



Clinical trial results:

Phase II multicentric randomized trial, evaluating the best protocol of chemotherapy, associated with targeted therapy according to the tumor RAS (KRAS and NRAS) status, in Metastatic Colorectal Cancer (MCRC) Patients With Initially Nonresectable Hepatic Metastases (METHEP-2)

Summary

EudraCT number	2009-012813-22
Trial protocol	FR
Global end of trial date	06 January 2021

Results information

Result version number	v1 (current)
This version publication date	05 January 2025
First version publication date	05 January 2025

Trial information

Trial identification

Sponsor protocol code	PRODIGE 14 - ACCORD 21/0905
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01442935
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, Paris, France,
Public contact	Nourredine AIT-RAHMOUNE,, UNICANCER, 33 0171936704, n.ait-rahmoune@unicancer.fr
Scientific contact	Nourredine AIT-RAHMOUNE,, UNICANCER, 33 0171936704, 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	15 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2015
Global end of trial reached?	Yes
Global end of trial date	06 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Prodige 14 - Accord 21 was a multicenter, open-label, randomized (1:1) phase II study. The primary objective was to assess which of BiCT or TriCT combined with a targeted therapy as conversion therapy would provide the better hepatic metastasis resection rates in colorectal cancer patients with initially non-resectable hepatic metastases. Patients randomized to the BiCT Arm were also randomly allocated BiCT, either FOLFIRI or FOLFOX.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 February 2011
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	France: 256
Worldwide total number of subjects	256
EEA total number of subjects	256

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)	181
From 65 to 84 years	75
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The Prodige 17 – Accord 21 study randomized 256 patients, in 33 centers in France, between 09-Feb-2011 and the 30-Apr-2015. Overall, 126 patients were randomized to bi-chemotherapy (BiCT) and 130 to tri-chemotherapy (TriCT).

Pre-assignment

Screening details:

The study consisted of screening phase to establish patients' eligibility and document baseline measurements, a treatment phase 12 cycles in both study arms, and a long-term follow-up to monitor the hepatic metastases resection, objective response rate, complete remission rate, relapse free survival rate, overall survival and the 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	BiCT Arm

Arm description:

Patients were randomly allocated either FOLFIRI or FOLFOX chemotherapy every 14 days (2-week cycles) combined with targeted therapy according to the patient tumor RAS status (initially KRAS): cetuximab if wt-RAS (initially wt-KRAS) or bevacizumab if mt-RAS (initially mt-KRAS).

*FOLFIRI or FOLFOX chemotherapy:

-FOLFOX: oxaliplatin (85 mg/m²), folinic acid (400 mg/m²) or L-folinic acid (200 mg/m²), a bolus dose of fluorouracil (400 mg/m²), and a 46-h infusion of fluorouracil (2400 mg/m²).

Or

-FOLFIRI: irinotecan (180 mg/m²), folinic acid (400 mg/m²) or L-folinic acid (200 mg/m²), a bolus dose of fluorouracil (400 mg/m²), and a 46-h infusion of fluorouracil (2400 mg/m²).

*targeted therapy: mt-RAS (initially mt-KRAS) patients received bevacizumab (5 mg/kg) and wt-RAS (initially wt-KRAS) patients received cetuximab (500 mg/m²) intravenously on day 1 of each chemotherapy cycle.

Arm type	Active comparator
Investigational medicinal product name	oxaliplatin or irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

85 mg/m² (oxaliplatin) on day 1 every 14 days (2-week cycles) for patients were randomly allocated to FOLFOX chemotherapy every 14 days (2-week cycles).

180 mg/m² (irinotecan) on day 1 every 14 days (2-week cycles) for patients were randomly allocated to FOLFIRI chemotherapy every 14 days (2-week cycles).

Investigational medicinal product name	folinic acid/L-folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use
Dosage and administration details:	
400 mg/m ² (folinic acid) or 200 mg/m ² (L-folinic acid) on day 1 every 14 days (2-week cycles)	
Investigational medicinal product name	fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use
Dosage and administration details:	
400 mg/m ² bolus on day 1 then 2400 mg/m ² infusion over 46 h every 14 days.	
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:	
5 mg/kg intravenously on day 1 of each chemotherapy cycle for mt-RAS (initially mt-KRAS) patients.	
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:	
500 mg/m ² intravenously on day 1 of each chemotherapy cycle for wt-RAS (initially wt-KRAS) patients.	
Arm title	TriCT Arm

Arm description:

Patients were administered FOLFIRINOX chemotherapy every 14 days (2-week cycles) combined with targeted therapy according to the patient tumor RAS status (initially KRAS): cetuximab if wt-RAS (initially wt-KRAS) or bevacizumab if mt-RAS (initially mt-KRAS).

*FOLFIRINOX regimen on day 1 of each 2-week cycle as follows: oxaliplatin (85 mg/m²) was administered as an intravenous infusion for 120 min, followed by irinotecan (150 mg/m²) as an intravenous infusion over 90 min and leucovorin (200 mg/m²) as an intravenous infusion over 120 min. Fluorouracil (400 mg/m²) was delivered as a bolus, followed by a 46-h continuous infusion at 2400 mg/m².

*targeted therapy: mt-RAS patients received bevacizumab (5 mg/kg) and wt-RAS patients received cetuximab (500 mg/m²) intravenously on day 1 of each chemotherapy cycle.

Arm type	Experimental
Investigational medicinal product name	oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
85 mg/m ² on day 1 every 14 days	
Investigational medicinal product name	irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
150 mg/m ² on day 1 every 14 days	

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 200 mg/m ² on day 1 every 14 days	
Investigational medicinal product name	fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m ² bolus on day 1 then 2400 mg/m ² infusion over 46 h every 14 days.	
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: 5 mg/kg intravenously on day 1 of each chemotherapy cycle for mt-RAS (initially mt-KRAS) patients.	
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: 500 mg/m ² intravenously on day 1 of each chemotherapy cycle for wt-RAS (initially wt-KRAS) patients.	

Number of subjects in period 1	BiCT Arm	TriCT Arm
Started	126	130
Completed	73	75
Not completed	53	55
Consent withdrawn by subject	1	-
Physician decision	18	23
Disease progression	11	9
Toxicity	10	11
Death	5	4
Other reason	7	7
Lost to follow-up	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	BiCT Arm
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Reporting group description:

Patients were randomly allocated either FOLFIRI or FOLFOX chemotherapy every 14 days (2-week cycles) combined with targeted therapy according to the patient tumor RAS status (initially KRAS): cetuximab if wt-RAS (initially wt-KRAS) or bevacizumab if mt-RAS (initially mt-KRAS).

*FOLFIRI or FOLFOX chemotherapy:

-FOLFOX: oxaliplatin (85 mg/m²), folinic acid (400 mg/m²) or L-folinic acid (200 mg/m²), a bolus dose of fluorouracil (400 mg/m²), and a 46-h infusion of fluorouracil (2400 mg/m²).

Or

-FOLFIRI: irinotecan (180 mg/m²), folinic acid (400 mg/m²) or L-folinic acid (200 mg/m²), a bolus dose of fluorouracil (400 mg/m²), and a 46-h infusion of fluorouracil (2400 mg/m²).

*targeted therapy: mt-RAS (initially mt-KRAS) patients received bevacizumab (5 mg/kg) and wt-RAS (initially wt-KRAS) patients received cetuximab (500 mg/m²) intravenously on day 1 of each chemotherapy cycle.

Reporting group title	TriCT Arm
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Reporting group description:

Patients were administered FOLFIRINOX chemotherapy every 14 days (2-week cycles) combined with targeted therapy according to the patient tumor RAS status (initially KRAS): cetuximab if wt-RAS (initially wt-KRAS) or bevacizumab if mt-RAS (initially mt-KRAS).

*FOLFIRINOX regimen on day 1 of each 2-week cycle as follows: oxaliplatin (85 mg/m²) was administered as an intravenous infusion for 120 min, followed by irinotecan (150 mg/m²) as an intravenous infusion over 90 min and leucovorin (200 mg/m²) as an intravenous infusion over 120 min. Fluorouracil (400 mg/m²) was delivered as a bolus, followed by a 46-h continuous infusion at 2400 mg/m².

*targeted therapy: mt-RAS patients received bevacizumab (5 mg/kg) and wt-RAS patients received cetuximab (500 mg/m²) intravenously on day 1 of each chemotherapy cycle.

Reporting group values	BiCT Arm	TriCT Arm	Total
Number of subjects	126	130	256
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)	84	97	181
From 65-84 years	42	33	75
85 years and over	0	0	0
Age continuous			
Units: years			
median	61	60	
full range (min-max)	29 to 75	27 to 78	-
Gender categorical			
Units: Subjects			
Female	44	47	91

Male	82	81	163
Missing data	0	2	2
ECOG			
Units: Subjects			
ECOG 0	84	82	166
ECOG 1	42	46	88
Missing data	0	2	2
Location of primary tumor			
Units: Subjects			
Right colon	32	28	60
Left colon	58	63	121
Rectum	33	34	67
Multiple sites	3	4	7
Missing data	0	1	1
Timing of primary tumor resection			
Units: Subjects			
Not resected	44	35	79
Before study inclusion	40	43	83
During the study	42	52	94
Proportion of liver cancerous			
Units: Subjects			
00-25%	32	40	72
26-50%	25	17	42
51-75%	14	12	26
>75%	6	5	11
Missing data	49	56	105
Reason for nonresectability			
Units: Subjects			
Technical	48	40	88
Oncological	62	64	126
Both	16	23	39
Missing data	0	3	3
Weight			
Units: Kg			
median	73	75	
full range (min-max)	43 to 140	43 to 153	-
Height			
Units: cm			
median	171	170	
full range (min-max)	148 to 193	149 to 192	-
Number of liver metastases			
Units: Median			
median	3	4	
full range (min-max)	0 to 52	0 to 31	-

End points

End points reporting groups

Reporting group title	BiCT Arm
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Reporting group description:

Patients were randomly allocated either FOLFIRI or FOLFOX chemotherapy every 14 days (2-week cycles) combined with targeted therapy according to the patient tumor RAS status (initially KRAS): cetuximab if wt-RAS (initially wt-KRAS) or bevacizumab if mt-RAS (initially mt-KRAS).

*FOLFIRI or FOLFOX chemotherapy:

-FOLFOX: oxaliplatin (85 mg/m²), folinic acid (400 mg/m²) or L-folinic acid (200 mg/m²), a bolus dose of fluorouracil (400 mg/m²), and a 46-h infusion of fluorouracil (2400 mg/m²).

Or

-FOLFIRI: irinotecan (180 mg/m²), folinic acid (400 mg/m²) or L-folinic acid (200 mg/m²), a bolus dose of fluorouracil (400 mg/m²), and a 46-h infusion of fluorouracil (2400 mg/m²).

*targeted therapy: mt-RAS (initially mt-KRAS) patients received bevacizumab (5 mg/kg) and wt-RAS (initially wt-KRAS) patients received cetuximab (500 mg/m²) intravenously on day 1 of each chemotherapy cycle.

Reporting group title	TriCT Arm
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Reporting group description:

Patients were administered FOLFIRINOX chemotherapy every 14 days (2-week cycles) combined with targeted therapy according to the patient tumor RAS status (initially KRAS): cetuximab if wt-RAS (initially wt-KRAS) or bevacizumab if mt-RAS (initially mt-KRAS).

*FOLFIRINOX regimen on day 1 of each 2-week cycle as follows: oxaliplatin (85 mg/m²) was administered as an intravenous infusion for 120 min, followed by irinotecan (150 mg/m²) as an intravenous infusion over 90 min and leucovorin (200 mg/m²) as an intravenous infusion over 120 min. Fluorouracil (400 mg/m²) was delivered as a bolus, followed by a 46-h continuous infusion at 2400 mg/m².

*targeted therapy: mt-RAS patients received bevacizumab (5 mg/kg) and wt-RAS patients received cetuximab (500 mg/m²) intravenously on day 1 of each chemotherapy cycle.

Primary: Hepatic metastases resection rate (R0 or R1)

End point title	Hepatic metastases resection rate (R0 or R1)
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End point description:

The primary endpoint was the hepatic metastases resection rate (R0 or R1) in the TriCT/Experimental Arm (tri-chemotherapy with targeted therapy) versus in the BiCT/Control Arm (bi-chemotherapy with targeted therapy).

End point type	Primary
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End point timeframe:

at least 4-6 weeks after the end of chemotherapy.

End point values	BiCT Arm	TriCT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	130		
Units: percent				
number (confidence interval 95%)	48.4 (39 to 57)	56.9 (48 to 66)		

Statistical analyses

Statistical analysis title	Hepatic metastases resection analysis
Comparison groups	BiCT Arm v TriCT Arm
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	2.7

Secondary: Objective response rate

End point title	Objective response rate
End point description: The objective response rate (complete response [CR] and partial response [PR]), at the first tumor assessment, after 4 cycles of treatment, according to the RECIST v1.1. Patients with symptoms suggesting disease progression had a tumor evaluation when the symptoms occurred.	
End point type	Secondary
End point timeframe: after 8 weeks	

End point values	BiCT Arm	TriCT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	130		
Units: percent				
median (confidence interval 95%)				
Objective response rate	67 (56.7 to 76.2)	76.5 (66.9 to 84.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete remission rate

End point title	Complete remission rate
End point description: The proportion of patients with remission at 6 months after the last study treatment (hepatic surgery or last chemotherapy cycle)	
End point type	Secondary

End point timeframe:

at 6 months after the last study treatment (hepatic surgery or last chemotherapy cycle).

End point values	BiCT Arm	TriCT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	130		
Units: percent				
median (confidence interval 95%)	52.0 (31 to 72)	41.9 (25 to 61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical resection rates (R0, R1, and R2)

End point title	Surgical resection rates (R0, R1, and R2)
End point description:	The surgical resection rates (R0, R1, and R2).
End point type	Secondary
End point timeframe:	24 weeks.

End point values	BiCT Arm	TriCT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	130		
Units: Number of patients				
R0	44	60		
R1	17	14		
R2	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse-free survival rate

End point title	Relapse-free survival rate
End point description:	
End point type	Secondary
End point timeframe:	Relapse-free Survival was evaluated between randomisation to the date of relapse or death for any

cause (1 , 2 and 3 years).

End point values	BiCT Arm	TriCT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	130		
Units: Months				
median (confidence interval 95%)	12.5 (11.1 to 13.9)	13.8 (13.1 to 15.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Response duration in patients not resected

End point title	Response duration in patients not resected
End point description:	
End point type	Secondary
End point timeframe:	
Duration of response is commonly defined as the time from onset of response to progression or death due to any reason.	

End point values	BiCT Arm	TriCT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	130		
Units: Months				
median (confidence interval 95%)	10.1 (8.9 to 11.5)	11.0 (9.5 to 12.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression –free survival

End point title	Progression –free survival
End point description:	
The progression-free survival (PFS) defined as the time from randomization to progression (RECIST v1.1) or death from any cause (disease relapse was considered as an event). Patients alive without progression were censored at the last follow-up.	
End point type	Secondary
End point timeframe:	
8 months.	

