Clinical trial results:
Ensayo clínico fase II de un solo brazo, multicéntrico y prospectivo para la validación de biomarcadores en pacientes con cáncer colorrectal avanzado y/o metastásico con gen KRAS no mutado tratados con quimioterapia más cetuximab bisemanal como terapia de primera línea.

Summary

EudraCT number	2010-019236-12
Trial protocol	ES
Global end of trial date	20 June 2017

Results information

Result version number	v1 (current)
This version publication date	02 June 2021
First version publication date	02 June 2021

Trial information

Trial identification

Sponsor protocol code	GEMCAD-1002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01276379
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo Español Multidisciplinar en Cáncer Digestivo (GEMCAD)
Sponsor organisation address	Ronda General Mitre 200, entresuelo 3a, Barcelona, Spain,
Public contact	Joan Maurel Santasusana, Grupo Español Multidisciplinar en Cáncer Digestivo (GEMCAD), jmaurel@clinic.cat
Scientific contact	Joan Maurel Santasusana, Grupo Español Multidisciplinar en Cáncer Digestivo (GEMCAD), jmaurel@clinic.cat

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	29 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2017
Global end of trial reached?	Yes
Global end of trial date	20 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Validación de los biomarcadores BRAF, IGF1P/MMp7 (DP) y PI3K-PTEN para predecir la SLP en pacientes con cáncer colorrectal avanzado y/o metastásico con KRAS no mutado tratados con quimioterapia estándar más cetuximab bisemanal como terapia de primera línea.
Identificar nuevos biomarcadores que puedan predecir la supervivencia libre de progresión (SLP) en pacientes KRAS no mutado tratados con quimioterapia (QT) y cetuximab bisemanal en terapia de primera línea.
La necesidad de identificar biomarcadores adicionales de la eficacia de cetuximab proviene del pequeño valor predictivo de la clasificación actual, basada en el estado mutacional de KRAS, de la eficacia de la administración de cetuximab bisemanal en el grupo de pacientes de la enfermedad a estudio.
Los biomarcadores propuestos son:
1.Mutaciones BRAF
2.IGF-1Rp/MMP-7 (DP)
3.PIK3CA-PTEN.

Protection of trial subjects:

The protocol provided all measures needed to grant the integrity of human patients enrolled and the conservation of their rights.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 June 2011
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	Spain: 221
Worldwide total number of subjects	221
EEA total number of subjects	221

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	221
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

221 recruited, 40 do not comply with all protocol specifications, total of 181 patients enrolled and evaluable

Pre-assignment

Screening details:

221 recruited, 40 do not comply with all protocol specifications, total of 181 patients enrolled and evaluable

Period 1

Period 1 title	Evaluable population (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Single-arm

Arms

Are arms mutually exclusive?	Yes
Arm title	BRAF WT

Arm description:

FOLFIRI (m): FOLFIRI (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:
• Irinotecan 180 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.
• l-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2), in infusion i.v., 120 minutes, on day 1.
• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.
• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.
FOLFOX-6 (m): FOLFOX6 (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:
• Oxaliplatin 85 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.
• l-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2) in infusion i.v., 120 minutes, on day 1.
• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.
• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.
Cetuximab: - 500 mg/m2 i.v. Every 2 weeks.

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

Dosage and administration details:

administered on day 1 of each 14-days-cycle. The administered doses will be: - Irinotecan 180 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle. - l-Leucovorin 200 mg/ m2 (or d,l-leucovorin 400 mg/m2), in infusion i.v., 120 minutes, on day 1.- One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1. - 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours

Investigational medicinal product name	FOLFOX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use, Intravenous bolus use

Dosage and administration details:

Administered on day 1 of each 14-days-cycle. The administered doses will be: -Oxaliplatin 85 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle. - l-Leucovorin 200 mg/
m2 (or d,l-leucovorin 400 mg/m2) in infusion i.v., 120 minutes, on day 1. -One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1. -5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours

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/m2 i.v. Every 2 weeks.

Arm title	Mutant BRAF

Arm description:

FOLFIRI (m): FOLFIRI (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:
• Irinotecan 180 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.
• l-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2), in infusion i.v., 120 minutes, on day 1.
• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.
• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.
FOLFOX-6 (m): FOLFOX6 (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:
• Oxaliplatin 85 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.
• l-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2) in infusion i.v., 120 minutes, on day 1.
• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.
• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.
Cetuximab: - 500 mg/m2 i.v. Every 2 weeks.

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

Dosage and administration details:

administered on day 1 of each 14-days-cycle. The administered doses will be: - Irinotecan 180 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle. - l-Leucovorin 200 mg/ m2 (or d,l-leucovorin 400 mg/m2), in infusion i.v., 120 minutes, on day 1.- One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1. - 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours

Investigational medicinal product name	FOLFOX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

Administered on day 1 of each 14-days-cycle. The administered doses will be: -Oxaliplatin 85 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle. - l-Leucovorin 200 mg/
m2 (or d,l-leucovorin 400 mg/m2) in infusion i.v., 120 minutes, on day 1. -One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1. -5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours

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/m2 i.v. Every 2 weeks.

Number of subjects in period 1[1]	BRAF WT	Mutant BRAF
Started	161	20
Completed	161	20

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: 221 recruited, 40 do not comply with all protocol specifications, total of 181 patients enrolled and evaluable

Baseline characteristics

Reporting groups	
Reporting group title	BRAF WT

Reporting group description:

FOLFIRI (m): FOLFIRI (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:
• Irinotecan 180 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.
• l-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2), in infusion i.v., 120 minutes, on day 1.
• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.
• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.
FOLFOX-6 (m): FOLFOX6 (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:
• Oxaliplatin 85 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.
• l-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2) in infusion i.v., 120 minutes, on day 1.
• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.
• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.
Cetuximab: - 500 mg/m2 i.v. Every 2 weeks.

Reporting group title	Mutant BRAF

Reporting group description:

FOLFIRI (m): FOLFIRI (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:
• Irinotecan 180 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.
• l-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2), in infusion i.v., 120 minutes, on day 1.
• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.
• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.
FOLFOX-6 (m): FOLFOX6 (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:
• Oxaliplatin 85 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.
• l-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2) in infusion i.v., 120 minutes, on day 1.
• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.
• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.
Cetuximab: - 500 mg/m2 i.v. Every 2 weeks.

Reporting group values	BRAF WT	Mutant BRAF	Total
Number of subjects	161	20	181
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	62	67	
standard deviation	± 10.5	± 7.4	-

Gender categorical Units: Subjects			
Female	46	7	53
Male	115	13	128
Stage			
Measure Description: The stage of a cancer describes the size and spread of a tumour: stage I – The cancer has grown through the mucosa and has invaded the muscular layer of the colon or rectum. stage II – The cancer has grown through the wall of the colon or rectum stage III – The cancer has grown through the inner lining or into the muscle layers of the intestine. It has spread to lymph nodes stage IV – The cancer has spread to a distant part of the body			
Units: Subjects			
Stage I	1	0	1
Stage II	13	0	13
Stage III	30	5	35
Stage IV	117	15	132
Primary location			
Measure Description: Part of the colon where the primary tumor was located			
Units: Subjects			
Ascending colon	23	9	32
Transverse colon	12	2	14
Descending colon	10	4	14
Sigmoid colon	73	3	76
Rectum	43	2	45
Surgery of the primary tumor			
Percentage of patients that had surgery for their primary colorectal tumor			
Units: Subjects			
Yes	91	10	101
No	70	10	80
ECOG PS			
Eastern Cooperative Oncology Group (ECOG) performance status (PS). ECOG scale measures the performance status of a patients. It ranges from 0 (fully active, able to carry on all pre-disease performance without restriction) to 5 (death).			
Units: Subjects			
ECOG 0	112	7	119
ECOG 1	49	13	62
Number of metastatic organs			
Percentage of patients presenting metastasis in one or more distant organs. The number of patients with 1,2, 3 or more than 4 affected organs are reported			
Units: Subjects			
1 organ	87	7	94
2 organs	58	11	69
3 organs	15	2	17
4 or higher organs	1	0	1

End points

End points reporting groups

Reporting group title	BRAF WT

Reporting group description:

FOLFIRI (m): FOLFIRI (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:
• Irinotecan 180 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.
• l-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2), in infusion i.v., 120 minutes, on day 1.
• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.
• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.
FOLFOX-6 (m): FOLFOX6 (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:
• Oxaliplatin 85 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.
• l-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2) in infusion i.v., 120 minutes, on day 1.
• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.
• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.
Cetuximab: - 500 mg/m2 i.v. Every 2 weeks.

Reporting group title	Mutant BRAF

Reporting group description:

FOLFIRI (m): FOLFIRI (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:
• Irinotecan 180 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.
• l-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2), in infusion i.v., 120 minutes, on day 1.
• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.
• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.
FOLFOX-6 (m): FOLFOX6 (m) chemotherapy will be administered on day 1 of each 14-days-cycle. The administered doses will be:
• Oxaliplatin 85 mg/m2 in infusion i.v., 120 minutes, on day 1 of each cycle.
• l-Leucovorin 200 mg/m2 (or d,l-leucovorin 400 mg/m2) in infusion i.v., 120 minutes, on day 1.
• One bolus i.v. (2-4 minutes) of 400 mg/m2 of 5-FU on day 1.
• 5-FU in continuous infusion (2400 mg/m2) administered through an ambulatory pump during 46-48 hours.
Cetuximab: - 500 mg/m2 i.v. Every 2 weeks.

Primary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

Measurements according to RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors). Main techniques: CTscan. Two groups will be defined based on the score built from the proposed clinical variables and biomarkers. Instead of a binomial distribution, a Log-rank method has been used to calculate the sample size in order to include all the incidents during the follow-up. Expecting a minimum 20% difference (60 vs. 40%) on PFS at 12 months between groups and with the following assumptions: Alpha error (bilateral): 5% Beta error: 20%

End point type	Primary

End point timeframe:

4 years

End point values	BRAF WT	Mutant BRAF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	20		
Units: Months				
median (confidence interval 95%)	11.4 (9.9 to 13.1)	5.9 (3.3 to 7.8)		

Statistical analyses

Statistical analysis title	Log rank
Comparison groups	BRAF WT v Mutant BRAF
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	3.29

Notes:

[1] - If pvalue <0.05 the null hypothesis is discarded and we asume there are statistically significant diferences between groups

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Proportion of patients alive at the end of study

End point type	Secondary

End point timeframe:

4 years

End point values	BRAF WT	Mutant BRAF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	20		
Units: Months				
median (confidence interval 95%)	32.6 (27.5 to 38.8)	9.3 (5.3 to 22)		

Statistical analyses

Statistical analysis title	Log rank
Comparison groups	BRAF WT v Mutant BRAF
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.33
upper limit	3.96

Notes:

[2] - If p-value was lower than P<0.05 the null hypothesis was discarded and it is assumed that there are statistically significant diferences among the groups

Secondary: Duration of response

End point title	Duration of response

End point description:

Duration of the partial or total response to the treatment. Evaluation and classification according to RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors)

End point type	Secondary

End point timeframe:

4 years

End point values	BRAF WT	Mutant BRAF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	20		
Units: months				
median (full range (min-max))	8.66 (1.16 to 53.49)	8.66 (1.16 to 53.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tumoral response

End point title	Tumoral response

End point description:

Measurements according to RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors). Main techniques: CT scan

End point type	Secondary

End point timeframe:

4 years

End point values	BRAF WT	Mutant BRAF		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	20		
Units: Patients				
Complete response (CR)	16	1		
Partial response (PR)	106	6		
Stable disease (SD)	25	6		
Pogression disease (PD)	8	4		
Not evaluable (NE)	6	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

4 years

Adverse event reporting additional description:

Safety assessments included patient history and physical examinations, vital signs, ECOG PS, AEs, blood chemistry, and blood counts at each visit.
AE severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0. Relation to cetuximab or chemotherapy assessed by PI

Assessment type	Non-systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	173 / 218 (79.36%)		
number of deaths (all causes)	136		
number of deaths resulting from adverse events	12		
Vascular disorders			
Vascular disorders NOS			
subjects affected / exposed	10 / 218 (4.59%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 4		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 218 (8.72%)		
occurrences causally related to treatment / all	0 / 19		
deaths causally related to treatment / all	0 / 0		
Edema			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fever			

subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General site reactions NOS			
subjects affected / exposed	2 / 218 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	2 / 218 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hand foot syndrome			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
multiorgan failure			
subjects affected / exposed	2 / 218 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Immune system disorders			
Allergic reaction to excipient			
subjects affected / exposed	7 / 218 (3.21%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory disorders NOS			
subjects affected / exposed	6 / 218 (2.75%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 3		
Cardiac disorders			
Cardiac disorders NOS			
subjects affected / exposed	2 / 218 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Neuropathy			
subjects affected / exposed	5 / 218 (2.29%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Paresthesia			
subjects affected / exposed	5 / 218 (2.29%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	5 / 218 (2.29%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Leucocytopenia			
subjects affected / exposed	4 / 218 (1.83%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	53 / 218 (24.31%)		
occurrences causally related to treatment / all	0 / 53		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	3 / 218 (1.38%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Ocular alterations			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ocular disorders			

subjects affected / exposed	3 / 218 (1.38%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 218 (1.38%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	2 / 218 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	28 / 218 (12.84%)		
occurrences causally related to treatment / all	0 / 28		
deaths causally related to treatment / all	0 / 0		
Fistula			
subjects affected / exposed	7 / 218 (3.21%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders NOS			
subjects affected / exposed	5 / 218 (2.29%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	10 / 218 (4.59%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Mucoitis			

subjects affected / exposed	11 / 218 (5.05%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	9 / 218 (4.13%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Rectal bleeding			
subjects affected / exposed	1 / 218 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
hepatic toxicity			
subjects affected / exposed	3 / 218 (1.38%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Transaminitis			
subjects affected / exposed	2 / 218 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 218 (1.83%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Skin reaction			
subjects affected / exposed	29 / 218 (13.30%)		
occurrences causally related to treatment / all	0 / 29		
deaths causally related to treatment / all	0 / 0		
Xerosis			
subjects affected / exposed	8 / 218 (3.67%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Urinary disorders NOS			
subjects affected / exposed	4 / 218 (1.83%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscluloskeletal disorders NOS			
subjects affected / exposed	5 / 218 (2.29%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infections			
subjects affected / exposed	9 / 218 (4.13%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 3		
Metabolism and nutrition disorders			
Anemia			
subjects affected / exposed	4 / 218 (1.83%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Anorexia			
subjects affected / exposed	2 / 218 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolic disorders NOS			
subjects affected / exposed	6 / 218 (2.75%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	198 / 218 (90.83%)		
Vascular disorders			

Vascular disorders NOS subjects affected / exposed occurrences (all)	12 / 218 (5.50%) 12		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fever subjects affected / exposed occurrences (all) Pain NOS subjects affected / exposed occurrences (all)	 101 / 218 (46.33%) 101 25 / 218 (11.47%) 25 21 / 218 (9.63%) 21		
Respiratory, thoracic and mediastinal disorders Respiratory disorders NOS subjects affected / exposed occurrences (all)	 29 / 218 (13.30%) 29		
Psychiatric disorders Psychiatric disorders NOS subjects affected / exposed occurrences (all)	 12 / 218 (5.50%) 12		
Congenital, familial and genetic disorders Trichomegaly subjects affected / exposed occurrences (all)	 11 / 218 (5.05%) 11		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) Neuropathy subjects affected / exposed occurrences (all) Paresthesia subjects affected / exposed occurrences (all)	 22 / 218 (10.09%) 22 72 / 218 (33.03%) 72 45 / 218 (20.64%) 45		
Blood and lymphatic system disorders			

Anemia			
subjects affected / exposed	34 / 218 (15.60%)		
occurrences (all)	34		
Leucopenia			
subjects affected / exposed	16 / 218 (7.34%)		
occurrences (all)	16		
Neutropenia			
subjects affected / exposed	37 / 218 (16.97%)		
occurrences (all)	37		
Thrombocytopenia			
subjects affected / exposed	22 / 218 (10.09%)		
occurrences (all)	22		
Eye disorders			
Ocular disorders NOS			
subjects affected / exposed	24 / 218 (11.01%)		
occurrences (all)	24		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	28 / 218 (12.84%)		
occurrences (all)	28		
Constipation			
subjects affected / exposed	40 / 218 (18.35%)		
occurrences (all)	40		
Diarrhoea			
subjects affected / exposed	80 / 218 (36.70%)		
occurrences (all)	80		
Fistula			
subjects affected / exposed	47 / 218 (21.56%)		
occurrences (all)	47		
Mucosa dryness			
subjects affected / exposed	13 / 218 (5.96%)		
occurrences (all)	13		
Mucositis			
subjects affected / exposed	87 / 218 (39.91%)		
occurrences (all)	87		
Nausea			

subjects affected / exposed occurrences (all) Gastrointestinal disorders NOS subjects affected / exposed occurrences (all)	60 / 218 (27.52%) 60 40 / 218 (18.35%) 40		
Hepatobiliary disorders Transaminitis subjects affected / exposed occurrences (all)	 13 / 218 (5.96%) 13		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Cutaneous reaction subjects affected / exposed occurrences (all) Xerosis subjects affected / exposed occurrences (all)	 29 / 218 (13.30%) 29 134 / 218 (61.47%) 134 36 / 218 (16.51%) 36		
Renal and urinary disorders Urinary disorders NOS subjects affected / exposed occurrences (all)	 13 / 218 (5.96%) 13		
Musculoskeletal and connective tissue disorders Musculoskeletal disorders NOS subjects affected / exposed occurrences (all)	 20 / 218 (9.17%) 20		
Infections and infestations Infections NOS subjects affected / exposed occurrences (all)	 17 / 218 (7.80%) 17		
Metabolism and nutrition disorders Anorexia and bulimia syndrome subjects affected / exposed occurrences (all) Metabolic disorders NOS	 27 / 218 (12.39%) 27 		

subjects affected / exposed occurrences (all)	36 / 218 (16.51%) 36		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2011	NA
13 July 2011	NA
15 December 2011	NA
17 April 2012	NA
14 December 2012	NA
18 April 2013	NA
15 May 2013	NA
04 July 2014	NA

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported