5.08%)	2 / 46 (4.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Tumour pain			
subjects affected / exposed	0 / 59 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase			

subjects affected / exposed	0 / 59 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase			
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood phosphorus decreased	Additional description: [1]: Phosphate serum low Grade 4 in context of diarrhea		
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Depressed level of consciousness	Additional description: Confusion Grade 2, somnolence/repressed level of consciousness Grade 3 due to repeated opioid overdose		
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue	Additional description: Arm SE: one patient: Fatigue Grade 3 with anorexia Grade 2 in context of persisting diarrhea Grade 2 and fever Grade 1; one patient: Fatigue Grade 4 (due to progressive disease)		
subjects affected / exposed	3 / 59 (5.08%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Performance status decreased	Additional description: Worsening of performance status (constitutional symptoms Grade 2 other)		
subjects affected / exposed	0 / 59 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death	Additional description: Arm SE - [1]: Death due to tumor progression		
subjects affected / exposed	1 / 59 (1.69%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Disease progression	Additional description: [1]: Confusion Grade 4 due to hepatic encephalopathy in context of hyperammonemia associated with progressive disease		

subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain	Additional description: Arm SE: Pain Grade 3 due to osteoarthritis, discus hernia, antelithesis and anal fissure Arm S: Pain Grade 4 due to coxarthrosis (Arthralgia)		
subjects affected / exposed	1 / 59 (1.69%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Gastric ulcer haemorrhage	Additional description: Anemia Grade 3 due to gastric ulcer bleeding		
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites	Additional description: One patient: Fatigue Grade 2-3 and ascites Grade 3		
subjects affected / exposed	0 / 59 (0.00%)	2 / 46 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 59 (3.39%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage	Additional description: Gastrointestinal hemorrhage Grade 2 and diarrhea Grade 2		
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia	Additional description: Hematochezia due to hemorrhoids (hemorrhage Grade 2 GI anus)		
subjects affected / exposed	0 / 59 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			

subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic erosive gastritis	Additional description: [1]: Hemorrhagic-erosive antrum gastritis Grade 3		
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain	Additional description: Arm SE: Abdominal pain NOS Grade 3, fatigue Grade 3, weight loss Grade 1 Arm S: Abdominal pain Grade 3, fever Grade 2		
subjects affected / exposed	1 / 59 (1.69%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic haemorrhage			
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure	Additional description: Arm S - [1]: Hypoglycemia Grade 4 due to hepatic failure		
subjects affected / exposed	3 / 59 (5.08%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	2 / 3	0 / 1	
Hepatic function abnormal	Additional description: Arm SE - [two patients]: Liver dysfunction Grade 3, ascites Grade 3, fatigue Grade 3 Arm S - [one patient]: Hepatic dysfunction (bilirubin Grade 3, AST Grade 3, ALT Grade 2, albumin Grade 2)		
subjects affected / exposed	2 / 59 (3.39%)	2 / 46 (4.35%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Hepatic cirrhosis	Additional description: Arm SE: [1]: Worsening of general condition in context of hepatic cirrhosis decompensation with weight loss Grade 3 and ascites Grade 3 Arm S: Encephalopathy Grade 3 in context of liver cirrhosis		
subjects affected / exposed	1 / 59 (1.69%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Additional description: [1]: Epistaxis (hemorrhage Grade 3) with anticoagulation treatment		

subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis	Additional description: [1]: Dyspnea Grade 3 in context of everolimus induced non-infectious pneumonitis Grade 3 and pulmonary fibrosis		
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea	Additional description: [1]: Sudden dyspnea Grade 5, syncope Grade 5		
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 59 (1.69%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer	Additional description: One event: [1] Leg ulcer Grade 3 in context of leg edema Grade 3; one event: [2] Ulcers (ankle L) in context of leg edema; Hyperammonemia Leg ulcers Ankle edema		
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome	Additional description: [1]: Hand-foot syndrome Grade 3, nausea Grade 3, weight loss Grade 3, fatigue Grade 3		
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure	Additional description: [1]: Renal failure (creatinine Grade 1), hyponatremia Grade 4 and fatigue Grade 2		
subjects affected / exposed	0 / 59 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Musculoskeletal and connective tissue disorders			
Soft tissue necrosis			

subjects affected / exposed	0 / 59 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Peritonitis	Additional description: Fatigue Grade 3 and Peritonitis Grade 3		
subjects affected / exposed	0 / 59 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis intestinal perforated			
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 59 (3.39%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 59 (1.69%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia	Additional description: [1]: Hypokalemia Grade 4, diarrhea Grade 3 and creatinine Grade 1		
subjects affected / exposed	0 / 59 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm SE: Sorafenib and everolimus	Arm S: Sorafenib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 59 (100.00%)	46 / 46 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	3 / 59 (5.08%)	4 / 46 (8.70%)	
occurrences (all)	4	4	
Vascular disorders			
Hypertension			
subjects affected / exposed	27 / 59 (45.76%)	21 / 46 (45.65%)	
occurrences (all)	30	23	
Embolism			
subjects affected / exposed	5 / 59 (8.47%)	0 / 46 (0.00%)	
occurrences (all)	5	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	37 / 59 (62.71%)	33 / 46 (71.74%)	
occurrences (all)	45	38	
Pyrexia			
subjects affected / exposed	12 / 59 (20.34%)	4 / 46 (8.70%)	
occurrences (all)	13	7	
Ulcer			
subjects affected / exposed	2 / 59 (3.39%)	4 / 46 (8.70%)	
occurrences (all)	2	4	
Oedema peripheral			

subjects affected / exposed occurrences (all)	11 / 59 (18.64%) 12	7 / 46 (15.22%) 8	
Influenza like illness subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 1	3 / 46 (6.52%) 3	
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3	1 / 46 (2.17%) 1	
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	6 / 59 (10.17%) 8	3 / 46 (6.52%) 3	
Cough subjects affected / exposed occurrences (all)	9 / 59 (15.25%) 15	4 / 46 (8.70%) 4	
Dyspnoea subjects affected / exposed occurrences (all)	8 / 59 (13.56%) 11	4 / 46 (8.70%) 4	
Pneumonitis subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3	0 / 46 (0.00%) 0	
Dysphonia subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 4	6 / 46 (13.04%) 6	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	8 / 59 (13.56%) 9	3 / 46 (6.52%) 3	
Anxiety subjects affected / exposed occurrences (all)	5 / 59 (8.47%) 5	3 / 46 (6.52%) 3	
Confusional state subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3	0 / 46 (0.00%) 0	
Investigations			

Haemoglobin			
subjects affected / exposed	6 / 59 (10.17%)	1 / 46 (2.17%)	
occurrences (all)	6	2	
Neutrophil count			
subjects affected / exposed	5 / 59 (8.47%)	1 / 46 (2.17%)	
occurrences (all)	9	1	
Weight decreased			
subjects affected / exposed	31 / 59 (52.54%)	20 / 46 (43.48%)	
occurrences (all)	35	21	
Oral cavity examination			
subjects affected / exposed	11 / 59 (18.64%)	5 / 46 (10.87%)	
occurrences (all)	13	5	
Alanine aminotransferase			
subjects affected / exposed	19 / 59 (32.20%)	16 / 46 (34.78%)	
occurrences (all)	26	18	
Aspartate aminotransferase			
subjects affected / exposed	8 / 59 (13.56%)	5 / 46 (10.87%)	
occurrences (all)	8	6	
Blood alkaline phosphatase			
subjects affected / exposed	3 / 59 (5.08%)	4 / 46 (8.70%)	
occurrences (all)	4	4	
Blood bilirubin			
subjects affected / exposed	17 / 59 (28.81%)	19 / 46 (41.30%)	
occurrences (all)	24	26	
Blood cholesterol			
subjects affected / exposed	7 / 59 (11.86%)	0 / 46 (0.00%)	
occurrences (all)	10	0	
Blood creatinine			
subjects affected / exposed	3 / 59 (5.08%)	3 / 46 (6.52%)	
occurrences (all)	3	4	
Gamma-glutamyltransferase			
subjects affected / exposed	2 / 59 (3.39%)	4 / 46 (8.70%)	
occurrences (all)	2	4	
Nervous system disorders			
Taste disorder			

subjects affected / exposed occurrences (all)	2 / 59 (3.39%) 2	4 / 46 (8.70%) 4	
Dizziness subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 4	3 / 46 (6.52%) 3	
Headache subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3	1 / 46 (2.17%) 2	
Blood and lymphatic system disorders Platelets abnormal subjects affected / exposed occurrences (all)	14 / 59 (23.73%) 15	4 / 46 (8.70%) 5	
Gastrointestinal disorders Ascites subjects affected / exposed occurrences (all)	10 / 59 (16.95%) 10	7 / 46 (15.22%) 7	
Colitis subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3	0 / 46 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	6 / 59 (10.17%) 6	6 / 46 (13.04%) 6	
Diarrhoea subjects affected / exposed occurrences (all)	39 / 59 (66.10%) 50	22 / 46 (47.83%) 28	
Dry mouth subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 4	3 / 46 (6.52%) 4	
Dysphagia subjects affected / exposed occurrences (all)	0 / 59 (0.00%) 0	3 / 46 (6.52%) 3	
Dyspepsia subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 4	2 / 46 (4.35%) 2	
Haemorrhoids			

subjects affected / exposed	4 / 59 (6.78%)	0 / 46 (0.00%)	
occurrences (all)	4	0	
Nausea			
subjects affected / exposed	12 / 59 (20.34%)	8 / 46 (17.39%)	
occurrences (all)	14	8	
Vomiting			
subjects affected / exposed	6 / 59 (10.17%)	7 / 46 (15.22%)	
occurrences (all)	7	8	
Abdominal pain			
subjects affected / exposed	18 / 59 (30.51%)	10 / 46 (21.74%)	
occurrences (all)	28	12	
Proctalgia			
subjects affected / exposed	3 / 59 (5.08%)	0 / 46 (0.00%)	
occurrences (all)	3	0	
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 59 (1.69%)	3 / 46 (6.52%)	
occurrences (all)	2	3	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	2 / 59 (3.39%)	3 / 46 (6.52%)	
occurrences (all)	2	3	
Alopecia			
subjects affected / exposed	0 / 59 (0.00%)	9 / 46 (19.57%)	
occurrences (all)	0	9	
Dry skin			
subjects affected / exposed	5 / 59 (8.47%)	4 / 46 (8.70%)	
occurrences (all)	6	4	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	17 / 59 (28.81%)	15 / 46 (32.61%)	
occurrences (all)	20	17	
Pruritus			
subjects affected / exposed	7 / 59 (11.86%)	6 / 46 (13.04%)	
occurrences (all)	7	6	
Rash			

subjects affected / exposed occurrences (all)	16 / 59 (27.12%) 17	11 / 46 (23.91%) 14	
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3	0 / 46 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 4 4 / 59 (6.78%) 4 4 / 59 (6.78%) 4 4 / 59 (6.78%) 4 3 / 59 (5.08%) 5	3 / 46 (6.52%) 3 1 / 46 (2.17%) 1 2 / 46 (4.35%) 2 3 / 46 (6.52%) 3 2 / 46 (4.35%) 3	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3 3 / 59 (5.08%) 3	2 / 46 (4.35%) 2 1 / 46 (2.17%) 1	
Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all)	6 / 59 (10.17%) 6 20 / 59 (33.90%) 32	5 / 46 (10.87%) 5 16 / 46 (34.78%) 19	

Dehydration			
subjects affected / exposed	3 / 59 (5.08%)	0 / 46 (0.00%)	
occurrences (all)	3	0	
Hyperglycaemia			
subjects affected / exposed	18 / 59 (30.51%)	0 / 46 (0.00%)	
occurrences (all)	25	0	
Hypertriglyceridaemia			
subjects affected / exposed	7 / 59 (11.86%)	0 / 46 (0.00%)	
occurrences (all)	9	0	
Hypokalaemia			
subjects affected / exposed	1 / 59 (1.69%)	3 / 46 (6.52%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26884590>