End point values	BiCT Arm	TriCT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	130		
Units: Months				
median (confidence interval 95%)	11.5 (10.2 to 13.0)	13.0 (11.3 to 13.8)		

Statistical analyses

Statistical analysis title	PFS Analysis
Comparison groups	BiCT Arm v TriCT Arm
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.734
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.39

Secondary: Overall survival

End point title	Overall survival
End point description:	
The overall survival (OS) was defined as the time from randomization to death due to any cause. Patients lost to follow-up were censored at the date last known to be alive.	
End point type	Secondary
End point timeframe:	
14 months.	

End point values	BiCT Arm	TriCT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	130		
Units: Months				
median (confidence interval 95%)	40.0 (34.4 to 46.5)	43.4 (36.7 to 49.4)		

Statistical analyses

Statistical analysis title	OS Analysis
Comparison groups	BiCT Arm v TriCT Arm
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7373
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall period of the study (up to 5 years after randomization)

Adverse event reporting additional description:

Informations about the occurrences of the non serious Adverse events were not available.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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Reporting groups

Reporting group title	BiCT Arm
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Reporting group description: -

Reporting group title	TriCT Arm
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Reporting group description: -

Serious adverse events	BiCT Arm	TriCT Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	72 / 126 (57.14%)	81 / 128 (63.28%)	
number of deaths (all causes)	76	78	
number of deaths resulting from adverse events	5	5	
Investigations			
GGT increased			
subjects affected / exposed	1 / 126 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Biloma			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical procedure repeated			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Atrial fibrillation paroxysmal			

subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary spastic angina			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decompensation cardiac			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Aplasia bone marrow			
alternative dictionary used: MedDRA 1			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile aplasia			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 126 (0.79%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Neutropenia			
subjects affected / exposed	3 / 126 (2.38%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device complication			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 126 (0.00%)	3 / 128 (2.34%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion associated discomfort			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiorgan failure			
subjects affected / exposed	0 / 126 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 2	
Multi-organ failure			

subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
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 / 126 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Unknown cause of death			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (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			
Allergic reaction			
subjects affected / exposed	1 / 126 (0.79%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	1 / 126 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug allergy			
subjects affected / exposed	3 / 126 (2.38%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal abscess			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 126 (0.79%)	4 / 128 (3.13%)	
occurrences causally related to treatment / all	1 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			

subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowel obstruction			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon obstruction			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colostomy prolapse			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	5 / 126 (3.97%)	9 / 128 (7.03%)	
occurrences causally related to treatment / all	4 / 5	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea bloody			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fecal peritonitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 126 (0.79%)	4 / 128 (3.13%)	
occurrences causally related to treatment / all	1 / 1	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis oral			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction intestinal			
subjects affected / exposed	0 / 126 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction small intestine			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	3 / 126 (2.38%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small bowel obstruction			

subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subacute intestinal obstruction			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subocclusive syndrome			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Watery diarrhea			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING GRADE 2 AND NAUSEA GRADE 3			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute cholecystitis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary fistula			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cytolysis			

subjects affected / exposed	1 / 126 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver cholestasis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver failure			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperosmolar (non-ketotic) coma			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Catheter infection			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 126 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septicemia			
subjects affected / exposed	1 / 126 (0.79%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Serratia sepsis			

subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcus aureus bacteraemia			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary infection			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	BiCT Arm	TriCT Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	126 / 126 (100.00%)	128 / 128 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 126 (7.14%)	10 / 128 (7.81%)	
occurrences (all)	9	10	
Thromboembolic events			
subjects affected / exposed	19 / 126 (15.08%)	15 / 128 (11.72%)	
occurrences (all)	19	15	
Edema			

