Clinical trial results:
ADJUVANT TREATMENT OF FULLY RESECTED STAGE III COLON CANCER WITH FOLFOX-4 VERSUS FOLFOX-4 PLUS CETUXIMAB

Tratamiento adyuvante con FOLFOX-4 versus FOLFOX-4 + cetuximab para el cáncer de colon en estadio III extirpado completamente

Summary

EudraCT number	2005-003463-23
Trial protocol	ES GB DE AT BE PT DK IT
Global end of trial date	15 October 2016

Results information

Result version number	v1 (current)
This version publication date	29 March 2022
First version publication date	29 March 2022

Trial information

Trial identification

Sponsor protocol code	PETACC 8

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00265811
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fédération Francophone de Cancérologie Digestive (FFCD)
Sponsor organisation address	7 Bd Jeanne d'Arc, Dijon, France,
Public contact	Karine Le Malicot, Fédération Francophone de Cancérologie Digestive (FFCD), karine.le-malicot@u-bourgogne.fr
Scientific contact	Karine Le Malicot, Fédération Francophone de Cancérologie Digestive (FFCD), karine.le-malicot@u-bourgogne.fr

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	31 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2011
Global end of trial reached?	Yes
Global end of trial date	15 October 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess and to compare the disease free survival curves according to treatment arm in completely resected stage III colon cancer.

Protection of trial subjects:

The study was done in accordance with the Declaration of Helsinki (amended 2000) and the International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) Note for Guidance on Good Clinical Practice and approved by the appropriate Ethics Committees.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 2005
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	Portugal: 72
Country: Number of subjects enrolled	Spain: 666
Country: Number of subjects enrolled	United Kingdom: 70
Country: Number of subjects enrolled	Austria: 127
Country: Number of subjects enrolled	Belgium: 205
Country: Number of subjects enrolled	Denmark: 28
Country: Number of subjects enrolled	France: 794
Country: Number of subjects enrolled	Germany: 278
Country: Number of subjects enrolled	Italy: 319
Worldwide total number of subjects	2559
EEA total number of subjects	2489

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	1711
From 65 to 84 years	848
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between Dec 22, 2005, and Nov 5, 2009, 2559 patients were enrolled from 340 sites in Europe and randomly assigned to treatment (2096 were randomised before June 17, 2008).

Pre-assignment

Screening details:

After checking the inclusion and non-inclusion criteria, patients were randomized to the protocol. We did this open-label randomised, controlled, multinational
phase 3 study in patients aged between 18 and 75 years with pathologically confi rmed stage III colon adenocarcinoma.

Period 1

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

Blinding implementation details:

Open-label study

Arms

Are arms mutually exclusive?	Yes
Arm title	FOLFOX4 plus Cetuximab

Arm description:

Patients received FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h), with weekly cetuximab, which was given on day 1, 400 mg/m² (2 h infusion) the fi rst week, then every week at 250 mg/m² (1 h infusion) for subsequent infusions. Treatment was continued for 12 cycles. Patients discontinued after completion of study treatment, occurrence of an unacceptable toxic eff ect, any disease recurrence, or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	FOLFOX4
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h).

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Weekly cetuximab, which was given on day 1, 400 mg/m² (2 h infusion) the first week, then every week at 250 mg/m² (1 h infusion) for subsequent infusions.

Arm title	FOLFOX4

Arm description:

Patients received FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h). Treatment was continued for 12 cycles. Patients

discontinued after completion of study treatment, occurrence of an unacceptable toxic eff ect, any disease recurrence, or withdrawal of consent.

Arm type	Active comparator
Investigational medicinal product name	FOLFOX4
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h).

Number of subjects in period 1[1]	FOLFOX4 plus Cetuximab	FOLFOX4
Started	791	811
Completed	785	805
Not completed	6	6
Kras mutated tumor	1	-
Not treated Patients	5	4
Kras Mutated Tumours	-	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The presented results are on the target population meaning the Kras Wild-type treated patients that is why numbers are different from the baseline period. Some patients were in fact Kras mutated patients or some were never treated.

Baseline characteristics

Reporting groups

Reporting group title	FOLFOX4 plus Cetuximab

Reporting group description:

Patients received FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h), with weekly cetuximab, which was given on day 1, 400 mg/m² (2 h infusion) the fi rst week, then every week at 250 mg/m² (1 h infusion) for subsequent infusions. Treatment was continued for 12 cycles. Patients discontinued after completion of study treatment, occurrence of an unacceptable toxic eff ect, any disease recurrence, or withdrawal of consent.

Reporting group title	FOLFOX4

Reporting group description:

Patients received FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h). Treatment was continued for 12 cycles. Patients discontinued after completion of study treatment, occurrence of an unacceptable toxic eff ect, any disease recurrence, or withdrawal of consent.

Reporting group values	FOLFOX4 plus Cetuximab	FOLFOX4	Total
Number of subjects	791	811	1602
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			
Age at baseline			
Units: years			
median	60	60	
full range (min-max)	19 to 75	21 to 75	-
Gender categorical Units: Subjects			
Female	323	343	666
Male	468	468	936

Subject analysis sets

Subject analysis set title	Kras Exon 2 Wild-type population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized KRAS wild-type patients with signed (Main and KRAS) Informed Consent Forms will be included in this analysis set, in the treatment arm assigned at randomization, irrespective of the

treatment actually received, and irrespective of the violation of baseline eligibility criteria, other protocol deviations or the availability of post-randomization data.
This population set will be used for the primary analyses of all primary and secondary efficacy variables.

Reporting group values	Kras Exon 2 Wild-type population		
Number of subjects	1602		
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			
Age at baseline			
Units: years median full range (min-max)	 60 19 to 75		
Gender categorical Units: Subjects			
Female Male	666 936		

End points

End points reporting groups

Reporting group title	FOLFOX4 plus Cetuximab

Reporting group description:

Patients received FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h), with weekly cetuximab, which was given on day 1, 400 mg/m² (2 h infusion) the fi rst week, then every week at 250 mg/m² (1 h infusion) for subsequent infusions. Treatment was continued for 12 cycles. Patients discontinued after completion of study treatment, occurrence of an unacceptable toxic eff ect, any disease recurrence, or withdrawal of consent.

Reporting group title	FOLFOX4

Reporting group description:

Patients received FOLFOX4 every 2 weeks (1 cycle): 85 mg/m² oxaliplatin (2 h infusion) on day 1, 200 mg/m² leucovorin on days 1 and 2, followed by 400 mg/m² fluorouracil (bolus), then 600 mg/m² fluorouracil (continuous infusion during 22 h). Treatment was continued for 12 cycles. Patients discontinued after completion of study treatment, occurrence of an unacceptable toxic eff ect, any disease recurrence, or withdrawal of consent.

Subject analysis set title	Kras Exon 2 Wild-type population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized KRAS wild-type patients with signed (Main and KRAS) Informed Consent Forms will be included in this analysis set, in the treatment arm assigned at randomization, irrespective of the treatment actually received, and irrespective of the violation of baseline eligibility criteria, other protocol deviations or the availability of post-randomization data.
This population set will be used for the primary analyses of all primary and secondary efficacy variables.

Primary: Disease-Free Survival (DFS)

End point title	Disease-Free Survival (DFS)

End point description:

DFS was defined as the interval from randomisation to locoregional or metastatic recurrence, the appearance of a secondary colon or rectal cancer, or death, whichever occurred first.

End point type	Primary

End point timeframe:

until the end of the follow-up or appearance of an event

End point values	FOLFOX4 plus Cetuximab	FOLFOX4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	791	811		
Units: patients				
Patients with locoregional or metastatic recurrenc	190	179		
Patients alive without event	601	632		

Statistical analyses

Statistical analysis title	Kaplan-Meier and log -rank test

Statistical analysis description:

DFS and overall survival with the Kaplan-Meier technique22 (primary analysis) and compared survival with a stratified two-sided log-rank test.

Comparison groups	FOLFOX4 plus Cetuximab v FOLFOX4
Number of subjects included in analysis	1602
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.29

Secondary: Overall Survival

End point title	Overall Survival

End point description:

OS was defined as the interval from randomisation to death, whichever occurred first.

End point type	Secondary

End point timeframe:

until the end of the follow-up or appearance of death

End point values	FOLFOX4 plus Cetuximab	FOLFOX4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	791	811		
Units: patients				
Death	94	85		
Alive patients	697	726		

Statistical analyses

Statistical analysis title	Kaplan-Meier and log -rank test
Comparison groups	FOLFOX4 plus Cetuximab v FOLFOX4
Number of subjects included in analysis	1602
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.47

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During treatment period and not earlier than 30 days after the last cycle.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Folfox + Cetuximab

Reporting group description:

all patients with signed (Main and KRAS) Informed Consent Forms who started treatment with available KRAS determination and with a KRAS wild-type status, i.e. without mutations located within the codon 12 and 13 of the KRAS gene and randomized in the Folfox +Ceuximab group

Reporting group title	Folfox

Reporting group description:

all patients with signed (Main and KRAS) Informed Consent Forms who started treatment with available KRAS determination and with a KRAS wild-type status, i.e. without mutations located within the codon 12 and 13 of the KRAS gene and randomized in the Folfox group

Serious adverse events	Folfox + Cetuximab	Folfox	
Total subjects affected by serious adverse events			
subjects affected / exposed	212 / 785 (27.01%)	148 / 805 (18.39%)	
number of deaths (all causes)	94	85	
number of deaths resulting from adverse events	5	3	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	10 / 785 (1.27%)	6 / 805 (0.75%)	
occurrences causally related to treatment / all	10 / 10	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 785 (0.13%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 785 (0.13%)	1 / 805 (0.12%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	14 / 785 (1.78%)	16 / 805 (1.99%)	
occurrences causally related to treatment / all	11 / 14	13 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 785 (0.00%)	1 / 805 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sudden death			
subjects affected / exposed	1 / 785 (0.13%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	8 / 785 (1.02%)	1 / 805 (0.12%)	
occurrences causally related to treatment / all	8 / 8	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	3 / 785 (0.38%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	39 / 785 (4.97%)	16 / 805 (1.99%)	
occurrences causally related to treatment / all	38 / 39	16 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	14 / 785 (1.78%)	4 / 805 (0.50%)	
occurrences causally related to treatment / all	13 / 14	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	11 / 785 (1.40%)	5 / 805 (0.62%)	
occurrences causally related to treatment / all	8 / 11	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	13 / 785 (1.66%)	10 / 805 (1.24%)	
occurrences causally related to treatment / all	9 / 13	9 / 10	
deaths causally related to treatment / all	1 / 1	1 / 1	
Pulmonary fibrosis			
subjects affected / exposed	2 / 785 (0.25%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 785 (0.13%)	1 / 805 (0.12%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infections and infestations			
Device related infection			
subjects affected / exposed	8 / 785 (1.02%)	4 / 805 (0.50%)	
occurrences causally related to treatment / all	1 / 8	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 785 (0.76%)	5 / 805 (0.62%)	
occurrences causally related to treatment / all	5 / 6	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	6 / 785 (0.76%)	4 / 805 (0.50%)	
occurrences causally related to treatment / all	4 / 6	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 785 (0.51%)	2 / 805 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Folfox + Cetuximab	Folfox	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	784 / 785 (99.87%)	804 / 805 (99.88%)	
Investigations			
Neutrophils count decreased			
subjects affected / exposed	533 / 785 (67.90%)	593 / 805 (73.66%)	
occurrences (all)	533	593	
Platelet count decreased			
subjects affected / exposed	497 / 785 (63.31%)	599 / 805 (74.41%)	
occurrences (all)	497	599	
Haemoglobin decreased			
subjects affected / exposed	449 / 785 (57.20%)	481 / 805 (59.75%)	
occurrences (all)	449	481	
Alanine aminotransferase increased			
subjects affected / exposed	202 / 785 (25.73%)	162 / 805 (20.12%)	
occurrences (all)	202	162	
Aspartate aminotransferase increased			
subjects affected / exposed	209 / 785 (26.62%)	177 / 805 (21.99%)	
occurrences (all)	209	177	
Gamma-glutamyltransferase increased			
subjects affected / exposed	133 / 785 (16.94%)	137 / 805 (17.02%)	
occurrences (all)	133	137	
Blood alkaline phosphatase increased			
subjects affected / exposed	115 / 785 (14.65%)	130 / 805 (16.15%)	
occurrences (all)	115	130	
White blood cell count decreased			
subjects affected / exposed	100 / 785 (12.74%)	124 / 805 (15.40%)	
occurrences (all)	100	124	
Nervous system disorders			

Neuropathy peripheral			
subjects affected / exposed	651 / 785 (82.93%)	723 / 805 (89.81%)	
occurrences (all)	651	723	
Dysgeusia			
subjects affected / exposed	146 / 785 (18.60%)	157 / 805 (19.50%)	
occurrences (all)	146	157	
Headache			
subjects affected / exposed	64 / 785 (8.15%)	89 / 805 (11.06%)	
occurrences (all)	64	89	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	502 / 785 (63.95%)	508 / 805 (63.11%)	
occurrences (all)	502	508	
Mucosal inflammation			
subjects affected / exposed	414 / 785 (52.74%)	289 / 805 (35.90%)	
occurrences (all)	414	289	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	117 / 785 (14.90%)	120 / 805 (14.91%)	
occurrences (all)	117	120	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	90 / 785 (11.46%)	37 / 805 (4.60%)	
occurrences (all)	90	37	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	491 / 785 (62.55%)	500 / 805 (62.11%)	
occurrences (all)	491	500	
Nausea			
subjects affected / exposed	447 / 785 (56.94%)	528 / 805 (65.59%)	
occurrences (all)	447	528	
Vomiting			
subjects affected / exposed	232 / 785 (29.55%)	268 / 805 (33.29%)	
occurrences (all)	232	268	
Constipation			

subjects affected / exposed	240 / 785 (30.57%)	240 / 805 (29.81%)	
occurrences (all)	240	240	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	121 / 785 (15.41%)	103 / 805 (12.80%)	
occurrences (all)	121	103	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	707 / 785 (90.06%)	25 / 805 (3.11%)	
occurrences (all)	707	25	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	210 / 785 (26.75%)	85 / 805 (10.56%)	
occurrences (all)	210	85	
Dry skin			
subjects affected / exposed	177 / 785 (22.55%)	22 / 805 (2.73%)	
occurrences (all)	177	22	
Dermatitis allergic			
subjects affected / exposed	102 / 785 (12.99%)	70 / 805 (8.70%)	
occurrences (all)	102	70	
Skin fissures			
subjects affected / exposed	148 / 785 (18.85%)	8 / 805 (0.99%)	
occurrences (all)	148	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	203 / 785 (25.86%)	158 / 805 (19.63%)	
occurrences (all)	203	158	
Hypokalemia			
subjects affected / exposed	80 / 785 (10.19%)	39 / 805 (4.84%)	
occurrences (all)	80	39	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2007	Correction of participating countries, provision of details of all involved groups and country coordinating investigators (changed for Austria and Germany) Provision of clear definitions of the conditions to be fulfilled and the expected time points for primary and final analyses, clarification of definition of end of trial Clarification of visit and assessment schedule At the request of the IDMC, introduction of electrolyte measurement at baseline, 3 months, 6 months after start of treatment, at the end of treatment Visit and at the second follow-up visit (12 months after surgery) if still abnormal Clarification of time intervals for colonoscopy Update of pretreatment recommendations before cetuximab administrations: addition of corticosteroid Clarification of dosage reduction and treatment continuation rules Harmonization of description of the adverse events page with the CRF Update of informed consent based on changes introduced by this amendment (main study and for translational research) Update of planned statistical analyses Correction of errors
30 April 2008	* Addition of a second primary objective, namely the comparison of treatments in patients with KRAS wild type tumors • Adjustment of the risk reduction (hazard ratio) expected from the addition of cetuximab, in the entire study population. • Implementation of one interim analysis for the entire study population and one for the population of patients with KRAS wild type tumors • Increase of the total sample size from 2000 to 2842 patients to achieve the necessary number of events for the primary statistical analysis within a reasonable time frame, considering the adjustments of the individual alpha required because of two primary endpoints and the implementation of interim analysis and the need to maintain the original power of 90%. • Update of the planned statistical analyses and related assumptions, considering the additional primary objective • Introduction of retrospective KRAS assessment in all patients • Clarification of time interval between curative R0 resection and start of treatment • Update of the Patient Information based on introduction of KRAS assessment (main study) • Update of the handling instructions and compatibility of cetuximab with various infusion set materials

14 August 2008	• Introduction of an inclusion criterion regarding KRAS status. • Introduction of prospective KRAS assessment in all new patients. The specific logistics are described in a separate document. • The only primary objective will be the comparison of disease free survival (DFS) between the two treatment arms in the population of patients with KRAS wild-type tumors. • Addition of a new secondary objective, namely the comparison of DFS in the entire population of all patients randomized up to 24:00h, 17 June 2008 (to be performed only if a significant effect on DFS, in the KRAS wild-type population is seen). • Interim analysis only for the primary objective in patients with a KRAS wild-type tumor. • In total 2099 patients have been included until the recruitment stop on 17 June 2008, of whom an estimated 957 patients have assessable KRAS wild-type tumors. An additional 450 patients with a KRAS wild-type tumor should be included to achieve the necessary number of events for the primary statistical analysis, within a reasonable time frame. Therefore, it is estimated that 825 patients will need to be assessed for the KRAS status of their tumors after the restart of patient enrollment (assuming 57.5% will be KRAS wild-type and there will be 5% withdrawals, for other reasons, prior to randomization). • Prolongation of the survival follow-up to 7 years after randomization of the last patient (i.e. 10.5 years in total assuming a recruitment period of 3.5 years). • Update of the planned statistical analyses and related assumptions, considering the population change for primary analysis. • Update of the Patient Information based on introduction of KRAS assessment (main study) and introduction of a new patient information and informed consent necessary for the prescreening of patients for KRAS status. • Update of Translational Research sections • Corrections of errors
30 June 2009	Change of an inclusion criterion regarding the age of the patients. The FFCD has decided to follow the additional DSMB recommendations regarding patients aged 71 or older which has strongly recommended taking a precautionary measure, no longer to include patients aged 71 or older (at screening), because of an increased risk of toxicity or death observed in the population > 70 years old in the PETACC8 study as compared to the population < 71 years old, whatever the treatment arm is. Furthermore, these results are in line with the analysis of the ACCENT database presented at the main ASCO meeting (2009) that support the use of 5-FU-based regimens without Oxaliplatin in elderly patients >70 years old (McCleary et al., ASCO 2009).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24928083