Clinical trial results:
Regorafenib Assessment in Refractory advanced Colorectal cancer

Summary

EudraCT number	2012-005655-16
Trial protocol	BE
Global end of trial date	26 January 2018

Results information

Result version number	v1 (current)
This version publication date	19 September 2021
First version publication date	19 September 2021

Trial information

Trial identification

Sponsor protocol code	Regard-CrC_2012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01929616
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut Jules Bordet
Sponsor organisation address	rue Héger Bordet 1, Brussels, Belgium, 1000
Public contact	Hendlisz, Dr Alain, 0032 25413196, alain.hendlisz@bordet.be
Scientific contact	Alain Hendlisz, Institut Jules Bordet, 32 25413196, alain.hendlisz@bordet.be

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	17 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

As a primary objective :
- To identify in a population of patients bearing advanced, refractory colorectal cancers, those who draw no benefit from treatment with regorafenib.
As secondary objectives :
- To analyse PFS and response rate (RR) in relationship with the same covariates as for OS
- To assess regorafenib efficacy (OS, PFS, RR) and safety profile in this study population.
- To assess the Disease control rate (DCR = Complete response [CR] + partial response [PR] + stable disease [SD])
-To compare the relative benefit (OS, PFS) of regorafenib according to history of treatment with bevacizumab.
- To validate the relationship that was found, in a previous study (the SoMore) conducted in the same patients population treated with Sorafenib, between overall survival and early metabolic homogeneous response (all lesions responding, yes or no)

Protection of trial subjects:

Some of the eligibility criteria that the subjects had to meet to be entered in the trial were chosen in order to minimize the risk of severe adverse events. In addition, the protocol planned rules for treatment modifications in case of the occurrence of specific adverse events. All subjects were free to withdraw from the clinical trial at any time for any reason given and the study was conducted in agreement with the declaration of Helsinki. It was controlled that the patients received before inclusion in the trial all standard medications that could be of benefit for them.

Background therapy:

Regorafenib (BAY 73-4506) is a novel oral diphenylurea-based multikinase inhibitor with both a distinct profile of biochemical kinase inhibition and distinct pharmacological characteristics. Preclinical studies have shown that regorafenib is a potent inhibitor of several angiogenic and stromal receptor tyrosine kinases (RTKs), including vascular endothelial growth factor receptor (VEGFR)-1, -2, -3, platelet-derived growth factor receptor (PDGFR)-β, fibroblast growth factor receptor (FGFR)-1 , and TIE2. In addition, regorafenib inhibits various oncogenic receptor tyrosine kinases (RTKs) (c-KIT and RET) and intracellular signalling kinases (cRAF/RAF-1, BRAF, and B-RAF V600E mutant).

Evidence for comparator: -

Actual start date of recruitment	06 August 2013
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	Belgium: 141
Worldwide total number of subjects	141
EEA total number of subjects	141

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)	62
From 65 to 84 years	79
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

There were 141 subjects registered between 06/08/2013 and 29/10/2014.
138 subjects were eligible to receive regorafenib. 136 subjects completed the trial and 2 subjects did not complete the trial.

Pre-assignment

Screening details:

During the conduct of the study, the strategy was changed for the timing of the baseline PET: first, it was not required to have it done at the time of registration and afterwards, it was required (as the result of this PET impacts on the eligibility status).

Period 1

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

Arms

Arm title	Regorafenib

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Regorafenib was administered every day orally at a dose of 160 mg, 3 weeks/4 (where a cycle was defined by a 28 day-period).

Number of subjects in period 1	Regorafenib
Started	141
Completed	136
Not completed	5
Not eligible	3
Lost to follow-up	1
Subject never treated	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	141	141	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	62	62	
From 65-84 years	79	79	
85 years and over	0	0	
Age continuous Units: years			
median	66		
full range (min-max)	31 to 84	-	
Gender categorical Units: Subjects			
Female	59	59	
Male	82	82	
ECOG performance status Units: Subjects			
Score 0	66	66	
Score 1	72	72	
Ineligible	3	3	
KRas status Units: Subjects			
Wild	63	63	
Mutated	74	74	
Missing	1	1	
Ineligible	3	3	
Delay from diagnosis Units: months			
median			
full range (min-max)		-	
Delay from last chemotherapy Units: weeks			
median			
full range (min-max)		-	

Subject analysis sets	
Subject analysis set title	Eligible patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients who satisfied all the eligibility criteria including measurable metabolic lesions seen on the baseline PET	
Subject analysis set title	Evaluable patients
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All subjects that underwent second PET (day 14)	
Subject analysis set title	Metabolic responder
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects who responded to treatment based on the second PET	
Subject analysis set title	Metabolic non-responder
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects who did not respond to treatment based on the second PET	

Reporting group values	Eligible patients	Evaluable patients	Metabolic responder
Number of subjects	138	113	69
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	67	67	
full range (min-max)	31 to 84	31 to 83	
Gender categorical Units: Subjects			
Female	58	44	
Male	80	69	
ECOG performance status Units: Subjects			
Score 0	66	58	
Score 1	72	55	
Ineligible	0	0	
KRas status Units: Subjects			
Wild	63	50	
Mutated	74	62	
Missing	1	1	

Ineligible	0	0	

Delay from diagnosis			
Units: months			
median	40	40	
full range (min-max)	2 to 155	2 to 155	
Delay from last chemotherapy			
Units: weeks			
median	6	6	
full range (min-max)	3 to 54	3 to 54	

Reporting group values	Metabolic non-responder		
Number of subjects	44		
Age categorical			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Units: years			
median			
full range (min-max)			
Gender categorical			
Units: Subjects			
Female Male			
ECOG performance status			
Units: Subjects			
Score 0 Score 1 Ineligible			
KRas status			
Units: Subjects			
Wild Mutated Missing Ineligible			
Delay from diagnosis			
Units: months			
median			
full range (min-max)			
Delay from last chemotherapy			

Units: weeks median full range (min-max)			

End points

End points reporting groups

Reporting group title	Regorafenib
Reporting group description: -	
Subject analysis set title	Eligible patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients who satisfied all the eligibility criteria including measurable metabolic lesions seen on the baseline PET	
Subject analysis set title	Evaluable patients
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All subjects that underwent second PET (day 14)	
Subject analysis set title	Metabolic responder
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects who responded to treatment based on the second PET	
Subject analysis set title	Metabolic non-responder
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects who did not respond to treatment based on the second PET	

Primary: Overall survival from second PET

End point title	Overall survival from second PET
End point description:	

End point type	Primary
End point timeframe:	
From subject's second PET until death or drop out	

End point values	Evaluable patients	Metabolic responder	Metabolic non-responder	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	113	69	44	
Units: Time from second PET to death (months)				
median (confidence interval 95%)	6.7 (5.4 to 8.8)	7.5 (5.0 to 10.1)	5.4 (2.9 to 6.5)	

Attachments (see zip file)	Overall Survival by Metabolic Response.docx

Statistical analyses

Statistical analysis title	Overall Survival by metabolic response

Statistical analysis description:	
Comparison of Overall Survival between metabolic responders and non-responders	
Comparison groups	Metabolic non-responder v Metabolic responder
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.04

Secondary: Overall survival from the time of registration

End point title	Overall survival from the time of registration
End point description:	
End point type	Secondary
End point timeframe:	
Time from subject's registration until death or drop out	

End point values	Eligible patients			
Subject group type	Subject analysis set			
Number of subjects analysed	138			
Units: Time from registration to death (months)				
median (confidence interval 95%)	6.3 (4.4 to 7.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival from the time of registration

End point title	Progression free survival from the time of registration
End point description:	
End point type	Secondary
End point timeframe:	
Time from registration until progression, death or drop out	

End point values	Eligible patients			
Subject group type	Subject analysis set			
Number of subjects analysed	138			
Units: Time from regr to progression (months)				
median (confidence interval 95%)	2.1 (1.8 to 3.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival from second PET

End point title	Progression free survival from second PET

End point description:

End point type	Secondary

End point timeframe:

Time from second PET to disease progression, death or drop out

End point values	Evaluable patients	Metabolic responder	Metabolic non-responder	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	113	69	44	
Units: Time to progression (months)				
median (confidence interval 95%)				
Metabolic response	2.1 (1.3 to 3.0)	3.1 (1.4 to 4.3)	1.3 (1.1 to 2.2)	

Statistical analyses

Statistical analysis title	PFS from second PET by metabolic response

Statistical analysis description:

Comparison of time to progression from second PET between metabolic responders and non-responders

Comparison groups	Metabolic responder v Metabolic non-responder
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.94

Secondary: One year overall survival rate from the time of registration

End point title	One year overall survival rate from the time of registration

End point description:

Percent of patients who were still alive at one year after the time of registration

End point type	Secondary

End point timeframe:

Time from registration to time of death or drop out

End point values	Eligible patients			
Subject group type	Subject analysis set			
Number of subjects analysed	138			
Units: Percent of patients				
number (confidence interval 95%)	24.8 (17.3 to 32.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: One year overall survival rate from the time of second PET

End point title	One year overall survival rate from the time of second PET

End point description:

Percent of patients who were still alive at one year after second PET

End point type	Secondary

End point timeframe:

Time of patient's registration until death or drop out

End point values	Evaluable patients	Metabolic responder	Metabolic non-responder	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	113	69	44	
Units: Percent of patients				
number (confidence interval 95%)	27.4 (18.9 to 35.9)	32.8 (21.6 to 44.0)	14.2 (3.4 to 25.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Six-month PFS rate from the time of registration

End point title	Six-month PFS rate from the time of registration

End point description:

Percent of patients without progression disease or death six months after the time of registration

End point type	Secondary

End point timeframe:

Time of patients' registration to time of death or drop out

End point values	Eligible patients			
Subject group type	Subject analysis set			
Number of subjects analysed	138			
Units: Percent of patients				
number (confidence interval 95%)	12.4 (7.4 to 19.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Six-month PFS rate from the second PET

End point title	Six-month PFS rate from the second PET

End point description:

Percent of patients without disease progression or death at six month after the second PET

End point type	Secondary

End point timeframe:

Time of patients' second PET to progression or death

End point values	Evaluable patients	Metabolic responder	Metabolic non-responder	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	113	69	44	
Units: Percent of patients				
number (confidence interval 95%)	13.3 (6.9 to 19.7)	14.5 (6.0 to 23.0)	11.4 (1.8 to 21.0)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from ICF signature until 28 days after the last administration of regorafenib. After this period, only SAEs which have a reasonable possibility to be related to regorafenib.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Safety analysis

Reporting group description: -

Serious adverse events	Safety analysis		
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 137 (30.66%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Fatigue			

subjects affected / exposed	3 / 137 (2.19%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Gait disturbance			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 4		
Mucosal inflammation			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	6 / 137 (4.38%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hiccups			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumonitis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Ataxia			

subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorder			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radicular pain			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal obstruction			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Nausea				
subjects affected / exposed	2 / 137 (1.46%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				
subjects affected / exposed	2 / 137 (1.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholestasis				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis				

subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis cholestatic				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	2 / 137 (1.46%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	3 / 137 (2.19%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Urinary tract obstruction				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				

subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Klebsiella sepsis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pseudomonas infection			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	3 / 137 (2.19%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety analysis		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	137 / 137 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Haemorrhage			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Hypertension			

subjects affected / exposed	44 / 137 (32.12%)		
occurrences (all)	69		
Hypotension			
subjects affected / exposed	5 / 137 (3.65%)		
occurrences (all)	5		
Pallor			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Peripheral coldness			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Phlebitis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 137 (5.11%)		
occurrences (all)	8		
Chest pain			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	106 / 137 (77.37%)		
occurrences (all)	119		
General physical health deterioration			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	3		
Hypothermia			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Influenza like illness			

subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	8 / 137 (5.84%)		
occurrences (all)	15		
Oedema			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	14 / 137 (10.22%)		
occurrences (all)	14		
Pain			
subjects affected / exposed	6 / 137 (4.38%)		
occurrences (all)	9		
Pyrexia			
subjects affected / exposed	27 / 137 (19.71%)		
occurrences (all)	31		
Secretion discharge			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Thirst			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Genital tract inflammation			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	2		
Pelvic pain			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Prostatitis			

subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Scrotal oedema			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Vaginal haemorrhage			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	13 / 137 (9.49%)		
occurrences (all)	17		
Dysphonia			
subjects affected / exposed	31 / 137 (22.63%)		
occurrences (all)	33		
Dyspnoea			
subjects affected / exposed	25 / 137 (18.25%)		
occurrences (all)	28		
Dyspnoea exertional			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences (all)	4		
Haemoptysis			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Hiccups			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Lung disorder			

subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Nasal dryness			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Oropharyngeal discomfort			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Sleep apnoea syndrome			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	15 / 137 (10.95%)		
occurrences (all)	15		
Confusional state			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	9 / 137 (6.57%)		
occurrences (all)	9		

Personality change			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	5 / 137 (3.65%)		
occurrences (all)	5		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Blood iron decreased			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	2		
Blood pressure orthostatic decreased			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences (all)	4		
International normalised ratio increased			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	3		
Liver function test abnormal			
subjects affected / exposed	7 / 137 (5.11%)		
occurrences (all)	7		
Thyroxine increased			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		

