Clinical trial results:
An Open-label Phase II Clinical trial of Panitumumab in Combination with Irinotecan for Patients with Advanced Metastatic Colorectal Cancer without KRAS mutation (Wild type) in third line chemotherapy (Patients pretreated with FOLFOX or XELOX ± bevacizumab and irinotecan alone or FOLFIRI or CAPIRI ± bevacizumab)

Summary

EudraCT number	2007-004806-28
Trial protocol	FR
Global end of trial date	30 June 2012

Results information

Result version number	v1 (current)
This version publication date	23 July 2016
First version publication date	23 July 2016

Trial information

Trial identification

Sponsor protocol code	C07-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00655499
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GERCOR
Sponsor organisation address	151 rue du faubourg saint Antoine , PARIS, France, 75011
Public contact	Regulatory affairs, GERCOR, 33 1 40 29 85 00, regulatory.affairs@gercor.com.fr
Scientific contact	coordinating investigator, Pr Thierry ANDRE, 33 1 40 29 85 00, regulatory.affairs@gercor.com.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	06 March 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 February 2012
Global end of trial reached?	Yes
Global end of trial date	30 June 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the objective response rate (ORR) when panitumumab is administered in combination with irinotecan for Patients with Advanced Metastatic Colorectal Cancer without KRAS mutation (Wild type) in third line chemotherapy = Patients pretreated with oxaliplatin and Fluorpyrimidines (5FU/FA or capecitabine) ± bevacizumab and Irinotecan alone or in association with Fluorpyrimidines (5FU/FA or capecitabine) ± bevacizumab

Protection of trial subjects:

Pre-medication is not required for routine panitumumab infusions. If, during or after any infusion, a reaction occurs, pre-medication may be used for subsequent panitumumab infusions (e.g. acetaminophen/paracetamol and/or a histamine H1 antagonist, e.g. diphenhydramine).
Prior to the administration of irinotecan, all subjects should receive antiemetics agents (e.g.: oral or IV dexamethasone, 5-hydroxtryptamine3 (5-HT3) receptor antagonists). Antiemetic agents should be given on the day of treatment, starting at least 30 minutes prior to administration of irinotecan. Alternative and additional antiemetics may be used, where clinically indicated, at the discretion of the investigator or according to standard institutional or regional practice. In case of cholinergic like syndrome after irinotecan administration, atropine sulphate injection is recommended.
In case of toxicities, panitumumab and irinoteacan may need to be withheld, reducted and delayed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 July 2008
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	France: 69
Worldwide total number of subjects	69
EEA total number of subjects	69

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)	36
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From July 2008 to Oct. 2010, 69 patients were enrolled in the study, 4 were not eligible. The study was conducted in France, in 11 active centers: CH Haut Lévêque Pessac, CH Beauvais, CHI Montfermeil, CHU Pitié salpêtrière, St Antoine et Bichat Paris, Centre Paul Papin Angers, Clinique V. Hugo Le Mans, Hop. Foch Suresnes, Jean Mermoz Lyon, CHSenlis

Pre-assignment

Screening details:

Patient wih pathologically confirmed mCRC, KRAS codon 12 and 13 wild type, previsously treated with irinotecan, oxaliplatin, fluoropyrimidines and bevacizumab. Eligibility criteria also included : age ≥ 18 years, normal hematopoietic , hepatic and renal fonctions, measurable disease.No prior treatment with anti-EGFR antibodies.

Period 1

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

Arms

Arm title	Panitumumab combined with Irinotecan

Arm description:

1cycle every 14 days (J1=J15)

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

Dosage and administration details:

Panitumumab : 6mg/kg in IV infusion over 60 minute on day 1

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	CPT11
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan: 180mg/m² in IV infusion over 90 minutes on day 1 just after panitumumab administration

Number of subjects in period 1[1]	Panitumumab combined with Irinotecan
Started	65
Completed	65

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: 69 patients enrolled in the study and 4 non eligible (2 prior anti-EGFR antibodies (mab); 1 non prior irinotecan; 1 patient received bevacizumab in combination with study drug)

Baseline characteristics

Reporting groups	
Reporting group title	Overall Period
Reporting group description:	
69 patients enrolled in the study and 4 non eligible (2 prior anti-EGFR antibodies (mab); 1 non prior irinotecan; 1 patient received bevacizumab in combination with study drug)	

Reporting group values	Overall Period	Total	
Number of subjects	65	65	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adult (18-64 years)	34	34	
From 65 to 84 years	31	31	
85 years and over	0	0	
Age continuous Units: years			
median	62		
full range (min-max)	34 to 84	-	
Gender categorical Units: Subjects			
Female	26	26	
Male	39	39	
ECOG Performance status Units: Subjects			
ECOG - PS =0	25	25	
ECOG - PS = 1	33	33	
ECOG - PS = 2	7	7	
Primary Tumor type Units: Subjects			
Colon	45	45	
Rectum	17	17	
Both	3	3	
Number of metastatic sites Units: Subjects			
1 site	37	37	
> 1 site	28	28	
Adjuvant Chemotherapy Units: Subjects			
Yes	17	17	
No	48	48	
Time between mets diagnosis and			

inclusion Units: Subjects			
< 12 months	13	13	
≥ 12 - < 24 months	21	21	
≥ 24 months	31	31	
Palliative first-line therapy Units: Subjects			
Oxaliplatin-based therapy	42	42	
Irinotecan-based therapy	22	22	
Oxaliplatin- and irinotecan-based therapy	1	1	
Palliative second-therapy Units: Subjects			
Oxaliplatin-based therapy	14	14	
Irinotecan-based therapy	43	43	
no second-line	8	8	
Prior treatment with bevacizumab Units: Subjects			
No	12	12	
Yes	53	53	

End points

End points reporting groups

Reporting group title	Panitumumab combined with Irinotecan
Reporting group description: 1cycle every 14 days (J1=J15)	
Subject analysis set title	Confirmed wild-type KRAS population
Subject analysis set type	Sub-group analysis
Subject analysis set description: 54 patients with wild-type KRAS confirmed at central assessment.	
Subject analysis set title	All Wild-type population
Subject analysis set type	Sub-group analysis
Subject analysis set description: 41 patients with no mutations : "all wild" after central assessment	
Subject analysis set title	Patients with KRAS, NRAS or BRAF mutation
Subject analysis set type	Sub-group analysis
Subject analysis set description: 19 patients with KRAS, NRAS and BRAF mutation after central assessment	

Primary: Objective response rate (ORR) of the combination in KRAS WT mCRC patients

End point title	Objective response rate (ORR) of the combination in KRAS WT mCRC patients[1]
End point description: Incidence of either a radiologically confirmed CR or PR while in the combination treatment phase; subjects prematurely discontinuing without a post baseline tumour response assessment, or subjects who respond during the optional panitumumab monotherapy phase, or subjects with an observed CR or PR in the combination phase that is not confirmed (in either the combination or monotherapy phases) will be considered non-responders.	
End point type	Primary
End point timeframe: Data from the combination therapy phase alone, defined as the period from enrolment through to the decision to end irinotecan Up to radiologically confirmed CR or PR while in the combination treatment phase	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The trial is descriptive with endpoints reported using counts, percents, conifdence interval and graphical methods.

End point values	Panitumumab combined with Irinotecan	Confirmed wild-type KRAS population	All Wild-type population	Patients with KRAS, NRAS or BRAF mutation
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65	54	41	19
Units: percentage				
median (confidence interval 95%)	29.2 (18.2 to 40.3)	35.2 (22.4 to 47.9)	46.3 (31.1 to 61.6)	0 (0 to 0)

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

Incidence of either a confirmed complete or partial response, or stable disease (SD) while in the combination therapy treatment phase; subjects prematurely discontinuing without a post-baseline tumour response assessment or subjects who have progressed by the first tumour response during the combination phase, or subjects with an observed complete or partial response in the combination phase that is not confirmed (in either the combination or monotherapy phases) will be considered non-responders otherwise.

End point type	Secondary

End point timeframe:

A confirmed complete or partial response, or stable disease (SD) while in the combination therapy treatment phase

End point values	Panitumumab combined with Irinotecan	Confirmed wild-type KRAS population	All Wild-type population	Patients with KRAS, NRAS or BRAF mutation
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65	54	41	19
Units: percentage				
median (confidence interval 95%)	63.1 (51.3 to 74.8)	66.7 (54.1 to 79.2)	80.5 (68.3 to 92.6)	21.1 (2.72 to 39.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

End point type	Secondary

End point timeframe:

The time from enrolment date to date of first radiologically observed progression or death (whichever comes first) combination therapy phase.

End point values	Panitumumab combined with Irinotecan	Confirmed wild-type KRAS population	All Wild-type population	Patients with KRAS, NRAS or BRAF mutation
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65	54	41	19
Units: months				
median (confidence interval 95%)	5.5 (3.7 to 7.6)	6.3 (3.7 to 8.7)	8.7 (5.5 to 10.4)	1.9 (1.5 to 2.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

End point type	Secondary

End point timeframe:

From the date of inclusion to the date of patient death, due to any cause, or to the last date the patient was known to be alive

End point values	Panitumumab combined with Irinotecan	Confirmed wild-type KRAS population	All Wild-type population	Patients with KRAS, NRAS or BRAF mutation
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	65	54	41	19
Units: months				
number (confidence interval 95%)	9.7 (6.6 to 15.8)	11.9 (6.8 to 18.2)	15.8 (9.5 to 25.1)	4.6 (3.3 to 7.9)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From date of inclusion to 56 ± 3 days after the last dosing of study treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	Eligible study population
Reporting group description: 1cycles every 14 days (J1=J15)	

Serious adverse events	Eligible study population		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 65 (15.38%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	1		
Vascular disorders			
Occular hemorraghe			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			

subjects affected / exposed	3 / 65 (4.62%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
occlusion			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	3 / 65 (4.62%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Respiratory, thoracic and mediastinal disorders			
dyspnea			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Eligible study population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 65 (44.62%)		
Blood and lymphatic system disorders			
Neutrophil count decreased	Additional description: grade 3/4		
subjects affected / exposed	8 / 65 (12.31%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea	Additional description: grade 3/4		
subjects affected / exposed	10 / 65 (15.38%)		
occurrences (all)	0		
Mucositis	Additional description: grade 3/4		
subjects affected / exposed	1 / 65 (1.54%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			

Skin toxicity	Additional description: grade 3/4		
subjects affected / exposed	21 / 65 (32.31%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 August 2008	Suppression of windows scheduled dose. Panitumumab and irinotecan can be administrated as soon as possible. Modification of intra dermal dose injection (ancillary study)
21 January 2009	The determination of Kras status could be performed locally, where the investigator usually requires such test. Nevertheless the wild type KRAS status will be confirmed by sending tumour block to the European Hospital Georges Pompidou following the enrolment step.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported