Clinical trial results:
A Multicentric randomized phase II trial evaluating dual targeting of the EGFR using the combination of cetuximab and afatinib versus cetuximab alone in patients with chemotherapy refractory wtRAS (KRAS and NRAS) metastatic colorectal cancer.

Summary

EudraCT number	2012-000167-25
Trial protocol	FR
Global end of trial date	30 March 2018

Results information

Result version number	v1 (current)
This version publication date	28 March 2021
First version publication date	28 March 2021

Trial information

Trial identification

Sponsor protocol code	UCGI 25

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01919879
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, PARIS, France, 75013
Public contact	Nourredine AIT-RAHMOUNE, UNICANCER, 33 01 71 93 67 04 , n.ait-rahmoune@unicancer.fr
Scientific contact	Nourredine AIT-RAHMOUNE, UNICANCER, 33 01 71 93 67 04 , 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	17 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2017
Global end of trial reached?	Yes
Global end of trial date	30 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The Primary objective was to evaluate the efficacy of the treatment with cetuximab alone or in combination with afatinib in terms of PFS rate at 6 months.

Protection of trial subjects:

In order to ensure the protection of the rights, safety and well-being of trial subjects, this clinical trial was performed in compliance with the principles laid down in the declaration of Helsinki, good Clinical Practice and European regulation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 75
Worldwide total number of subjects	75
EEA total number of subjects	75

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)	41
From 65 to 84 years	34

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

National multicentric phase II trial
Studied period (years): 5
Date of first inclusion: 05-Nov-2012
Date of database lock: 13-Jun-2017

Pre-assignment

Screening details:

Metastatic colorectal cancer expressing the wtKRAS and wtNRAS status

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	Arm A

Arm description:

Afatinib: 40 mg, oral, once daily continuous.
Cetuximab: 500 mg/m2, intravenous (IV), every 2 weeks.

Arm type	Experimental
Investigational medicinal product name	AFATINIB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Afatinib: 40 mg, oral, once daily continuous.

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

Dosage and administration details:

Cetuximab: 500 mg/m2, intravenous (IV), every 2 weeks.

Arm title	Arm B

Arm description:

Cetuximab: 500 mg/m2, intravenous (IV), every 2 weeks.

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

Dosage and administration details:
Cetuximab: 500 mg/m2, intravenous (IV), every 2 weeks.

Number of subjects in period 1	Arm A	Arm B
Started	51	24
Completed	51	24

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	75	75	
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	
Adults (18-64 years)	40	40	
From 65-84 years	35	35	
85 years and over	0	0	
18 years and over	0	0	
Age continuous Units: years			
median	64		
full range (min-max)	38 to 85	-	
Gender categorical Units: Subjects			
Female	24	24	
Male	51	51	

Subject analysis sets

Subject analysis set title	Arm A
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Arm A:
Afatinib: 40 mg, oral, once daily continuous.
Cetuximab: 500 mg/m2, intravenous (IV), every 2 weeks

Subject analysis set title	Arm B
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Arm B:
Cetuximab: 500 mg/m2, IV, every 2 weeks

Reporting group values	Arm A	Arm B	
Number of subjects	51	24	

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over 18 years and over	28 23	12 12	
Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female Male	15 36	9 15	

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Afatinib: 40 mg, oral, once daily continuous.
Cetuximab: 500 mg/m2, intravenous (IV), every 2 weeks.

Reporting group title	Arm B

Reporting group description:

Cetuximab: 500 mg/m2, intravenous (IV), every 2 weeks.

Subject analysis set title	Arm A
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Arm A:
Afatinib: 40 mg, oral, once daily continuous.
Cetuximab: 500 mg/m2, intravenous (IV), every 2 weeks

Subject analysis set title	Arm B
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Arm B:
Cetuximab: 500 mg/m2, IV, every 2 weeks

Primary: Primary end point: PFS rate at 6 months

End point title	Primary end point: PFS rate at 6 months[1]

End point description:

The Primary objective was to evaluate the efficacy of the treatment with cetuximab alone or in combination with afatinib in terms of PFS rate at 6 months. The main criterion was the non-progression rate at 6 months assessed by CT scan according to RECIST v1.1. The non-progression rate at 6 months was defined as the % of patients without progression at 6 months after the observation of all patients at 6 months.

End point type	Primary

End point timeframe:

At 6 months

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: Primary endpoint was to evaluate the non-progression rate at 6 months. It was presented by frequency and percentage of patients without progression at 6 months with his 95% confidence interval.
The decision rule is: After the inclusion of 49 patients, it can be concluded that the experimental arm is inefficient if the number of successes (non-progressive patients at 6 months) is less than or equal to 19, and is effective if the number of successes is greater or equal to 20.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	24		
Units: percent				
arithmetic mean (confidence interval 95%)	17.7 (8.4 to 30.9)	20.8 (7.1 to 42.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Toxicity was evaluated before progression, i.e. in Arm B before afatinib treatment in patients eligible for crossover.

Adverse event reporting additional description:

Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Arm A

Reporting group description: -

Reporting group title	Arm B

Reporting group description: -

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 49 (73.47%)	13 / 24 (54.17%)	
number of deaths (all causes)	43	23	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Portal hypertension			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter thrombosis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			

subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 49 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	2 / 49 (4.08%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Interstitial lung disease			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Alkaline phosphatase increased			
subjects affected / exposed	3 / 49 (6.12%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma GT increased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GGT increased			
subjects affected / exposed	6 / 49 (12.24%)	3 / 24 (12.50%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalemia			
subjects affected / exposed	2 / 49 (4.08%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function tests raised			
subjects affected / exposed	0 / 49 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Transaminases increased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Heart failure			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Confusion			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 49 (2.04%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 49 (2.04%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowel obstruction			

subjects affected / exposed	1 / 49 (2.04%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 49 (0.00%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	4 / 49 (8.16%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 49 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised intraabdominal fluid collection			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
HEPATIC DYSFUNCTION			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Erythema facial			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			
subjects affected / exposed	4 / 49 (8.16%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected rash			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pustular rash			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 49 (2.04%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash acneiform			
subjects affected / exposed	2 / 49 (4.08%)	2 / 24 (8.33%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			

subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pustular			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute renal insufficiency			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain bone			
subjects affected / exposed	0 / 49 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycemic coma			

subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesemia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			
subjects affected / exposed	1 / 49 (2.04%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphatemia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 49 (100.00%)	24 / 24 (100.00%)	
Vascular disorders			
Superficial thrombophlebitis	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	2 / 49 (4.08%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Arterial hypertension	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	3 / 49 (6.12%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
General disorders and administration site conditions			

Injection-site reactions	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	0 / 49 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Fever	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	12 / 49 (24.49%)	5 / 24 (20.83%)	
occurrences (all)	12	5	
Fatigue	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	32 / 49 (65.31%)	16 / 24 (66.67%)	
occurrences (all)	32	16	
Pain	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	18 / 49 (36.73%)	11 / 24 (45.83%)	
occurrences (all)	18	11	
Limbs edema	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	7 / 49 (14.29%)	3 / 24 (12.50%)	
occurrences (all)	7	3	
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	5 / 49 (10.20%)	4 / 24 (16.67%)	
occurrences (all)	5	4	
Rhinitis	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	3 / 49 (6.12%)	4 / 24 (16.67%)	
occurrences (all)	3	4	
Cough	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	2 / 49 (4.08%)	4 / 24 (16.67%)	
occurrences (all)	2	4	
Dyspnea	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	5 / 49 (10.20%)	5 / 24 (20.83%)	
occurrences (all)	5	5	
Psychiatric disorders			
Anxiety	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	3 / 49 (6.12%)	2 / 24 (8.33%)	
occurrences (all)	3	2	
Investigations			

Weight loss	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	8 / 49 (16.33%)	3 / 24 (12.50%)	
occurrences (all)	8	3	
Increased serum creatinine	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	7 / 49 (14.29%)	3 / 24 (12.50%)	
occurrences (all)	7	3	
Increased Gama GT	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	43 / 49 (87.76%)	19 / 24 (79.17%)	
occurrences (all)	43	19	
Leucopenia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	6 / 49 (12.24%)	4 / 24 (16.67%)	
occurrences (all)	6	4	
Neutropenia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	3 / 49 (6.12%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
Increased blood bilirubin	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	14 / 49 (28.57%)	7 / 24 (29.17%)	
occurrences (all)	14	7	
Alkaline phosphatase increase	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	36 / 49 (73.47%)	18 / 24 (75.00%)	
occurrences (all)	36	18	
Increased ASAT	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	27 / 49 (55.10%)	14 / 24 (58.33%)	
occurrences (all)	27	14	
Increased ALAT	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	18 / 49 (36.73%)	5 / 24 (20.83%)	
occurrences (all)	18	5	
Lymphopenia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	16 / 49 (32.65%)	7 / 24 (29.17%)	
occurrences (all)	16	7	
Nervous system disorders			
Dysgeusia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		

subjects affected / exposed	5 / 49 (10.20%)	3 / 24 (12.50%)	
occurrences (all)	5	3	
Motor peripheral neuropathy	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Sensitive peripheral neuropathy	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	7 / 49 (14.29%)	2 / 24 (8.33%)	
occurrences (all)	7	2	
Paresthesia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	8 / 49 (16.33%)	2 / 24 (8.33%)	
occurrences (all)	8	2	
Insomnia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	1 / 49 (2.04%)	3 / 24 (12.50%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Anaemia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	23 / 49 (46.94%)	11 / 24 (45.83%)	
occurrences (all)	23	11	
leukocytosis	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	12 / 49 (24.49%)	5 / 24 (20.83%)	
occurrences (all)	12	5	
Thrombopenia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	8 / 49 (16.33%)	3 / 24 (12.50%)	
occurrences (all)	8	3	
LDH increase	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	9 / 49 (18.37%)	3 / 24 (12.50%)	
occurrences (all)	9	3	
Ear and labyrinth disorders			
Dizziness	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Dry eyes	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		

subjects affected / exposed	4 / 49 (8.16%)	1 / 24 (4.17%)	
occurrences (all)	4	1	
Conjunctivitis	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	9 / 49 (18.37%)	4 / 24 (16.67%)	
occurrences (all)	9	4	
Gastrointestinal disorders			
Lower gastrointestinal bleeding	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	2 / 49 (4.08%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Abdominal pain	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	12 / 49 (24.49%)	4 / 24 (16.67%)	
occurrences (all)	12	4	
Oral mucositis	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	17 / 49 (34.69%)	3 / 24 (12.50%)	
occurrences (all)	17	3	
Vomiting	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	9 / 49 (18.37%)	3 / 24 (12.50%)	
occurrences (all)	9	3	
Diarrhea	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	31 / 49 (63.27%)	10 / 24 (41.67%)	
occurrences (all)	31	10	
Nausea	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	14 / 49 (28.57%)	4 / 24 (16.67%)	
occurrences (all)	14	4	
Constipation	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	8 / 49 (16.33%)	5 / 24 (20.83%)	
occurrences (all)	8	5	
Meteorism	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	3 / 49 (6.12%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
Hemorrhoids	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	5 / 49 (10.20%)	2 / 24 (8.33%)	
occurrences (all)	5	2	

Bowel incontinence	Additional description: Only subjects affected number is available. No occurrences all number is available in the table of value for non serious AE		
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gastroesophageal reflux	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	3 / 49 (6.12%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
Epigastralgia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	2 / 49 (4.08%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Dysphagia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	2 / 49 (4.08%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	3 / 49 (6.12%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Palmar-plantar erythrodysesthesia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	6 / 49 (12.24%)	2 / 24 (8.33%)	
occurrences (all)	6	2	
Skin hyperpigmentation	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	3 / 49 (6.12%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
Papulopustular rash	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	16 / 49 (32.65%)	4 / 24 (16.67%)	
occurrences (all)	16	4	
Pruritus	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	12 / 49 (24.49%)	5 / 24 (20.83%)	
occurrences (all)	12	5	
Dry skin	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	24 / 49 (48.98%)	10 / 24 (41.67%)	
occurrences (all)	24	10	
Rash acneiform	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		

subjects affected / exposed	32 / 49 (65.31%)	18 / 24 (75.00%)	
occurrences (all)	32	18	
Folliculitis	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	15 / 49 (30.61%)	4 / 24 (16.67%)	
occurrences (all)	15	4	
Paronychia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	4 / 49 (8.16%)	3 / 24 (12.50%)	
occurrences (all)	4	3	
Cervices	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	3 / 49 (6.12%)	3 / 24 (12.50%)	
occurrences (all)	3	3	
Erythema	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	9 / 49 (18.37%)	6 / 24 (25.00%)	
occurrences (all)	9	6	
Onycholysis	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	3 / 49 (6.12%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
Hypertrichosis	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	2 / 49 (4.08%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Urticaria	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	6 / 49 (12.24%)	4 / 24 (16.67%)	
occurrences (all)	6	4	
Digitale fissures	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	3 / 49 (6.12%)	4 / 24 (16.67%)	
occurrences (all)	3	4	
Renal and urinary disorders			
Proteinuria	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	15 / 49 (30.61%)	5 / 24 (20.83%)	
occurrences (all)	15	5	
Pollakiuria	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

Nocturia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	1 / 49 (2.04%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Myalgia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	4 / 49 (8.16%)	2 / 24 (8.33%)	
occurrences (all)	4	2	
Infections and infestations			
Paronychia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	11 / 49 (22.45%)	2 / 24 (8.33%)	
occurrences (all)	11	2	
Metabolism and nutrition disorders			
Hypokalemia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	18 / 49 (36.73%)	6 / 24 (25.00%)	
occurrences (all)	18	6	
Hyperkalemia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	10 / 49 (20.41%)	6 / 24 (25.00%)	
occurrences (all)	10	6	
Hyponatremia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	21 / 49 (42.86%)	8 / 24 (33.33%)	
occurrences (all)	21	8	
Hypernatremia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	2 / 49 (4.08%)	3 / 24 (12.50%)	
occurrences (all)	2	3	
Hypocalcemia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	17 / 49 (34.69%)	7 / 24 (29.17%)	
occurrences (all)	17	7	
Hypercalcemia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	5 / 49 (10.20%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Hypomagnesemia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	25 / 49 (51.02%)	10 / 24 (41.67%)	
occurrences (all)	25	10	
Hypermagnesemia	Additional description: Only subjects affected number is available. in the table		

	of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	3 / 49 (6.12%)	3 / 24 (12.50%)	
occurrences (all)	3	3	
Hypoglycemia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	7 / 49 (14.29%)	2 / 24 (8.33%)	
occurrences (all)	7	2	
Hypophosphatemia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	2 / 49 (4.08%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Hyperglycemia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	15 / 49 (30.61%)	7 / 24 (29.17%)	
occurrences (all)	15	7	
Anorexia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	14 / 49 (28.57%)	8 / 24 (33.33%)	
occurrences (all)	14	8	
Hypoalbuminemia	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
subjects affected / exposed	15 / 49 (30.61%)	8 / 24 (33.33%)	
occurrences (all)	15	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2012	•Modification of stratification factors. •Eliminate screening visit (#0) which was similar to visit baseline visit (#1). •Add optional ancillary study before randomization. •Eliminate end of study test already performed before each treatment cycle. •Specify patient follow-up after progression in each arm. •Description of the discontinuation of treatment parameters. •Correction of typographic and numbering errors within the protocol. •Correction of the publication rules section. •Modification of the investigators list. •Modification of the consent form.
22 February 2013	•Update protocol and consent form with respect to the new IB. •Addition of non inclusion criteria #17: "Previous history of keratitis, ulcerative keratitis or severe dry eye". •Modification of the incusion criteria #10: the sentence "GammaGT <3 x ULN (<5 x ULN in case of liver involvement)" was removed. •Modification of the investigators list. •Modification of the regulatory agency name (Afssaps became ANSM) in the protocol
05 February 2014	•Modification of the inclusion (#2) and non-inclusion (#1) criteria to select patients with wild type NRAS and KRAS tumors, and to allow recruitment of patient without progression under previously anti-EGFR therapy. •Reevaluation of the AE and AESI list. •Modification of the test used to assess cardiac evaluation. •Modification of the volume of whole blood sampling. •Modification of the investigators list. •Update of the IB •Update of the insurance certificate •Update of the consent form (blood and tumor sampling).
22 April 2014	•Presentation of the modified IB to the regulatory agency
28 November 2014	•Extension of the recruitment period by 24 months. •Update the safety section of the consent form. •Update of the insurance certificate. •Modification of the investigators list.
06 May 2015	•Modification of the investigators list.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported