Clinical trial results:
Essai de phase II, randomisé multicentrique, évaluant l'efficacité d'une chimiothérapie standard à base de fluoropyrimidine associée au cétuximab ou au bévacizumab, chez des patients kras sauvage, atteints d'un cancer colorectal métastatique, en progression après une 1ere ligne de traitement avec bévacizumab.

Summary

EudraCT number	2009-012942-22
Trial protocol	FR
Global end of trial date	20 February 2019

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information

Trial identification

Sponsor protocol code	PRODIGE 18 - ACCORD 22/0906

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01442649
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75013
Public contact	Nourredine AIT-RAHMOUNE, UNICANCER, 33 171936704, n.ait-rahmoune@unicancer.fr
Scientific contact	Nourredine AIT-RAHMOUNE, UNICANCER, 33 171936704, n.ait-rahmoune@unicancer.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	01 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of standard fluoropyrimidine-based chemotherapy associated with either cetuximab or bevacizumab for the treatment of wild-type RAS (KRAS and NRAS) metastatic colorectal cancer after a first-line of treatment with bevacizumab, in terms of progression-free survival (PFS).

Protection of trial subjects:

This study was conducted in accordance with the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) and the applicable local regulatory requirements and laws.
Furthermore, an independent Ethics Committees reviewed and gave a favorable opinion to the study documents, including the initial protocol and all subsequent amendments, and all information and documents provided to subjects/patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 December 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 132
Worldwide total number of subjects	132
EEA total number of subjects	132

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)	76
From 65 to 84 years	56
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Prodige 18 - Accord 22 was a phase II open-label randomized multicenter study, evaluating the efficacy of standard fluoropyrimidine-based chemotherapy associated with either cetuximab or bevacizumab for the treatment of wild-type RAS (KRAS and NRAS) metastatic colorectal cancer after a first-line of treatment with bevacizumab.+

Pre-assignment

Screening details:

The study consisted of a screening phase before randomization to establish eligibility, a treatment phase, and a long-term follow-up to monitor the progression-free survival, overall response rate, overall survival, and safety.

Period 1

Period 1 title	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	Bevacizumab

Arm description:

Bevacizumab was administered at a dose of 5 mg/kg intravenously (IV) every 14 days associated with standard fluoropyrimidine-based chemotherapy (either mFOLFOX6 or FOLFIRI).
* mFOLFOX6: Oxaliplatin at 85 mg/m², IV, over 120 min on D1. Folinic acid at 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with oxaliplatin, IV, over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a continuous IV perfusion of 5-FU (2400 mg/m²) over 46 h. The treatment cycle was repeated every 14 days.
* FOLFIRI: Irinotecan at 180 mg/m², IV, 90 min on D1. Folinic acid at either 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with irinotecan, IV over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a perfusion of 5-fluorouracil of 2400 mg/m² perfusion IV over 46 h. The treatment cycle was repeated every 14 days.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was dministered at a dose of 5 mg/kg intravenously (IV) every 14 days associated with standard fluoropyrimidine- based chemotherapy (either mFOLFOX6 or FOLFIRI).
Initially bevacizumab was administered IV over 90 min (±15 min). If this first perfusion was well tolerated the 2nd perfusion could be administered over 60 min (±15 min). Similarly, if this was well tolerated bevacizumab could subsequently be administered over 30 min (±15 min). If however, the initial administration was not well tolerated subsequent administrations of bevacizumab were to be administrated over 90 min with premedication as per local standards.

Arm title	Cetuximab

Arm description:

Cetuximab was administered at a dose of 500 mg/m² intravenously (IV) every 14 days associated with standard fluoropyrimidine- based chemotherapy (either mFOLFOX6 or FOLFIRI).
* mFOLFOX6: Oxaliplatin at 85 mg/m², IV, over 120 min on D1. Folinic acid at 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with oxaliplatin, IV, over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a continuous IV perfusion of 5-FU (2400 mg/m²) over 46 h. The treatment cycle was repeated every 14 days.
* FOLFIRI: Irinotecan at 180 mg/m², IV, 90 min on D1. Folinic acid at either 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with irinotecan, IV over 2 h on D1. 5-FU

bolus (400 mg/m²) on D1, and then a perfusion of 5-fluorouracil of 2400 mg/m² perfusion IV over 46 h. The treatment cycle was repeated every 14 days.

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab was administered at a dose of 500 mg/m² intravenously (IV) every 14 days associated with standard fluoropyrimidine-based chemotherapy (either mFOLFOX6 or FOLFIRI).
Allergic reactions and hypersensitivity to cetuximab are known to occur during the perfusion. As a preventative measure all patients received premedication with antihistamines and corticosteroids (methylprednisolone [Solumedrol®] 120 mg and an anti-H1 IV) before the first, second, and third cetuximab administration. The premedication could be stopped at subsequent administrations in absence of a reaction.
Preventative treatment with a systemic antibiotherapy (e.g. doxycycline 100 mg/day) could be administered to reduce the frequency and intensity of cutaneous toxicities.

Number of subjects in period 1	Bevacizumab	Cetuximab
Started	65	67
Completed	26	18
Not completed	39	49
Physician decision	7	4
Consent withdrawn by subject	-	2
Disease progression	31	35
Adverse event, non-fatal	1	1
Death	-	4
Hospitalisation	-	1
Second line treatment	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Bevacizumab

Reporting group description:

Bevacizumab was administered at a dose of 5 mg/kg intravenously (IV) every 14 days associated with standard fluoropyrimidine-based chemotherapy (either mFOLFOX6 or FOLFIRI).
* mFOLFOX6: Oxaliplatin at 85 mg/m², IV, over 120 min on D1. Folinic acid at 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with oxaliplatin, IV, over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a continuous IV perfusion of 5-FU (2400 mg/m²) over 46 h. The treatment cycle was repeated every 14 days.
* FOLFIRI: Irinotecan at 180 mg/m², IV, 90 min on D1. Folinic acid at either 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with irinotecan, IV over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a perfusion of 5-fluorouracil of 2400 mg/m² perfusion IV over 46 h. The treatment cycle was repeated every 14 days.

Reporting group title	Cetuximab

Reporting group description:

Cetuximab was administered at a dose of 500 mg/m² intravenously (IV) every 14 days associated with standard fluoropyrimidine- based chemotherapy (either mFOLFOX6 or FOLFIRI).
* mFOLFOX6: Oxaliplatin at 85 mg/m², IV, over 120 min on D1. Folinic acid at 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with oxaliplatin, IV, over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a continuous IV perfusion of 5-FU (2400 mg/m²) over 46 h. The treatment cycle was repeated every 14 days.
* FOLFIRI: Irinotecan at 180 mg/m², IV, 90 min on D1. Folinic acid at either 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with irinotecan, IV over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a perfusion of 5-fluorouracil of 2400 mg/m² perfusion IV over 46 h. The treatment cycle was repeated every 14 days.

Reporting group values	Bevacizumab	Cetuximab	Total
Number of subjects	65	67	132
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	37	39	76
From 65-84 years	28	28	56
85 years and over	0	0	0
Age continuous Units: years			
median	61	63	
full range (min-max)	33 to 83	37 to 84	-
Gender categorical Units: Subjects			
Female	24	23	47
Male	41	44	85
Eastern Cooperative Oncology Group Units: Subjects			
ECOG 0	36	38	74

ECOG 1	27	27	54
Missing	2	2	4
ECG Units: Subjects			
Abnormal	8	6	14
Normal	49	56	105
Unknown	8	5	13
Characteristics of the primary tumor Units: Subjects			
Right colon	12	7	19
left colon	11	14	25
left and right colon	1	1	2
Colon	0	1	1
Rectum	18	21	39
Other	23	23	46
Systolic blood pressure Units: mm Hg			
median	82	80	
full range (min-max)	39 to 130	50 to 117	-
Diastoloic blood pressure Units: mm Hg			
median	132	133	
full range (min-max)	80 to 185	98 to 181	-

End points

End points reporting groups

Reporting group title	Bevacizumab

Reporting group description:

Bevacizumab was administered at a dose of 5 mg/kg intravenously (IV) every 14 days associated with standard fluoropyrimidine-based chemotherapy (either mFOLFOX6 or FOLFIRI).
* mFOLFOX6: Oxaliplatin at 85 mg/m², IV, over 120 min on D1. Folinic acid at 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with oxaliplatin, IV, over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a continuous IV perfusion of 5-FU (2400 mg/m²) over 46 h. The treatment cycle was repeated every 14 days.
* FOLFIRI: Irinotecan at 180 mg/m², IV, 90 min on D1. Folinic acid at either 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with irinotecan, IV over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a perfusion of 5-fluorouracil of 2400 mg/m² perfusion IV over 46 h. The treatment cycle was repeated every 14 days.

Reporting group title	Cetuximab

Reporting group description:

Cetuximab was administered at a dose of 500 mg/m² intravenously (IV) every 14 days associated with standard fluoropyrimidine- based chemotherapy (either mFOLFOX6 or FOLFIRI).
* mFOLFOX6: Oxaliplatin at 85 mg/m², IV, over 120 min on D1. Folinic acid at 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with oxaliplatin, IV, over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a continuous IV perfusion of 5-FU (2400 mg/m²) over 46 h. The treatment cycle was repeated every 14 days.
* FOLFIRI: Irinotecan at 180 mg/m², IV, 90 min on D1. Folinic acid at either 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with irinotecan, IV over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a perfusion of 5-fluorouracil of 2400 mg/m² perfusion IV over 46 h. The treatment cycle was repeated every 14 days.

Primary: 4-month progression-free survival rate

End point title	4-month progression-free survival rate

End point description:

Progression-free Survival was defined as the time from randomisation to progression (according to RECIST v1.1) or death. Patients alive without progression were censored at the last follow-up

End point type	Primary

End point timeframe:

4 months after randomisation

End point values	Bevacizumab	Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	67		
Units: Number of subjects				
median (confidence interval 95%)	80.3 (68.0 to 88.3)	66.7 (53.6 to 76.8)		

Statistical analyses

Statistical analysis title	4-month PFS analysis
Comparison groups	Bevacizumab v Cetuximab

Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.495
upper limit	1.018
Variability estimate	Standard deviation

Secondary: Objective tumor response rate

End point title	Objective tumor response rate

End point description:

Objective response rate was defined as the rate of occurrence of a complete response or a partial response (according to RECIST v1.1) from the date of randomization until the end of treatment.

End point type	Secondary

End point timeframe:

Up to approximately 45 months

End point values	Bevacizumab	Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	67		
Units: Number of subjects				
median (confidence interval 95%)	24.6 (14.1 to 35.1)	31.8 (20.3 to 43.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival was defined as the time from randomization until progression (according to RECIST v1.1) or death. Patients alive without progression were censored at the last follow-up.

End point type	Secondary

End point timeframe:

Up to approximately 45 months

End point values	Bevacizumab	Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	67		
Units: Number of patients				
median (confidence interval 95%)	7.1 (5.7 to 8.2)	5.6 (4.2 to 6.5)		

Statistical analyses

Statistical analysis title	PFS analysis
Comparison groups	Bevacizumab v Cetuximab
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Logrank
Dispersion value	0.0603

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was defined as the time from randomization until death of any cause or last follow-up (censored data).

End point type	Secondary

End point timeframe:

Up to approximately 45 months

End point values	Bevacizumab	Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	67		
Units: Number of patients				
median (confidence interval 95%)	15.8 (9.5 to 22.3)	10.4 (7.0 to 16.2)		

Statistical analyses

Statistical analysis title	OS analysis
Comparison groups	Bevacizumab v Cetuximab

Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Logrank
Dispersion value	0.0732

Secondary: Overall survival from the start of first-line chemotherapy for the meatastatic disease

End point title	Overall survival from the start of first-line chemotherapy for the meatastatic disease

End point description:

Overall survival from the start of first-line chemotherapy for mCRC was defined as the time from the start date of first-line chemotherapy for the metastatic disease until death of any cause or last follow-up news (censored data).

End point type	Secondary

End point timeframe:

Up to approximately 45 months

End point values	Bevacizumab	Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	67		
Units: Number of subjects				
median (confidence interval 95%)	32.7 (25.4 to 36.6)	25.5 (21.8 to 34.8)		

Statistical analyses

Statistical analysis title	OS from first metastasis treatment analysis
Comparison groups	Bevacizumab v Cetuximab
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Logrank
Dispersion value	0.5763

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall period of the study (up to 48 months after first study intake)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Bevacizumab

Reporting group description:

Bevacizumab was administered at a dose of 5 mg/kg intravenously (IV) every 14 days associated with standard fluoropyrimidine-based chemotherapy (either mFOLFOX6 or FOLFIRI).
* mFOLFOX6: Oxaliplatin at 85 mg/m², IV, over 120 min on D1. Folinic acid at 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with oxaliplatin, IV, over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a continuous IV perfusion of 5-FU (2400 mg/m²) over 46 h. The treatment cycle was repeated every 14 days.
* FOLFIRI: Irinotecan at 180 mg/m², IV, 90 min on D1. Folinic acid at either 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with irinotecan, IV over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a perfusion of 5-fluorouracil of 2400 mg/m² perfusion IV over 46 h. The treatment cycle was repeated every 14 days.

Reporting group title	Cetuximab

Reporting group description:

Cetuximab was administered at a dose of 500 mg/m² intravenously (IV) every 14 days associated with standard fluoropyrimidine- based chemotherapy (either mFOLFOX6 or FOLFIRI).
* mFOLFOX6: Oxaliplatin at 85 mg/m², IV, over 120 min on D1. Folinic acid at 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with oxaliplatin, IV, over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a continuous IV perfusion of 5-FU (2400 mg/m²) over 46 h. The treatment cycle was repeated every 14 days.
* FOLFIRI: Irinotecan at 180 mg/m², IV, 90 min on D1. Folinic acid at either 400 mg/m² if racemic or at 200 mg/m² if enantiomeric (L-folinic acid), simultaneously with irinotecan, IV over 2 h on D1. 5-FU bolus (400 mg/m²) on D1, and then a perfusion of 5-fluorouracil of 2400 mg/m² perfusion IV over 46 h. The treatment cycle was repeated every 14 days.

Serious adverse events	Bevacizumab	Cetuximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 65 (36.92%)	24 / 67 (35.82%)	
number of deaths (all causes)	43	50	
number of deaths resulting from adverse events	5	5	
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 65 (3.08%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fever			
subjects affected / exposed	1 / 65 (1.54%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 65 (4.62%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Immune system disorders			
Allergic respiratory symptom			
subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allergic reaction			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug allergy			
subjects affected / exposed	1 / 65 (1.54%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian torsion			
subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemoptysis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumopathy			
subjects affected / exposed	1 / 65 (1.54%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alkaline phosphatase increased			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 65 (9.23%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	2 / 65 (3.08%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	4 / 65 (6.15%)	5 / 67 (7.46%)	
occurrences causally related to treatment / all	1 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Bowel obstruction			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 65 (1.54%)	3 / 67 (4.48%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis oral			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain abdominal			
subjects affected / exposed	0 / 65 (0.00%)	2 / 67 (2.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Icterus			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Cellulitis of leg			
subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral dilatation			
subjects affected / exposed	0 / 65 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Diabetes mellitus aggravated			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Femur fracture			

subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Septicemia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 65 (3.08%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Bevacizumab	Cetuximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 65 (100.00%)	67 / 67 (100.00%)	
Cardiac disorders			
Epistaxis			
subjects affected / exposed	12 / 65 (18.46%)	5 / 67 (7.46%)	
occurrences (all)	12	5	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	26 / 65 (40.00%)	27 / 67 (40.30%)	
occurrences (all)	26	27	
Motor neurone disease			
subjects affected / exposed	6 / 65 (9.23%)	1 / 67 (1.49%)	
occurrences (all)	6	1	
Paraesthesia			
subjects affected / exposed	29 / 65 (44.62%)	27 / 67 (40.30%)	
occurrences (all)	29	27	
Taste disorder			
subjects affected / exposed	5 / 65 (7.69%)	5 / 67 (7.46%)	
occurrences (all)	5	5	

Blood and lymphatic system disorders			
Haemoglobin			
subjects affected / exposed	43 / 65 (66.15%)	46 / 67 (68.66%)	
occurrences (all)	43	46	
Neutrophil			
subjects affected / exposed	40 / 65 (61.54%)	35 / 67 (52.24%)	
occurrences (all)	40	35	
Platelet			
subjects affected / exposed	40 / 65 (61.54%)	30 / 67 (44.78%)	
occurrences (all)	40	30	
Leukocyte			
subjects affected / exposed	37 / 65 (56.92%)	29 / 67 (43.28%)	
occurrences (all)	37	29	
Lymphocyte			
subjects affected / exposed	30 / 65 (46.15%)	36 / 67 (53.73%)	
occurrences (all)	30	36	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	55 / 65 (84.62%)	50 / 67 (74.63%)	
occurrences (all)	55	50	
Fever			
subjects affected / exposed	9 / 65 (13.85%)	4 / 67 (5.97%)	
occurrences (all)	9	4	
Weight decreased			
subjects affected / exposed	13 / 65 (20.00%)	14 / 67 (20.90%)	
occurrences (all)	13	14	
Pain			
subjects affected / exposed	21 / 65 (32.31%)	25 / 67 (37.31%)	
occurrences (all)	21	25	
Immune system disorders			
Hypersensitivity to oxaliplatin			
subjects affected / exposed	5 / 65 (7.69%)	2 / 67 (2.99%)	
occurrences (all)	5	2	
Gastrointestinal disorders			
Anorexia			

subjects affected / exposed	21 / 65 (32.31%)	22 / 67 (32.84%)	
occurrences (all)	21	22	
Constipation			
subjects affected / exposed	18 / 65 (27.69%)	19 / 67 (28.36%)	
occurrences (all)	18	19	
Diarrhoea			
subjects affected / exposed	42 / 65 (64.62%)	25 / 67 (37.31%)	
occurrences (all)	42	25	
Nausea			
subjects affected / exposed	38 / 65 (58.46%)	25 / 67 (37.31%)	
occurrences (all)	38	25	
Vomiting			
subjects affected / exposed	15 / 65 (23.08%)	14 / 67 (20.90%)	
occurrences (all)	15	14	
Stomatitis			
subjects affected / exposed	20 / 65 (30.77%)	24 / 67 (35.82%)	
occurrences (all)	20	24	
Abdominal pain			
subjects affected / exposed	13 / 65 (20.00%)	9 / 67 (13.43%)	
occurrences (all)	13	9	
Hepatobiliary disorders			
Bilirubin			
subjects affected / exposed	13 / 65 (20.00%)	14 / 67 (20.90%)	
occurrences (all)	13	14	
alkaline phophatase			
subjects affected / exposed	47 / 65 (72.31%)	46 / 67 (68.66%)	
occurrences (all)	47	46	
Alanine aminotransferase			
subjects affected / exposed	39 / 65 (60.00%)	37 / 67 (55.22%)	
occurrences (all)	39	37	
Aspartate aminotransferase			
subjects affected / exposed	43 / 65 (66.15%)	42 / 67 (62.69%)	
occurrences (all)	43	42	
Gamma-glutamyltransferase			
subjects affected / exposed	59 / 65 (90.77%)	56 / 67 (83.58%)	
occurrences (all)	59	56	

Lactate dehydrogenase			
subjects affected / exposed	40 / 65 (61.54%)	41 / 67 (61.19%)	
occurrences (all)	40	41	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 65 (10.77%)	5 / 67 (7.46%)	
occurrences (all)	7	5	
Rash			
subjects affected / exposed	3 / 65 (4.62%)	30 / 67 (44.78%)	
occurrences (all)	3	30	
Hand and foot skin reaction			
subjects affected / exposed	7 / 65 (10.77%)	11 / 67 (16.42%)	
occurrences (all)	7	11	
Paronychia			
subjects affected / exposed	0 / 65 (0.00%)	13 / 67 (19.40%)	
occurrences (all)	0	13	
Skin fissures			
subjects affected / exposed	2 / 65 (3.08%)	19 / 67 (28.36%)	
occurrences (all)	2	19	
Pruritus			
subjects affected / exposed	3 / 65 (4.62%)	11 / 67 (16.42%)	
occurrences (all)	3	11	
Dermatitis acneiform			
subjects affected / exposed	1 / 65 (1.54%)	46 / 67 (68.66%)	
occurrences (all)	1	46	
Skin hyperpigmentation			
subjects affected / exposed	0 / 65 (0.00%)	4 / 67 (5.97%)	
occurrences (all)	0	4	
Dry skin			
subjects affected / exposed	7 / 65 (10.77%)	27 / 67 (40.30%)	
occurrences (all)	7	27	
Renal and urinary disorders			
Creatinine			
subjects affected / exposed	24 / 65 (36.92%)	16 / 67 (23.88%)	
occurrences (all)	24	16	
Haematuria			

subjects affected / exposed	4 / 65 (6.15%)	6 / 67 (8.96%)	
occurrences (all)	4	6	
Proteinuria			
subjects affected / exposed	18 / 65 (27.69%)	6 / 67 (8.96%)	
occurrences (all)	18	6	
Infections and infestations			
Infection			
subjects affected / exposed	3 / 65 (4.62%)	4 / 67 (5.97%)	
occurrences (all)	3	4	
Localised infection			
subjects affected / exposed	4 / 65 (6.15%)	6 / 67 (8.96%)	
occurrences (all)	4	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2011	The cetuximab infusion duration was modified. It was calculated for a body surface of 1.20 m² in the amended version of the protocol.
19 September 2014	- Results from other studies (N Engl J Med, 2013. 369(11): p. 1023-34 and EJC, Vol. 49. 2013. Abstract 17) published during the recruitment period of this clinical trial demonstrated that treatment with anti-EGFR plus FOLFOX or FOLFIRI as no benefits for patients with rare KRAS or NRAS mutations. Inclusion criteria were modified to exclude these patients from the study. - During the recruitment period of the Prodige 18 - Accord 22 trial, results of a clinical trial published by Loprinzi et al (J Clin Oncol, 2014. 32(10): p. 997-1005), demonstrated that calcium gluconate and magnesium sulfate do not prevent oxaliplatin-induced neurotoxicity. Thus, the recommendation to perfuse patients with a solution of gluconate calcium and sulfate magnesium before and after each oxaliplatin injection was removed from the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The results must be interpreted with caution owing to the low number of patients included and the phase II study design.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30422156