Weight decreased			
subjects affected / exposed	17 / 137 (12.41%)		
occurrences (all)	17		
Hyperglycaemia			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Humerus fracture			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Stoma complication			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	2		
Stoma site irritation			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Cyanosis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Intracardiac mass			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Sinus tachycardia			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Tachycardia			

subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	3		
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 137 (4.38%)		
occurrences (all)	6		
Dysaesthesia			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	14 / 137 (10.22%)		
occurrences (all)	20		
Language disorder			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Motor dysfunction			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Nervous system disorder			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	14 / 137 (10.22%)		
occurrences (all)	16		

Sciatica subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Spinal cord compression subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Tremor subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	16 / 137 (11.68%) 21		
Haemolysis subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Neutropenia subjects affected / exposed occurrences (all)	2 / 137 (1.46%) 2		
Thrombocytopenia subjects affected / exposed occurrences (all)	8 / 137 (5.84%) 10		
Ear and labyrinth disorders			
Tinnitus subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Vertigo subjects affected / exposed occurrences (all)	2 / 137 (1.46%) 2		
Dry eye subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Eye disorders			
Diplopia subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Eye disorder			

subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Eyelid oedema			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	25 / 137 (18.25%)		
occurrences (all)	28		
Abdominal pain upper			
subjects affected / exposed	15 / 137 (10.95%)		
occurrences (all)	19		
Anal incontinence			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Anal inflammation			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Ascites			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	3		
Colonic fistula			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	24 / 137 (17.52%)		
occurrences (all)	25		
Diarrhoea			
subjects affected / exposed	56 / 137 (40.88%)		
occurrences (all)	92		
Dry mouth			
subjects affected / exposed	7 / 137 (5.11%)		
occurrences (all)	7		
Dyspepsia			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences (all)	5		

Dysphagia				
subjects affected / exposed	3 / 137 (2.19%)			
occurrences (all)	3			
Enteritis				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Gastritis				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Gastrointestinal pain				
subjects affected / exposed	2 / 137 (1.46%)			
occurrences (all)	2			
Gastrooesophageal reflux disease				
subjects affected / exposed	3 / 137 (2.19%)			
occurrences (all)	3			
Glossitis				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Intestinal dilatation				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Haemorrhoids				
subjects affected / exposed	2 / 137 (1.46%)			
occurrences (all)	2			
Nausea				
subjects affected / exposed	25 / 137 (18.25%)			
occurrences (all)	29			
Oesophagitis				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Periodontal disease				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Proctalgia				
subjects affected / exposed	3 / 137 (2.19%)			
occurrences (all)	4			

Rectal haemorrhage			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	44 / 137 (32.12%)		
occurrences (all)	58		
Toothache			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Varices oesophageal			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	15 / 137 (10.95%)		
occurrences (all)	19		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Hepatic failure			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Hepatomegaly			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Hyperbilirubinaemia			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	3		
Jaundice			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Liver disorder			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Portal hypertension			

subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 137 (5.84%)		
occurrences (all)	8		
Blister			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	3		
Dermatitis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	8 / 137 (5.84%)		
occurrences (all)	8		
Eczema			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences (all)	4		
Hyperhidrosis			
subjects affected / exposed	4 / 137 (2.92%)		
occurrences (all)	4		
Onycholysis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Pain of skin			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	3		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	63 / 137 (45.99%)		
occurrences (all)	88		
Petechiae			

subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	21 / 137 (15.33%)		
occurrences (all)	23		
Skin exfoliation			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Skin induration			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Skin reaction			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Xeroderma			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Haematoma			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Bladder disorder			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		

Hydronephrosis subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Polyuria subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Proteinuria subjects affected / exposed occurrences (all)	3 / 137 (2.19%) 3		
Renal failure subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Vesical fistula subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Urinary incontinence subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all)	2 / 137 (1.46%) 2		
Hypothyroidism subjects affected / exposed occurrences (all)	3 / 137 (2.19%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	6 / 137 (4.38%) 7		
Back pain subjects affected / exposed occurrences (all)	19 / 137 (13.87%) 19		
Bone pain subjects affected / exposed occurrences (all)	4 / 137 (2.92%) 6		
Flank pain			

subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Intervertebral disc disorder				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	2			
Joint swelling				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Muscle fatigue				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Muscle spasms				
subjects affected / exposed	10 / 137 (7.30%)			
occurrences (all)	11			
Muscle twitching				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Muscular weakness				
subjects affected / exposed	3 / 137 (2.19%)			
occurrences (all)	3			
Musculoskeletal chest pain				
subjects affected / exposed	3 / 137 (2.19%)			
occurrences (all)	3			
Musculoskeletal pain				
subjects affected / exposed	7 / 137 (5.11%)			
occurrences (all)	7			
Musculoskeletal stiffness				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Myalgia				
subjects affected / exposed	3 / 137 (2.19%)			
occurrences (all)	3			
Neck pain				
subjects affected / exposed	2 / 137 (1.46%)			
occurrences (all)	2			
Osteoarthritis				

subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	8 / 137 (5.84%)		
occurrences (all)	8		
Tendonitis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Torticollis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	6 / 137 (4.38%)		
occurrences (all)	8		
Candida infection			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	3		
Cystitis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Furuncle			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	2 / 137 (1.46%)		
occurrences (all)	2		
Gastrointestinal fungal infection			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		

Gingivitis				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	2			
Herpes infection				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	3 / 137 (2.19%)			
occurrences (all)	3			
Lung infection				
subjects affected / exposed	2 / 137 (1.46%)			
occurrences (all)	3			
Mucosal infection				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Oral fungal infection				
subjects affected / exposed	2 / 137 (1.46%)			
occurrences (all)	2			
Oral herpes				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Paronychia				
subjects affected / exposed	2 / 137 (1.46%)			
occurrences (all)	2			
Pharyngitis				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	2			
Respiratory tract infection				
subjects affected / exposed	2 / 137 (1.46%)			
occurrences (all)	2			
Sinusitis				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			
Tooth abscess				
subjects affected / exposed	1 / 137 (0.73%)			
occurrences (all)	1			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 137 (1.46%) 2		
Urinary tract infection subjects affected / exposed occurrences (all)	8 / 137 (5.84%) 8		
Viral skin infection subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Metabolism and nutrition disorders Appetite disorder subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Cell death subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Decreased appetite subjects affected / exposed occurrences (all)	74 / 137 (54.01%) 81		
Dehydration subjects affected / exposed occurrences (all)	4 / 137 (2.92%) 4		
Folate deficiency subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Hyperammonaemia subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 1		
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 137 (0.73%) 2		
Hypocalcaemia subjects affected / exposed occurrences (all)	3 / 137 (2.19%) 3		
Hypomagnesaemia			

subjects affected / exposed	3 / 137 (2.19%)		
occurrences (all)	4		
Hypophosphataemia			
subjects affected / exposed	17 / 137 (12.41%)		
occurrences (all)	22		
Hypovitaminosis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		
Iron deficiency			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 August 2013	Making the initial frozen biopsy optional (because of the bias risk of limiting the study for patients bearing liver metastasis only due to many contraindications and limitations for biopsies outside the liver) along with making mandatory the collection of previously obtained tumoral tissue material (frozen of FFPE). Making other minor changes in the protocol wording and contact details Changing the ICF in order to reflect the changes of making initial frozen biopsy optional Adding secondary objective to validate the relationship that was found, in a previous study (the SoMore study) conducted in the same patients population treated with Sorafenib, between overall survival and early metabolic homogeneous response (all lesions responding, yes or no).
15 January 2014	Modifications in the inclusion criteria The clarification on Imaging Time Point o Subjects should have been on Regorafenib at least 4 days priortheir second PET scan. o Latest time point for the second PET scan is 21 calendar days after the start of treatment Study call to patients by Research Nurse at J10 instead of J8. This will allow to reduce the dose and not to interrupt it. Translational : Research Recommended to collect the tissue block. In the event that the tissue block cannot be provided, slides (20-25 slides of approximately 5up) will suffice. Precision about the estimated sample: between 124 and 140 patients will be accrued. It will be eventually adapted according to the observed drop out rate, in order to reach the number of 105 evaluable patients.
10 April 2014	Modifications in the inclusion criteria : -Precision of previsous use for the oxaliplatin - Bilirubin (in order to reflect Gilbert's syndrome) - P-ALK level New exclusion criterion Safety : modifications in the report procedure Precision for the FDG PET-CT
05 August 2014	Making the initial biopsies mandatory Changing the ICF in order to reflect the changes of making initial frozen biopsy mandatory New inclusion criteria (related to the biopsy) New exclusion criteria (related to the biopsy) Addition of tumour markers CEA and CA19 9 in the protocol and in the CRF (Case Report Form)

18 September 2014	Modification in the inclusion criterion # 9 o Clarification on the collection of tissue New exclusion criteria o Venous thrombosis o Proteinuria Update in the concomitant medication section Modification for the blood pressure monitoring Precision on the liver function test Precisions on statistical points

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Non-randomized nature forbides any differentiation between the prognostic and the predictive value of biomarkers limited information of progressive disease for patients with “clinically-only” progressive disease without radiological demonstration

Notes: