Clinical trial results:
Randomized phase II trial evaluating the efficacy of FOLFOX alone, FOLFOX plus bevacizumab and FOLFOX plus panitumumab as perioperative treatment in patients with resectable liver metastases from wild type KRAS and NRAS colorectal cancer

Summary

EudraCT number	2010-019238-29
Trial protocol	BE AT GB DE NL ES
Global end of trial date	25 July 2018

Results information

Result version number	v1 (current)
This version publication date	28 August 2019
First version publication date	28 August 2019

Trial information

Trial identification

Sponsor protocol code	40091

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01508000
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Organisation for Research and Treatment of Cancer
Sponsor organisation address	Avenue E. Mounier 83/11, Brussels, Belgium, 1200
Public contact	Project, Budget& Regulatory Dept, European Organisation for Research and Treatment of Cancer, 32 2774 1654, regulatory@eortc.be
Scientific contact	Project, Budget& Regulatory Dept, European Organisation for Research and Treatment of Cancer, 32 2774 1654, regulatory@eortc.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	25 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 July 2018
Global end of trial reached?	Yes
Global end of trial date	25 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to detect an increase in progression free survival (PFS*) rate at 1 year in each experimental arm (mFOLFOX6 + bevacizumab or panitumumab) compared to mFOLFOX6 alone arm as perioperative treatment for resectable liver metastasis from wild type Kirsten rat sarcoma viral oncogene homolog (KRAS) and NRAS colorectal cancer (CRC).

Protection of trial subjects:

The responsible investigator ensured that this study was conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.
The protocol has been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf). The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	France: 34
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	26
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study opened for recruitment in June 2013 and despite many efforts from all the parties involved, only few patients (44 patients in total) were recruited. The study was closed for recruitment on 14/12/2015 for poor accrual.

Pre-assignment

Screening details:

Each patient considered by the Investigator to be a potential patient for the study underwent the informed consent process. If the patient agreed to participate in the study and an informed consent form was duly completed, dated and signed, then the Investigator assessed the patient's eligibility for the study.

Period 1

Period 1 title	Randomization (overall trial) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	modified FOLFOX6 + Surgery

Arm description:

Day 1 of a 14 day cycle:
Hour 0: Oxaliplatin 85 mg/m² IV 2-h infusion
Hour 0: Folinic Acid 400 mg/m² (DL form) or 200 mg/m2 (L form) IV 2-h infusion
Hour 2: 5-FU 400 mg/m² IV bolus over 2-4 minutes
Hour 2: 5-FU 2400 mg/m² given as a continuous infusion over 46h.

Six cycles pre and six cycles post surgery

Arm type	Active comparator
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

85 mg/m² IV 2-h infusion

Investigational medicinal product name	Folinic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m² (DL form) or 200 mg/m2 (L form) IV 2-h infusion

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-FU 400 mg/m² IV bolus over 2-4 minutes
5-FU 2400 mg/m² given as a continuous infusion over 46h.

Arm title	modified FOLFOX6 + Bevacizumab + Surgery

Arm description:

Day 1 of a 14 day cycle
Hour 0: Oxaliplatin 85 mg/m2 2-h infusion
Hour 0: Folinic Acid 400 mg/m2 (DL form) or 200 mg/m2 (L form) 2-h infusion
Hour 2 (before 5-FU bolus): Bevacizumab 5 mg/kg IV over 90 minutes infusion*.
Hour 3.5: 5-FU bolus 400 mg/m2 IV bolus over 2-4 minutes
Hour 3.5: 5-FU 2400 mg/m² given as a continuous infusion over 46h.
* First infusion over 90 minutes (following other antineoplastic agents); if the infusion is well tolerated, the second dose may be infused over 60 minutes. If this second infusion also is well tolerated, subsequent doses may be infused over 30 minutes.
Bevacizumab should be administered in all cycles, except cycle 6 of pre-operative treatment.
If a central venous access device (CVAD) is required, at least a 2-day interval between placement of a central line and first bevacizumab administration is recommended.

Six cycles pre and six cycles post surgery

Arm type	Experimental
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

85 mg/m² IV 2-h infusion

Investigational medicinal product name	Folinic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m² (DL form) or 200 mg/m2 (L form) IV 2-h infusion

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-FU 400 mg/m² IV bolus over 2-4 minutes
5-FU 2400 mg/m² given as a continuous infusion over 46h.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

(before 5-FU bolus): Bevacizumab 5 mg/kg IV over 90 minutes infusion

Arm title	modified FOLFOX6 + Panitumumab + Surgery

Arm description:

Day 1 of a 14 days cycle
Hour - 1 (pre chemotherapy): Panitumumab 6 mg/kg IV over 60 minutes (≤ 1000 mg) or 90 minutes (> 1000 mg) +/- 15 min. infusion*.
Hour 0: Oxaliplatin 85 mg/m² IV 2-h infusion
Hour 0: Folinic Acid 400 mg/m² (DL form) or 200 mg/m2 (L form) IV 2-h infusion
Hour 2: 5-FU 400 mg/m² IV bolus over 2-4 minutes
Hour 2: 5-FU 2400 mg/m² given as a continuous infusion over 46h.
* If the first infusion is well tolerated (i.e. without any serious infusion-related reactions) all subsequent infusions may be administered over 30 ± 10 minutes.

Arm type	Experimental
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

85 mg/m² IV 2-h infusion

Investigational medicinal product name	Folinic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m² (DL form) or 200 mg/m2 (L form) IV 2-h infusion

Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-FU 400 mg/m² IV bolus over 2-4 minutes
5-FU 2400 mg/m² given as a continuous infusion over 46h.

Investigational medicinal product name	Panitumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

(pre chemotherapy): Panitumumab 6 mg/kg IV over 60 minutes (≤ 1000 mg) or 90 minutes (> 1000 mg) +/- 15 min. infusion

Number of subjects in period 1	modified FOLFOX6 + Surgery	modified FOLFOX6 + Bevacizumab + Surgery	modified FOLFOX6 + Panitumumab + Surgery
Started	16	15	13
Completed	9	10	8
Not completed	7	5	5
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	1	-	1
Other	1	2	2
Unknown	1	-	-
Missing End of treatment form	1	1	2
Lack of efficacy	2	1	-
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	modified FOLFOX6 + Surgery

Reporting group description:

Day 1 of a 14 day cycle:
Hour 0: Oxaliplatin 85 mg/m² IV 2-h infusion
Hour 0: Folinic Acid 400 mg/m² (DL form) or 200 mg/m2 (L form) IV 2-h infusion
Hour 2: 5-FU 400 mg/m² IV bolus over 2-4 minutes
Hour 2: 5-FU 2400 mg/m² given as a continuous infusion over 46h.

Six cycles pre and six cycles post surgery

Reporting group title	modified FOLFOX6 + Bevacizumab + Surgery

Reporting group description:

Day 1 of a 14 day cycle
Hour 0: Oxaliplatin 85 mg/m2 2-h infusion
Hour 0: Folinic Acid 400 mg/m2 (DL form) or 200 mg/m2 (L form) 2-h infusion
Hour 2 (before 5-FU bolus): Bevacizumab 5 mg/kg IV over 90 minutes infusion*.
Hour 3.5: 5-FU bolus 400 mg/m2 IV bolus over 2-4 minutes
Hour 3.5: 5-FU 2400 mg/m² given as a continuous infusion over 46h.
* First infusion over 90 minutes (following other antineoplastic agents); if the infusion is well tolerated, the second dose may be infused over 60 minutes. If this second infusion also is well tolerated, subsequent doses may be infused over 30 minutes.
Bevacizumab should be administered in all cycles, except cycle 6 of pre-operative treatment.
If a central venous access device (CVAD) is required, at least a 2-day interval between placement of a central line and first bevacizumab administration is recommended.

Six cycles pre and six cycles post surgery

Reporting group title	modified FOLFOX6 + Panitumumab + Surgery

Reporting group description:

Day 1 of a 14 days cycle
Hour - 1 (pre chemotherapy): Panitumumab 6 mg/kg IV over 60 minutes (≤ 1000 mg) or 90 minutes (> 1000 mg) +/- 15 min. infusion*.
Hour 0: Oxaliplatin 85 mg/m² IV 2-h infusion
Hour 0: Folinic Acid 400 mg/m² (DL form) or 200 mg/m2 (L form) IV 2-h infusion
Hour 2: 5-FU 400 mg/m² IV bolus over 2-4 minutes
Hour 2: 5-FU 2400 mg/m² given as a continuous infusion over 46h.
* If the first infusion is well tolerated (i.e. without any serious infusion-related reactions) all subsequent infusions may be administered over 30 ± 10 minutes.

Reporting group values	modified FOLFOX6 + Surgery	modified FOLFOX6 + Bevacizumab + Surgery	modified FOLFOX6 + Panitumumab + Surgery
Number of subjects	16	15	13
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	61.3	63.9	62.2
full range (min-max)	30.4 to 82.4	34.4 to 74.6	42.0 to 75.8
Gender categorical Units: Subjects			
Female	4	5	4
Male	12	10	9
WHO Performance Status Units: Subjects			
PS 0	9	13	11
PS 1	7	2	2

Reporting group values	Total		
Number of subjects	44		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
median			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	13		
Male	31		
WHO Performance Status Units: Subjects			
PS 0	33		
PS 1	11		

End points

End points reporting groups

Reporting group title	modified FOLFOX6 + Surgery

Reporting group description:

Day 1 of a 14 day cycle:
Hour 0: Oxaliplatin 85 mg/m² IV 2-h infusion
Hour 0: Folinic Acid 400 mg/m² (DL form) or 200 mg/m2 (L form) IV 2-h infusion
Hour 2: 5-FU 400 mg/m² IV bolus over 2-4 minutes
Hour 2: 5-FU 2400 mg/m² given as a continuous infusion over 46h.

Six cycles pre and six cycles post surgery

Reporting group title	modified FOLFOX6 + Bevacizumab + Surgery

Reporting group description:

Day 1 of a 14 day cycle
Hour 0: Oxaliplatin 85 mg/m2 2-h infusion
Hour 0: Folinic Acid 400 mg/m2 (DL form) or 200 mg/m2 (L form) 2-h infusion
Hour 2 (before 5-FU bolus): Bevacizumab 5 mg/kg IV over 90 minutes infusion*.
Hour 3.5: 5-FU bolus 400 mg/m2 IV bolus over 2-4 minutes
Hour 3.5: 5-FU 2400 mg/m² given as a continuous infusion over 46h.
* First infusion over 90 minutes (following other antineoplastic agents); if the infusion is well tolerated, the second dose may be infused over 60 minutes. If this second infusion also is well tolerated, subsequent doses may be infused over 30 minutes.
Bevacizumab should be administered in all cycles, except cycle 6 of pre-operative treatment.
If a central venous access device (CVAD) is required, at least a 2-day interval between placement of a central line and first bevacizumab administration is recommended.

Six cycles pre and six cycles post surgery

Reporting group title	modified FOLFOX6 + Panitumumab + Surgery

Reporting group description:

Day 1 of a 14 days cycle
Hour - 1 (pre chemotherapy): Panitumumab 6 mg/kg IV over 60 minutes (≤ 1000 mg) or 90 minutes (> 1000 mg) +/- 15 min. infusion*.
Hour 0: Oxaliplatin 85 mg/m² IV 2-h infusion
Hour 0: Folinic Acid 400 mg/m² (DL form) or 200 mg/m2 (L form) IV 2-h infusion
Hour 2: 5-FU 400 mg/m² IV bolus over 2-4 minutes
Hour 2: 5-FU 2400 mg/m² given as a continuous infusion over 46h.
* If the first infusion is well tolerated (i.e. without any serious infusion-related reactions) all subsequent infusions may be administered over 30 ± 10 minutes.

Primary: Pathological response (according to Rubbia-Brandt)

End point title	Pathological response (according to Rubbia-Brandt)[1]

End point description:

The study was closed for poor accrual in 2015. Statistical guidelines for data analysis as specified in the protocol could not be applied due to the low number of patients. No follow-up data has been collected. Therefore the primary endpoint specified in the protocol "progression-free survival (PFS)" could not be computed. The secondary endpoint pathological response (according to Rubbia-Brandt) is the only efficacy endpoint that has been collected. Also, the database cannot be considered complete and clean. Descriptive analysis of pathological response has been done in the subset of patients that have completed a surgery and central pathology form (N=30).

End point type	Primary

End point timeframe:

Pathologists graded the resected specimens according to the grading systems by Rubbia-Brandt et al. Pathological response has been determined by central reference laboratory.

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: The study was closed for poor accrual. As a consequence, the database cannot be considered complete and clean. No formal statistical analysis could be carried out. The analysis for the pathological response is just descriptive.

End point values	modified FOLFOX6 + Surgery	modified FOLFOX6 + Bevacizumab + Surgery	modified FOLFOX6 + Panitumumab + Surgery	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12[2]	11[3]	7[4]	
Units: Patient				
1- Major or complete response (MjHR)	1	7	3	
2- Partial response (PHR)	4	3	2	
3- No regressive or response changes (NHR)	6	0	0	
Missing	1	1	2	

Notes:

[2] - Randomized patients who have completed a surgery and a central pathology form.

[3] - Randomized patients who have completed a surgery and a central pathology form.

[4] - Randomized patients who have completed a surgery and a central pathology form.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected on a CRF to be submitted at pre-specified timepoint : at baseline, at the end of each preop cycle, 1week after surgery, within 4-8weeks post surgery, at the end of each postop cycle

Adverse event reporting additional description:

AEs are evaluated using CTC grading, SAEs using MedDRA.
Non-SAEs have not been collected specifically, therefore AEs will be reported in non-SAE section. Only the pre-specified items of the CRF are reported; laboratory values and "Other" AEs from the CRF are not reported (unless they are SAEs in which case they are reported in the SAE section).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	modified FOLFOX6 + Surgery

Reporting group description:

The analysis of the safety endpoints “Toxicity” were carried out in the safety population defined as all patients who have started their allocated treatment (at least one dose of the study drug(s) in chemotherapy trials).

Reporting group title	modified FOLFOX6 + Bevacizumab + Surgery

Reporting group description:

The analysis of the safety endpoints “Toxicity” were carried out in the safety population defined as all patients who have started their allocated treatment (at least one dose of the study drug(s) in chemotherapy trials).

Reporting group title	modified FOLFOX6 + Panitumumab + Surgery

Reporting group description:

The analysis of the safety endpoints “Toxicity” were carried out in the safety population defined as all patients who have started their allocated treatment (at least one dose of the study drug(s) in chemotherapy trials).

Serious adverse events	modified FOLFOX6 + Surgery	modified FOLFOX6 + Bevacizumab + Surgery	modified FOLFOX6 + Panitumumab + Surgery
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 16 (43.75%)	5 / 15 (33.33%)	7 / 12 (58.33%)
number of deaths (all causes)	2	1	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
POST PROCEDURAL COMPLICATION			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND EVISCERATION			

alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE CORONARY SYNDROME			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEUKOPENIA			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
MUCOSAL INFLAMMATION			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUDDEN DEATH			

alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Immune system disorders			
DRUG HYPERSENSITIVITY			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
MACULAR DETACHMENT			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	2 / 12 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEUS			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEUS PARALYTIC			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INGUINAL HERNIA			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MECHANICAL ILEUS			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBILEUS			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	2 / 12 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
BILOMA			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLANGITIS			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC HAEMORRHAGE			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY DISTRESS SYNDROME			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATELECTASIS			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONITIS			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOTHORAX			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
RASH			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RASH ERYTHEMATOUS			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABDOMINAL INFECTION			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTION			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 16 (12.50%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LIVER ABSCESS			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIHEPATIC ABSCESS			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL PNEUMONIA			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOKALAEMIA			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	modified FOLFOX6 + Surgery	modified FOLFOX6 + Bevacizumab + Surgery	modified FOLFOX6 + Panitumumab + Surgery
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	15 / 15 (100.00%)	12 / 12 (100.00%)
Injury, poisoning and procedural complications			
WOUND DEHISCENCE			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 16 (0.00%)	3 / 15 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Vascular disorders			
HYPERTENSION			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 16 (0.00%)	3 / 15 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	18	0
THROMBOEMBOLIC EVENT			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Cardiac disorders			
MYOCARDIAL INFARCTION			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
DIZZINESS			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	3
PERIPHERAL MOTOR NEUROPATHY			
alternative dictionary used: CTCAE			

3.0			
subjects affected / exposed	2 / 16 (12.50%)	2 / 15 (13.33%)	2 / 12 (16.67%)
occurrences (all)	5	2	6
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	14 / 16 (87.50%)	11 / 15 (73.33%)	10 / 12 (83.33%)
occurrences (all)	86	75	44
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
FATIGUE			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	8 / 16 (50.00%)	7 / 15 (46.67%)	6 / 12 (50.00%)
occurrences (all)	47	25	22
FEVER			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	3 / 16 (18.75%)	2 / 15 (13.33%)	3 / 12 (25.00%)
occurrences (all)	3	3	9
INJECTION SITE REACTION			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Immune system disorders			
ALLERGIC REACTION			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	5 / 12 (41.67%)
occurrences (all)	0	0	10
Gastrointestinal disorders			
CONSTIPATION			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	6 / 16 (37.50%)	3 / 15 (20.00%)	7 / 12 (58.33%)
occurrences (all)	11	7	13

DIARRHEA			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	11 / 16 (68.75%)	6 / 15 (40.00%)	5 / 12 (41.67%)
occurrences (all)	28	19	22
MUCOSITIS ORAL			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	3 / 16 (18.75%)	6 / 15 (40.00%)	6 / 12 (50.00%)
occurrences (all)	8	13	12
NAUSEA			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	8 / 16 (50.00%)	10 / 15 (66.67%)	8 / 12 (66.67%)
occurrences (all)	36	28	29
VOMITING			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	6 / 16 (37.50%)	4 / 15 (26.67%)	6 / 12 (50.00%)
occurrences (all)	9	12	13
Respiratory, thoracic and mediastinal disorders			
COUGH			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 16 (6.25%)	3 / 15 (20.00%)	1 / 12 (8.33%)
occurrences (all)	2	6	1
DYSPNEA			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 16 (6.25%)	3 / 15 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	5	0
EPISTAXIS			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 16 (0.00%)	4 / 15 (26.67%)	0 / 12 (0.00%)
occurrences (all)	0	12	0
PLEURAL EFFUSION			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
RESPIRATORY FAILURE			
alternative dictionary used: CTCAE			

3.0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	1	6	3
DRY SKIN			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	6
PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	5 / 12 (41.67%)
occurrences (all)	0	4	14
PRURITUS			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	4 / 12 (33.33%)
occurrences (all)	10	1	12
RASH MACULO-PAPULAR			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	8 / 12 (66.67%)
occurrences (all)	0	0	28
Infections and infestations			
WOUND INFECTION			
alternative dictionary used: CTCAE 3.0			
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	3	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2012	Rationale for the amendment 1) Stratification factors : A few selected stratification factors related to liver metastases' number, size and location were judged more appropriate in the)setting of a perioperative chemotherapy than the Nordlinger scoring system. In addition, the numerous categories from the Nordlinger scoring system would not have allowed an easy adjustment of the analyses for this factor in the context of sensitivity analyses. 2) Prognostic factor analyses : Some clarifications were brought on the statistical analyses to be performed in order to investigate the correlation between pathological response and disease free survival. 3) Add details about the FDG-PET/CT imaging TR sub-study 4) Update the Reporting of Serious Adverse Events chapter (chapter 14) according to the new standard chapter
07 February 2013	Rationale for the amendment: 1) a demand from the French authorities to include a condition on creatinine clearance in the patient selection criteria. 2) the need to include guidelines for the local pathologist in charge of reviewing the pathological response. 3) the need to modify the description of the type of biological material to be collected in order to centrally assess the pathological response and to conduct further translational research on tissue blocks.
03 April 2014	Rationale for the amendment: 1) Redefinition of which mutations constitute KRAS and NRAS wild type (WT)/mutated patients, with the inclusion or NRAS mutations. 2) With the inclusion of extended KRAS and NRAS mutations the frequency of wild type patients will drop in the patient population from 60% to nearly 50% therefore this will require the screening of an estimated additional 120 patients. 3) The possibility of central testing for extended KRAS and NRAS, in centers who do not perform it locally. 4) The need to include in the protocol a new adverse effect for bevacizumab: necrotizing fasciitis and update information on other adverse events. 5) The need to address some comments from the Swiss authorities (AEs follow-up duration). 6) Addition of a new optional Translational Research (TR) project. 7) Statistical clarifications (Clarification of PFS* definition and addition of a definition for DFS)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 December 2015	In December 2015 the study was closed for poor accrual. 44 patients had entered the study at this time.	-

Notes:

Limitations and caveats

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

Due to the low accrual, the statistical analysis plan could not be applied (only descriptive). No follow-up data was collected. Also, the database cannot be considered complete and clean.

Notes: