FINAL STUDY REPORT

Full title of the trial:	Preoperative chemosensitivity testing as Predictor of Treatment benefit in Adjuvant stage III colon cancer
Short title of the trial:	PePiTA
EudraCT number:	2009-011445-13
Sponsor protocol number:	IJB-BGDO-2009-001
ClinicalTrials.gov Number:	NCT00994864
Sponsor	Institut Jules Bordet Rue Meylemeersch 90, 1070 Anderlecht Belgique/België
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Report date	03/12/2024

APPROVAL

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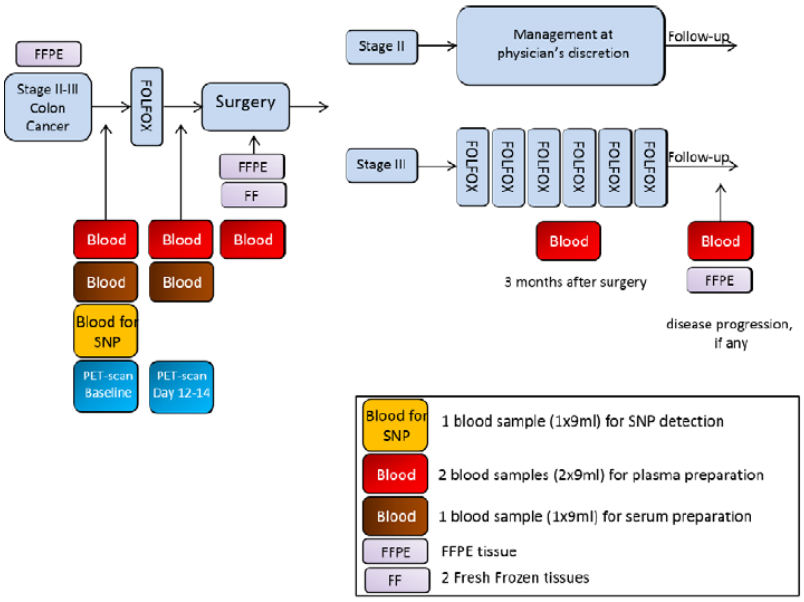
1 TRIAL INFORMATION

PHASE	Phase II
TRIAL DESIGN	Prospective multicentre -interventional non-randomized phase II study 
SCIENTIFIC BACKGROUND	Colorectal cancer (CRC) is a major public health problem accounting for over one million new cases and about half a million deaths worldwide per year. In Belgium, there are about 7700 new patients per year. Adjuvant chemotherapy is the current standard of care in stage III colon cancer, associated with a statistically significant improvement in overall survival (OS) compared to surgery alone. The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-01 trial, reported in 1988, was the first study to show a survival advantage for adjuvant chemotherapy. Drug regimens improved substantially over the years, and a 6-month combination of 5FU, folinic acid, and oxaliplatin (FOLFOX) became the reference treatment in 2004 after the Mosaic trial showed a 0.76 HR (95% CI 0.62–0.92) for relapse with FOLFOX versus 5FU/LV. In stage II-III colon cancer, FOLFOX is associated with a 3-year disease-free survival (DFS) of 72.2% and a 5-year survival rate of 78.5%. Testing tumour chemo-sensitivity in the adjuvant setting is difficult because no tumour

	is available after surgery for measurement. Predictive models based on the primary tumour characteristics could overcome this problem. Several early response detection techniques are potentially emerging: serial FDG-PET(-CT), dynamic MRI (DCE-MRI) and diffusion MR techniques, and Circulating Tumour Cells (CTCs). Among these, FDG-PET is the most studied and widely available in Belgium.
RATIONALE	The primary working hypothesis to be tested is that preoperative chemo-sensitivity testing using FDG-PET performed before and after one course of FOLFOX can identify the patients that will least likely have a significant benefit from adjuvant FOLFOX for stage III colon cancer. The benefit will be analysed by correlating the preoperative FDG-PET uptake changes to the disease free and overall survival.
OBJECTIVES	Primary objective: To validate the PET-assessed tumour FDG uptake response of the primary tumour after one course of preoperative chemotherapy as a predictor of outcome of adjuvant therapy, measured by 3-year DFS. Secondary objectives: 1. Compare responders' 5 years OS to non-responders, as assessed by FDG- PET/CT. 2. Evaluate the best DFS and OS predictive cut-off value for delta SUV in assessment of preoperative chemotherapy response by FDG-PET/CT imaging 3. To assess the DFS predictive value of the primary tumour FDG uptake on the baseline PET(CT) 4. To assess the predictive value of the presence of locoregional lymph node involvement seen on the baseline FDG-PET(CT), and of its response assessment after one course of preoperative chemotherapy 5. To assess the added value of the standardization and data analysis centralization performed by the Imaging Core Lab.

	6. Evaluate the cost-effectiveness of preoperative chemosensitivity testing strategy. 7. Translational research a. Assess the predictive value of SNPs on toxicity- and drug target-related genes on DFS. b. To assess genomic and transcriptomic rearrangements associated with response or resistance to FOLFOX treatment. c. To identify an immunologic signature associated with metabolic tumour response to FOLFOX therapy d. Create a frozen-tumour bank for future studies.
INCLUSION CRITERIA	• Age 18 years or older • Clinical/radiological evaluation compatible with stage III colon adenocarcinoma • No prior chemotherapy • No prior abdominal or pelvic irradiation • WHO performance status 0 or 1 • Effective contraception during the study and the following six months • Signed informed consent obtained prior to any study-specific screening procedures • Tumour considered as curatively resectable (R0) based on standard preoperative evaluations • White blood cell count ≥ 3×10^9/L with neutrophils ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, haemoglobin ≥ 9 g/dL (5.6 mmol/L) • Direct bilirubin ≤ 1.5×ULN; ASAT and ALAT ≤ 2.5×ULN; Alkaline phosphatase ≤ 2.5×ULN; Serum creatinine ≤ 1.5×ULN

EXCLUSION CRITERIA	• Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to screening. Incompletely healed wounds or anticipation of the need for major surgical procedure during the course of the study • Any suspicion of metastatic disease • Rectal cancer located within 15 cm from the anal verge by endoscopy or under the peritoneal reflection at surgery • Inflammatory bowel disease • Pregnancy (absence to be confirmed by ß-hCG blood test) or breast-feeding • History or current central nervous system disease or peripheral neuropathy • Hypersensitivity to any of the components of study treatments • Previous malignancy in the last five years except basal-cell carcinoma of the skin or in situ cervical carcinoma • Clinically relevant coronary artery disease or history of myocardial infarction in the last 6 weeks or high risk of uncontrolled arrhythmia • Medical, geographical, sociological, psychological or legal conditions that would not permit the patient to complete the study or sign informed consent • Any significant disease which, in the investigator's opinion, would excuse the patient from the study
INVESTIGATIONAL MEDICINAL PRODUCTS	The FOLFOX regimen was under the PI's discretion. The possible regimens in neoadjuvant and adjuvant settings were the same and were either: FOLFOX4: A two-hour infusion of leucovorin 200 mg/m^2 followed by a 400 mg/m^2 bolus 5-fluorouracil (5-FU) followed by a 22-hour infusion of

	5-FU 600 mg/m^2 given on two consecutive days plus a two-hour infusion of 85 mg/m^2 oxaliplatin, on day 1, simultaneously with leucovorin. Or Modified FOLFOX6: Oxaliplatin 85 mg/m^2 intravenous (IV) infusion with leucovorin 400 mg/m^2 over two hours, followed by 400 mg/m^2 bolus 5-FU followed by an IV infusion of 5-FU 2400 mg/m^2 for 46 hours
INDICATION OF USE	Stage III colon adenocarcinoma (ypTNM)
TARGETED POPULATION	Patients with histological confirmed colon adenocarcinoma compatible with clinical stage II or III
PARTICIPATING COUNTRY/-IES	Belgium
START DATE OF THE TRIAL	18/09/2009
PARTICIPATING SITES NUMBER	22
LENGTH OF THE STUDY	Actual start date of recruitment to the protocol: First ICF signed: 05/01/2010 First inclusion: 07/01/2010 Actual date stop date of recruitment to the protocol: Last ICF signed: 15/12/2017 Last inclusion: 18/12/2017 Long term follow-up planned? Yes, for scientific research as it was planned to assess disease free survival and overall survival with a minimum follow-up of 5 years for every patient (unless loss to follow-up) – Duration: 5 years.
INDEPENDENT DATA MONITORING COMMITTEE	No

PROTECTION OF TRIAL SUBJECTS	The protection of trial subjects was ensured through several measures. Eligibility criteria were designed to minimize the risk of severe adverse events, and subjects had the right to withdraw at any time. Investigators were required to make clinical decisions based on their best judgment. The study team verified data to guarantee that subjects' rights and well-being were safeguarded, that trial data was accurate and verifiable, and that the trial complied with ICH-GCP guidelines, regulatory requirements, and the study protocol.
STATISTICAL METHODS USED	Descriptive analyses were done to describe patient's evaluability for primary objective, to describe complications of surgery, adverse events in general, dose intensity of chemotherapy and metabolic response after 1 cycle of chemotherapy. Frequency tables for categorical variables and summary parameters for continuous variables (mean, standard deviation, median, range) were used. For the primary objective aiming at assessing the predictive value of metabolic response on disease free survival for pathological stage III, Kaplan Meier estimates and log rank test were used with median of SUV evolution for the definition of responder versus non-responder. Secondary analyses were done using Cox regression models with stepwise methods (to analyse SUV response as continuous covariate, to adjust for other covariates). Other time to event variables as relapse free survival and overall survival were analysed the same way. For other stages, distributions of time to event variables were estimated using the Kaplan Meier methods for descriptive purposes. The threshold for assessing statistical significance was set at 5%. All p values were reported for bilateral tests. Confidence intervals at 95% for hazard ratios estimated were provided too.
PRIMARY COMPLETION DATA	Is this the analysis of the primary completion data? No Primary completion date: 25/06/2019

GLOBAL END OF TRIAL DATE	Global end of trial reached? Yes Global end of trial date: 27/11/2023
PREMATURE END OF TRIAL	No

2 POPULATION OF TRIAL SUBJECTS

The actual number of subjects enrolled in the PePiTA trial per country is

Country	Number of subjects
Belgium	240

The number of subjects enrolled per age group is displayed in the below table.

Age of subjects	Number of subjects
In utero	0
Preterm new born - gestational age <37 wk	0
New-borns (0-27 days)	0
Infants and toddlers (28 days - 23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (between 18 and 64 years)	113
From 65 years	127
From 65 to 84 years	125
85 years and over	2

3 SUBJECT DISPOSITION

3.1 Recruitment

Recruitment details	The study was opened in September 2009. The recruitment period started on 05/01/2010 and ended on 18/12/2017. The principal investigators were in charge of identifying patients susceptible to be eligible for the study. They were responsible for the eligibility assessment. They sent inclusion forms to the coordinating centre (Institut Jules Bordet) where a last check of eligibility was performed and a trial number was allocated.
Screening details	Screening was done by the local investigators. In case the coordinating centre received an inclusion form corresponding to a non-eligible patient, the study PI was informed.

3.2 Pre-assignment period

This section is not applicable.

3.3 Post assignment period(s)

Period title:	Overall trial
Baseline period:	Yes
Allocation method:	Not applicable
Blinding used:	Not blinded: same treatment as study start for all patients.
Roles blinded:	Nuclearists in charge of assessing metabolic response.
Numbers of subjects in the trial	
Started	240
Completed	Patients who were surgically treated: 216 Patients who achieved the 12 cycles of chemotherapy (with pathological stage III): 72
Not completed	Consent withdrawal before treatment: 5 Early AE before treatment: 2 Second cancer: 4 Baseline hyperglycaemia: 2 Stage IV documented at baseline PET scan: 9 Stage IV clinically documented: 2
Adverse event, not serious	2
Adverse event, serious fatal	-
Adverse event, serious non-fatal	-
Consent withdrawn by subject	5
Physician decision	-
Protocol violation	-
Other	Second cancer: 4 Baseline hyperglycaemia: 2 Stage IV documented at baseline PET scan: 9 Stage IV clinically documented: 2

4 BASELINE CHARACTERISTICS

Baseline characteristics reporting groups	
Reporting group title	All patients except those who withdrew consent
Reporting group description	All patients were entered in the analysis independently of the treatment administration, provided they did not withdraw consent
Number of subjects	**235**
Age categories	
Units: Subjects	
In utero	0
Preterm new born - gestational age <37 week	0
New-borns (0-27 days)	0
Infants and toddlers (28 days - 23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (between 18 and 64 years)	110
From 65 years	125
From 65 to 84 years	123
85 years and over	2
Age continuous	
Units: years:	
Median	65
Inter-quartile range (Q1-Q3) Full range (min-max)	57-70 26-87

Gender	
Units: Subjects	
Female	95
Male	140
ECOG PS	
Units: Subject	
0 1	209 26
Grade of differentiation	
Units: Subject	
Well Moderately Poorly Unknown	68 116 15 34

Subject analysis sets	
Subject analysis set title	Patients evaluable for the primary objective
Subject analysis set type	Per protocol
Subject analysis set description	
Number of subjects	90

Age categories	
Units: Subjects	
In utero	0
Preterm new born - gestational age <37 week	0
New-borns (0-27 days)	0
Infants and toddlers (28 days - 23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (between 18 and 64 years)	46
From 65 years	44
From 65 to 84 years	44
85 years and over	0
Age continuous	
Units: years	
Median	64
Inter-quartile range (Q1-Q3) Full range (min-max)	58-70 32-84
Gender	
Units: Subjects	
Female	26
Male	64

ECOG PS	
Units: Subject	
0	76
1	14
Grade of differentiation	
Well	31
Moderately	45
Poorly	4
Unknown	10

5 END POINTS

5.1 End point title

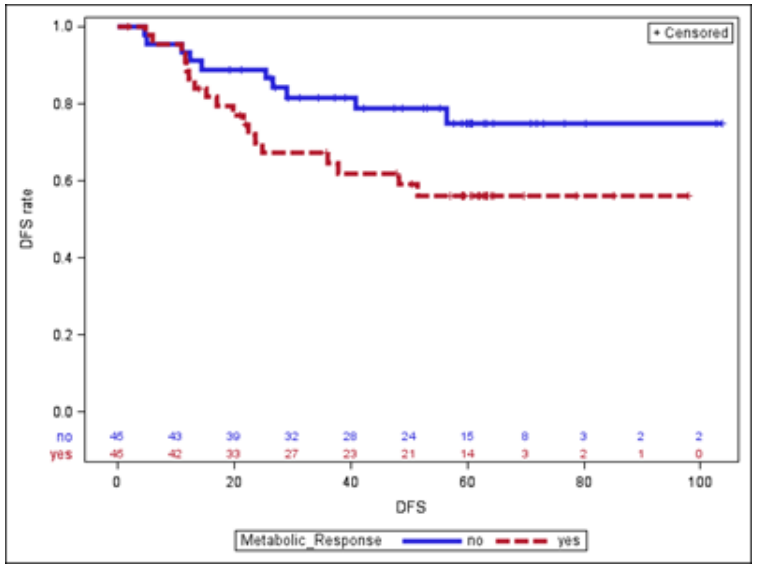
End point type	Primary
End point description	/
End point time frame	The endpoint was calculated from the date of second PET scan until disease progression or death

End point values		
	Patients with metabolic response	Patients without metabolic response
Number of subjects analysed	45	45
Units: months	/	/
Rate disease free at 36 months	82% (95% CI: 70%-94%)	65% (95% CI: 50%-80%)

5.1.1 Statistical analysis of end point

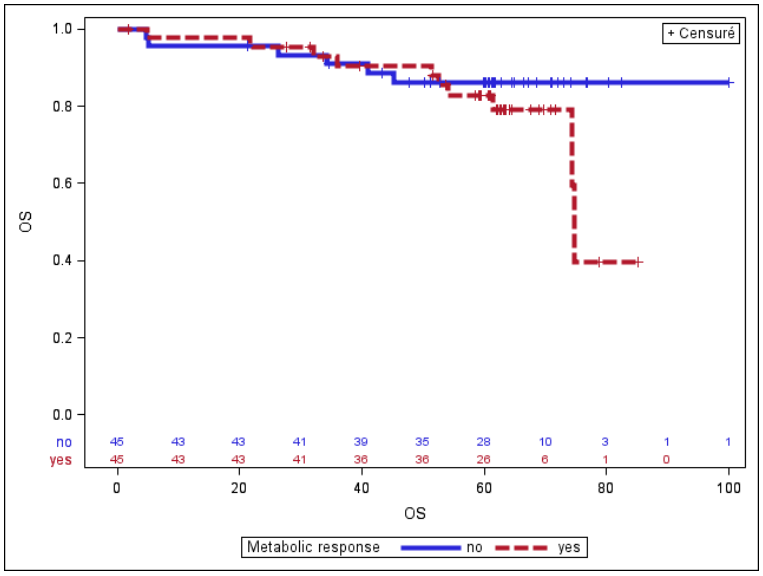
Statistical analysis title	Distribution of disease-free survival according to metabolic response	**Analyse type**	Superiority
		Comment	Per protocol, the goal of this analysis was to assess whether metabolic response could be associated with higher disease-free survival
Statistical analysis description	Distributions for each of the 2 groups defined according to the relative evolution of SUV between baseline and after 1 cycle of chemotherapy.		
Comparison group	Responders: decrease in SUV of 22% or more Non-responders: decrease in SU of less than 22%		
Number of subjects	90, 45 in each group		
Analysis specification	Pre-specified		
Statistical hypothesis test			
p-value	=0.06	**Comment**	The primary analysis was unadjusted for other covariates

Parameter estimate								
Point estimate	HR = 0.60 (reference group = responders)							
Confidence interval	Level	95%	Sides	2	Lower limit	0.33	Upper limit	1.07
Parameter type	Hazard ratio							
Variability estimate	Standard deviation of log(HR)			0.31				
Charts								



Statistical analysis title	Distribution of disease-free survival according to metabolic response	**Analyse type**	Superiority
		Comment	Per protocol, the goal of this analysis was to assess whether metabolic response could be associated with higher disease-free survival
Statistical analysis description	Distributions for each of the 2 groups defined according to the relative evolution of SUV between baseline and after 1 cycle of chemotherapy.		
Comparison group	Responders: decrease in SUV of 22% or more Non-responders: decrease in SU of less than 22%		
Number of subjects	90, 45 in each group		
Analysis specification	Pre-specified		
Statistical hypothesis test			
p-value	=0.28	**Comment**	The analysis was unadjusted for other covariates
Method	Unadjusted Cox regression analysis. No adjusted analysis was carried out due to the limited number of events.		

Parameter estimate								
Point estimate	HR = 0.57 (reference group = responders)							
Confidence interval	Level	95%	Sides	2	Lower limit	0.19	Upper limit	1.57
Parameter type	Hazard ratio							
Variability estimate	Standard deviation of log(HR)			0.31				
Charts								



6 ADVERSE EVENTS

6.1 Adverse events information

Timeframe for reporting adverse events	The investigators had to report all adverse events (related and unrelated) on the CRF from the pre-operative chemotherapy until 30 days after the last administration of the adjuvant chemotherapy: The investigators had to report: • Only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies) from informed consent (IC) signature until the pre-operative chemotherapy administration • All SAEs from preoperative chemotherapy administration and up to 30 days after the last dose of adjuvant chemotherapy. After this period, only SAEs which have a reasonable possibility to be related to the adjuvant chemotherapy and/or surgery
Adverse event reporting additional description	Exceptions to AE/SAE reporting were: Recurrence or progression of underlying malignancy is not reported as an AE or SAE if it is clearly consistent with the suspected recurrence or progression of the underlying cancer but will be reported on the appropriate CRF page. Hospitalization due solely to the recurrence or progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of recurrence or progression may be reported as AEs or SAEs if the symptoms cannot be determined as exclusively due to the recurrence or progression of the underlying malignancy, or does not fit the expected pattern of recurrence or progression for the disease under study. Deaths related to progression of the underlying disease during the course of the study will not be reported as a SAE, but should be reported on the appropriate CRF section (unless the patient has withdrawn consent). Similarly, clinical symptoms of underlying malignancy may be reported as AEs or SAEs if the symptoms cannot be determined as exclusively due to the underlying malignancy, or does not fit the expected pattern of the disease under study.

Dictionary used for adverse event reporting	MedDRA
Assessment type	Systematic
Reporting group title(s)	Safety assessed on all patients who started treatment
Reporting group description:	All patients who did not withdraw consent and started treatment with the first chemotherapy cycle before surgery were analysed for adverse event. Seven of the included patients were not analysed (5 patients who withdrew consent and 2 patients who did not start treatment)

6.2 Serious adverse events (SAEs)

Number of subjects exposed	233
Number of subjects affected by SAEs	31
Number of death (all causes)	27
Number of deaths resulting from adverse events	2

6.2.1 Serious adverse events in all patients having started treatment

MedDRA Primary SOC	MedDRA PT	Number of subjects affected	All SAEs occurrences	SAE occurrences related to IMP	Number of fatalities	Number of fatalities causally related to IMP
Blood and lymphatic system disorders	Anaemia	1	1	0	0	0
Blood and lymphatic system disorders	Lymphopenia	1	1	0	0	0
Blood and lymphatic system disorders	Neutropenia	1	1	1 to OXA/5FU	0	0
Blood and lymphatic system disorders	Splenic haematoma	1	1	0	0	0
Blood and lymphatic system disorders	Thrombocytopenia	2	2	1 to OXA/5FU	0	0
Cardiac disorders	Atrial fibrillation	2	2	0	0	0
Cardiac disorders	Cardiac arrest	1	1	0	1	0
Gastrointestinal disorders	Abdominal hernia	1	1	0	0	0
Gastrointestinal disorders	Colitis	1	1	1 to OXA/FA/5FU	0	0
Gastrointestinal disorders	Colitis ischaemic	1	1	0	0	0
Gastrointestinal disorders	Colonic fistula	1	1	0	0	0
Gastrointestinal disorders	Diarrhoea	1	1	0	0	0
Gastrointestinal disorders	Enteritis	1	1	1 to OXA/5FU	0	0
Gastrointestinal disorders	Enterocolitis	1	1	1 to OXA/FA/5FU	0	0
Gastrointestinal disorders	Gastrointestinal fistula	1	1	1 to OXA/FA/5FU	0	0
Gastrointestinal disorders	Gastrointestinal haemorrhage	1	1	0	0	0
Gastrointestinal disorders	Gastrointestinal ischaemia	1	1	0	0	0
Gastrointestinal disorders	Ileus	1	1	0	0	0
Gastrointestinal disorders	Ileus paralytic	1	1	0	0	0
Gastrointestinal disorders	Lower gastrointestinal haemorrhage	1	1	0	0	0
Gastrointestinal disorders	Peritoneal necrosis	1	1	0	0	0
Gastrointestinal disorders	Pneumatosis intestinalis	1	1	0	0	0
Gastrointestinal disorders	Subileus	1	1	1 to 5FU	0	0
General disorders and administration site conditions	Administration site inflammation	1	1	0	0	0
General disorders and administration site conditions	Extravasation	1	1	0	0	0
General disorders and administration site conditions	Pyrexia	1	3	2 to OXA	0	0
Infections and infestations	Bronchiolitis	1	1	0	0	0
Infections and infestations	Endocarditis	1	1	0	0	0
Infections and infestations	Genital infection fungal	1	1	0	0	0
Infections and infestations	Infection	1	1	0	0	0
Infections and infestations	Peritonitis	3	3	2 to OXA/5FU	0	0
Infections and infestations	Pneumonia	4	4	1 to OXA/5FU	0	0
Infections and infestations	Prostatitis Escherichia coli	1	1	1 to OXA/5FU	0	0
Infections and infestations	Sepsis	2	2	0	1	0
Infections and infestations	Septic shock	1	1	0	0	0
Infections and infestations	Splenic abscess	1	1	0	0	0
Infections and infestations	Wound infection	1	1	0	0	0
Injury, poisoning and procedural complications	Anastomotic fistula	2	2	0	0	0
Injury, poisoning and procedural complications	Anastomotic leak	2	2	1 to OXA/5FU	0	0
Injury, poisoning and procedural complications	Gastrointestinal anastomotic leak	1	1	0	0	0
Investigations	Blood creatinine increased	2	2	0	0	0
Investigations	Hepatic enzyme increased	1	1	1 to OXA/FA/5FU	0	0
Metabolism and nutrition disorders	Hyperglycaemia	1	1	0	0	0
Renal and urinary disorders	Acute kidney injury	1	1	0	0	0
Renal and urinary disorders	Renal failure	1	1	0	0	0
Renal and urinary disorders	Urinary retention	2	2	0	0	0
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	3	3	0	0	0
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1	1	1 to OXA/5FU	0	0
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	2	2	1 to OXA/5FU	0	0
Vascular disorders	Hypovolaemic shock	1	1	0	0	0
Vascular disorders	Phlebitis superficial	1	1	1 to OXA/5FU	0	0

6.3 Adverse events in all patients having started treatment

Number of subjects exposed	233
Number of subjects affected by AEs	164
Frequency threshold for reporting AEs	*2%*

6.3.1 Adverse events in all patients having started treatment

MedDRA Primary SOC	N affected subjects	All AEs occurrences	All AES occurrences related to OXA/FA/5FU
Blood and lymphatic system disorders	**163**	**731**	**590**
Thrombocytopenia	52	311	285
Anaemia	42	210	191
Neutropenia	63	204	110
Febrile neutropenia	5	5	4
Splenic haematoma	1	1	
Gastrointestinal disorders	**251**	**738**	**515**
Diarrhoea	80	265	147
Nausea	78	231	215
Stomatitis	24	91	85
Vomiting	18	35	33
Dyspepsia	10	30	12
Oesophagitis	2	13	
Abdominal pain	10	12	2
Gastroesophageal reflux disease	1	12	3
Abnormal faeces	1	10	
Dysphagia	3	6	6
Dry mouth	1	5	
Salivary gland pain	1	4	4
Angular cheilitis	1	3	3
Aphthous ulcer	2	2	1
Colitis	2	2	
Flatulence	2	2	
Gastrointestinal pain	2	2	
Rectal haemorrhage	2	2	
Abdominal discomfort	1	1	1
Abdominal pain upper	1	1	
Barrett's oesophagus	1	1	
Colonic fistula	1	1	
Faecaloma	1	1	
Gastrointestinal disorder	1	1	
Gingival erythema	1	1	
Intestinal ischaemia	1	1	
Mouth ulceration	1	1	1
Periodontal disease	1	1	1
Swollen tongue	1	1	1

General disorders and administration site conditions	**125**	**553**	**444**
Fatigue	99	509	421
Mucosal inflammation	4	9	9
Pyrexia	6	9	2
Asthenia	2	6	6
Chest pain	2	4	1
Pain	1	4	
Oedema peripheral	2	3	3
Influenza like illness	2	2	1
Oedema	2	2	1
Catheter site pain	1	1	
Chills	1	1	
Extravasation	1	1	
Injection site inflammation	1	1	
Injection site pain	1	1	
Investigations	**45**	**224**	**165**
Weight decreased	11	40	35
Protein total	7	30	9
White blood cell count decreased	2	17	17
Blood magnesium decreased	1	9	9
Weight increased	1	7	
Gamma-glutamyl transferase increased	5	24	13
Aspartate aminotransferase increased	7	35	33
Alanine aminotransferase increased	4	23	23
Blood bilirubin increased	1	1	
Blood lactate dehydrogenase increased	3	21	9
Alkaline phosphatase increase	2	16	16
White blood cell count increased	1	1	1
Metabolism and nutrition disorders	**40**	**123**	**76**
Decreased appetite	29	78	66
Hypokalaemia	4	17	10
Hypalbuminaemia	1	10	
Hyperglycaemia	2	7	
Vitamin D deficiency	1	5	
Carbohydrate intolerance	1	4	
Hypomagnesaemia	1	1	
Hyponatraemia	1	1	
Nervous system disorders	162	981	891
Peripheral sensory neuropathy	104	669	641
Peripheral motor neuropathy	14	47	47
Paraesthesia	10	46	40
Dysgeusia	12	39	30

Headache	10	17	5
Taste disorder	3	14	14
Memory impairment	1	9	9
Neuropathy peripheral	1	9	9
Neurotoxicity	1	8	8
Ageusia	1	5	
Balance disorder	2	3	1
Dizziness	1	2	
Migraine	1	2	1
Syncope	1	1	0
Skin and subcutaneous tissue disorders			
Alopecia		54	54
Palmar-plantar erythrodysaesthesia syndrome		19	19
Pruritus		8	1
Rash		7	3
Erythema		6	1
Urticaria		6	
Dry skin		4	3
Eczema		3	2
Photosensitivity reaction		1	1
Skin disorder		1	1
Skin hyperpigmentation		1	1

7 ADDITIONAL INFORMATION

7.1 Global substantial modifications

The global substantial modifications are summarised in the below table.

Modifications date	Description
SA1 - V1.1 27/10/2009 EC 26/11/2009	The assessment of the predictive value of diffusion MRI on DFS has been dropped. Some minor changes in the study timeline have been made. The EuroQoL quality of life questionnaire will be additionally used. Antibodies for erbB-2 protein will also be used in circulating tumour cells and correlated with study outcomes. Addition of an exclusion criterion at screening Minor changes in study timelines

Modifications date	Description
	Addition of Joint Study Management Team section Modification of section 18. Publication policy section: addition of the Publication Committee and authorship sections
SA2 - V2.0 18/01/2010 EC 19/03/2010 CA 09/02/2010	Update of study personnel on the first protocol page.
SA3 - V3.0 21/02/2011 EC 03/05/2011	New version of the protocol but no modification in this protocol amendment (only a change of PI and addition of 2 new sites).
SA4 - V4.0 24/05/2011 EC 29/06/2011	Suppression of the MRI sub-study FOLFOX regimen let at the investigator's discretion
SA5 - V5.0 19/02/2013 EC 28/05/2013	A new sentence clarifying the follow up for stage IV patients discovered at baseline or during the surgical removal of the primitive tumour has been added Change of end date of the trial due to lower than expected accrual Change of the patients' number due to low accrual and longer follow up for these patients Adding of new translational research endpoints - To assess genomic rearrangements associated with response or resistance to FOLFOX treatment. - To identify an immunologic signature associated with metabolic tumour response to FOLFOX therapy.

SA8 - V6.0 05/09/2016 EC 15/09/2016 CA 03/10/2016	Increasing of sample size (but decrease of required number of events for the primary analysis) AE reporting section added Translational research corrections Administrative corrections
SA13 - V7.0 26/11/2019 EC 23/12/2019	The translational part of the study was amended.

7.2 Global interruptions and re-starts

There were no global interruptions to the trial.

7.3 Limitations, addressing sources of potential bias and imprecisions and caveats

There were no limitations and caveats.