subjects affected / exposed occurrences (all)	6 / 126 (4.76%) 6	3 / 128 (2.34%) 3	
General disorders and administration site conditions			
Mucositis			
subjects affected / exposed	40 / 126 (31.75%)	37 / 128 (28.91%)	
occurrences (all)	40	37	
Pain			
subjects affected / exposed	43 / 126 (34.13%)	46 / 128 (35.94%)	
occurrences (all)	43	46	
Weakness			
subjects affected / exposed	3 / 126 (2.38%)	2 / 128 (1.56%)	
occurrences (all)	3	2	
Fatigue			
subjects affected / exposed	89 / 126 (70.63%)	108 / 128 (84.38%)	
occurrences (all)	89	108	
Fever			
subjects affected / exposed	17 / 126 (13.49%)	17 / 128 (13.28%)	
occurrences (all)	17	17	
Weight loss			
subjects affected / exposed	29 / 126 (23.02%)	47 / 128 (36.72%)	
occurrences (all)	29	47	
Immune system disorders			
Hypersensitivity reaction to oxaliplatin			
subjects affected / exposed	3 / 126 (2.38%)	8 / 128 (6.25%)	
occurrences (all)	3	8	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	34 / 126 (26.98%)	27 / 128 (21.09%)	
occurrences (all)	34	27	
Bronchospasm			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences (all)	0	1	
Thoracic pain			
subjects affected / exposed	3 / 126 (2.38%)	5 / 128 (3.91%)	
occurrences (all)	3	5	

Dyspnea subjects affected / exposed occurrences (all)	13 / 126 (10.32%) 13	18 / 128 (14.06%) 18	
Cough subjects affected / exposed occurrences (all)	14 / 126 (11.11%) 14	8 / 128 (6.25%) 8	
Pulmonary edema subjects affected / exposed occurrences (all)	2 / 126 (1.59%) 2	2 / 128 (1.56%) 2	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	10 / 126 (7.94%) 10	12 / 128 (9.38%) 12	
Investigations ALAT/SGPT abnormal subjects affected / exposed occurrences (all)	71 / 126 (56.35%) 71	89 / 128 (69.53%) 89	
ASAT/SGOT abnormal subjects affected / exposed occurrences (all)	70 / 126 (55.56%) 70	82 / 128 (64.06%) 82	
GGT abnormal subjects affected / exposed occurrences (all)	86 / 126 (68.25%) 86	91 / 128 (71.09%) 91	
Phosphatase alkaline abnormal subjects affected / exposed occurrences (all)	89 / 126 (70.63%) 89	114 / 128 (89.06%) 114	
Prothrombin time subjects affected / exposed occurrences (all)	8 / 126 (6.35%) 8	13 / 128 (10.16%) 13	
Creatinine abnormal subjects affected / exposed occurrences (all)	24 / 126 (19.05%) 24	28 / 128 (21.88%) 28	
Cardiac disorders Arrhythmia subjects affected / exposed occurrences (all)	1 / 126 (0.79%) 1	3 / 128 (2.34%) 3	
Ischemic cardiac event/infarction			

subjects affected / exposed occurrences (all)	2 / 126 (1.59%) 2	0 / 128 (0.00%) 0	
Nervous system disorders			
Dysgeusia (altered taste)			
subjects affected / exposed	26 / 126 (20.63%)	27 / 128 (21.09%)	
occurrences (all)	26	27	
Encephalopathy			
subjects affected / exposed	22 / 126 (17.46%)	17 / 128 (13.28%)	
occurrences (all)	22	17	
Peripheral sensory neuropathy			
subjects affected / exposed	66 / 126 (52.38%)	107 / 128 (83.59%)	
occurrences (all)	66	107	
Somnolence			
subjects affected / exposed	1 / 126 (0.79%)	0 / 128 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Hemoglobin level disorder			
subjects affected / exposed	85 / 126 (67.46%)	106 / 128 (82.81%)	
occurrences (all)	85	106	
Leucopenia			
subjects affected / exposed	67 / 126 (53.17%)	60 / 128 (46.88%)	
occurrences (all)	67	60	
Lymphopenia			
subjects affected / exposed	55 / 126 (43.65%)	55 / 128 (42.97%)	
occurrences (all)	55	55	
Neutrophils/granulocytes disorder			
subjects affected / exposed	82 / 126 (65.08%)	78 / 128 (60.94%)	
occurrences (all)	82	78	
Platelets disorder			
subjects affected / exposed	46 / 126 (36.51%)	88 / 128 (68.75%)	
occurrences (all)	46	88	
Febrile neutropenia			
subjects affected / exposed	5 / 126 (3.97%)	6 / 128 (4.69%)	
occurrences (all)	5	6	
Ear and labyrinth disorders			

Hearing impaired subjects affected / exposed occurrences (all)	5 / 126 (3.97%) 5	2 / 128 (1.56%) 2	
Eye disorders			
Conjunctivitis subjects affected / exposed occurrences (all)	5 / 126 (3.97%) 5	7 / 128 (5.47%) 7	
Visual problems subjects affected / exposed occurrences (all)	2 / 126 (1.59%) 2	3 / 128 (2.34%) 3	
Gastrointestinal disorders			
Anorexia subjects affected / exposed occurrences (all)	26 / 126 (20.63%) 26	50 / 128 (39.06%) 50	
Ascites subjects affected / exposed occurrences (all)	1 / 126 (0.79%) 1	2 / 128 (1.56%) 2	
Constipation subjects affected / exposed occurrences (all)	46 / 126 (36.51%) 46	47 / 128 (36.72%) 47	
Diarrhea subjects affected / exposed occurrences (all)	64 / 126 (50.79%) 64	96 / 128 (75.00%) 96	
Abdominal pain subjects affected / exposed occurrences (all)	50 / 126 (39.68%) 50	58 / 128 (45.31%) 58	
Digestive hemorrhage subjects affected / exposed occurrences (all)	8 / 126 (6.35%) 8	10 / 128 (7.81%) 10	
Nausea subjects affected / exposed occurrences (all)	66 / 126 (52.38%) 66	94 / 128 (73.44%) 94	
Pancreatitis subjects affected / exposed occurrences (all)	0 / 126 (0.00%) 0	1 / 128 (0.78%) 1	
Stomatitis			

subjects affected / exposed	17 / 126 (13.49%)	21 / 128 (16.41%)	
occurrences (all)	17	21	
Vomiting			
subjects affected / exposed	28 / 126 (22.22%)	48 / 128 (37.50%)	
occurrences (all)	28	48	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 128 (0.78%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 126 (0.79%)	1 / 128 (0.78%)	
occurrences (all)	1	1	
Alopecia			
subjects affected / exposed	18 / 126 (14.29%)	38 / 128 (29.69%)	
occurrences (all)	18	38	
Nail disorder			
subjects affected / exposed	15 / 126 (11.90%)	8 / 128 (6.25%)	
occurrences (all)	15	8	
Eruptions/desquamation			
subjects affected / exposed	51 / 126 (40.48%)	38 / 128 (29.69%)	
occurrences (all)	51	38	
Erythroderma			
subjects affected / exposed	10 / 126 (7.94%)	6 / 128 (4.69%)	
occurrences (all)	10	6	
Pruritus			
subjects affected / exposed	23 / 126 (18.25%)	10 / 128 (7.81%)	
occurrences (all)	23	10	
Rash			
subjects affected / exposed	41 / 126 (32.54%)	29 / 128 (22.66%)	
occurrences (all)	41	29	
Hands and feet skin reaction			
subjects affected / exposed	39 / 126 (30.95%)	33 / 128 (25.78%)	
occurrences (all)	39	33	
Injection site reaction			

subjects affected / exposed occurrences (all)	2 / 126 (1.59%) 2	1 / 128 (0.78%) 1	
Dry skin subjects affected / exposed occurrences (all)	43 / 126 (34.13%) 43	32 / 128 (25.00%) 32	
Wound healing disorder subjects affected / exposed occurrences (all)	5 / 126 (3.97%) 5	2 / 128 (1.56%) 2	
Urticaria subjects affected / exposed occurrences (all)	3 / 126 (2.38%) 3	4 / 128 (3.13%) 4	
Skin edema subjects affected / exposed occurrences (all)	4 / 126 (3.17%) 4	1 / 128 (0.78%) 1	
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	3 / 126 (2.38%) 3	1 / 128 (0.78%) 1	
Abnormal urination/urinary frequency subjects affected / exposed occurrences (all)	1 / 126 (0.79%) 1	1 / 128 (0.78%) 1	
Hematuria subjects affected / exposed occurrences (all)	6 / 126 (4.76%) 6	5 / 128 (3.91%) 5	
Proteinuria subjects affected / exposed occurrences (all)	13 / 126 (10.32%) 13	15 / 128 (11.72%) 15	
Urinary retention subjects affected / exposed occurrences (all)	0 / 126 (0.00%) 0	1 / 128 (0.78%) 1	
Infections and infestations			
Infection with neutropenia subjects affected / exposed occurrences (all)	2 / 126 (1.59%) 2	2 / 128 (1.56%) 2	
Infection without neutropenia			

subjects affected / exposed	7 / 126 (5.56%)	11 / 128 (8.59%)	
occurrences (all)	7	11	
Local infections			
subjects affected / exposed	27 / 126 (21.43%)	27 / 128 (21.09%)	
occurrences (all)	27	27	
Septicemia			
subjects affected / exposed	3 / 126 (2.38%)	2 / 128 (1.56%)	
occurrences (all)	3	2	
Bilirubin			
subjects affected / exposed	14 / 126 (11.11%)	17 / 128 (13.28%)	
occurrences (all)	14	17	
Paronychia			
subjects affected / exposed	17 / 126 (13.49%)	8 / 128 (6.25%)	
occurrences (all)	17	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2011	<ul style="list-style-type: none">· Change of study contact, as project leader from Christine Montoto-Grillot to Beata Juzyna.· Correction of errors in the protocol: inconsistencies and spelling errors.· Modification of the Investigator's list.
12 April 2011	<ul style="list-style-type: none">· Modification and clarification of the dose adaption.· Modification of the SAE declaration document/form.· Correction of errors in the protocol: inconsistencies and spelling errors.· Modification of the investigators list.
05 July 2011	<ul style="list-style-type: none">· Modification of the investigators list.
02 August 2011	<ul style="list-style-type: none">· Updating of the abbreviation list.· Addition of an upper age limit of 75 years old to the Inclusion criterion N°10.· Modification of the study rational.· Addition of calcium testing during the study treatment phase.· Addition of a translational research concerning circulating DNA.· Modification of the investigators list.
13 December 2011	<ul style="list-style-type: none">· Change of the trial sponsor from the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) to UNICANCER.
20 March 2012	<ul style="list-style-type: none">· Modification of the investigators list.· Modification of the statistical analysis.
10 September 2013	<p>examined by the EC on the 29-Jul-2013, with EC approval letter dated the 10-Sep-2013)</p> <ul style="list-style-type: none">· Prolongation of the inclusion period by 2 years.· Updating of the study contacts.· Correction of the logistics concerning the blood sampling.· Correction of the numbering of the annexes in the study protocol.· Modification of the investigators list.
08 July 2014	<ul style="list-style-type: none">· Modification of the protocol following the publication by Douillard et.al. showing a diminished survival in patients with mt-NRAS tumours treated with the anti-EGFR - panitumumab [20]. Obligation to verify the NRAS status of tumors. Only patients with wt-RAS tumors were eligible for cetuximab.· Updating of the study contacts: a new fax number.· Clarification of the non-inclusion criterion N°9.· Correction of the statistical analysis.· Modification of the investigators list.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported