



## 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
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#### 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



## 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
<b>Arm title</b>	Arm A

Arm description:

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

<b>Arm title</b>	Arm B
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Arm description:

Cetuximab: 500 mg/m<sup>2</sup>, 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

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Dosage and administration details:

Cetuximab: 500 mg/m<sup>2</sup>, intravenous (IV), every 2 weeks.

<b>Number of subjects in period 1</b>	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/m<sup>2</sup>, 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/m<sup>2</sup>, 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
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Reporting group description:

Afatinib: 40 mg, oral, once daily continuous.

Cetuximab: 500 mg/m<sup>2</sup>, intravenous (IV), every 2 weeks.

Reporting group title	Arm B
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Reporting group description:

Cetuximab: 500 mg/m<sup>2</sup>, intravenous (IV), every 2 weeks.

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

Arm A:

Afatinib: 40 mg, oral, once daily continuous.

Cetuximab: 500 mg/m<sup>2</sup>, intravenous (IV), every 2 weeks

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

Arm B:

Cetuximab: 500 mg/m<sup>2</sup>, IV, every 2 weeks

### Primary: Primary end point: PFS rate at 6 months

End point title	Primary end point: PFS rate at 6 months <sup>[1]</sup>
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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
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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**

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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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### Reporting groups

Reporting group title	Arm A
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Reporting group description: -

Reporting group title	Arm B
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Reporting group description: -

<b>Serious adverse events</b>	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	
<b>Hyperthermia</b>			
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	
<b>Mucositis</b>			
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	
<b>Pain</b>			
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	
<b>Performance status decreased</b>			
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	
<b>Immune system disorders</b>			
<b>Allergic reaction</b>			
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	
<b>Anaphylactic shock</b>			
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	
<b>Reproductive system and breast disorders</b>			
<b>Interstitial lung disease</b>			
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	
<b>Constipation</b>			
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	
<b>Diarrhea</b>			
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	
<b>Gastrointestinal disorder</b>			
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	
<b>Intestinal obstruction</b>			
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	
<b>Localised intraabdominal fluid collection</b>			
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	
<b>Hepatobiliary disorders</b>			
<b>HEPATIC DYSFUNCTION</b>			
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	
<b>Skin and subcutaneous tissue disorders</b>			
<b>Acne</b>			
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	
<b>Hypomagnesaemia</b>			
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	
<b>Hypomagnesemia</b>			
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	
<b>Hyponatremia</b>			
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	
<b>Hypophosphatemia</b>			
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 %

<b>Non-serious adverse events</b>	Arm A	Arm B	
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	49 / 49 (100.00%)	24 / 24 (100.00%)	
<b>Vascular disorders</b>			
<b>Superficial thrombophlebitis</b>	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	
<b>Arterial hypertension</b>	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	
<b>General disorders and administration site conditions</b>			

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 occurrences (all)	0 / 49 (0.00%) 0
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 occurrences (all)	12 / 49 (24.49%) 12
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 occurrences (all)	32 / 49 (65.31%) 32
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 occurrences (all)	18 / 49 (36.73%) 18
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 occurrences (all)	7 / 49 (14.29%) 7
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 occurrences (all)	5 / 49 (10.20%) 5
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 occurrences (all)	3 / 49 (6.12%) 3
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 occurrences (all)	2 / 49 (4.08%) 2
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 occurrences (all)	5 / 49 (10.20%) 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 occurrences (all)	3 / 49 (6.12%) 3
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 occurrences (all)	8 / 49 (16.33%) 8	3 / 24 (12.50%) 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 occurrences (all)	7 / 49 (14.29%) 7	3 / 24 (12.50%) 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 occurrences (all)	43 / 49 (87.76%) 43	19 / 24 (79.17%) 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 occurrences (all)	6 / 49 (12.24%) 6	4 / 24 (16.67%) 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 occurrences (all)	3 / 49 (6.12%) 3	1 / 24 (4.17%) 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 occurrences (all)	14 / 49 (28.57%) 14	7 / 24 (29.17%) 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 occurrences (all)	36 / 49 (73.47%) 36	18 / 24 (75.00%) 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 occurrences (all)	27 / 49 (55.10%) 27	14 / 24 (58.33%) 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 occurrences (all)	18 / 49 (36.73%) 18	5 / 24 (20.83%) 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 occurrences (all)	16 / 49 (32.65%) 16	7 / 24 (29.17%) 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 occurrences (all)	5 / 49 (10.20%) 5	3 / 24 (12.50%) 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 occurrences (all)	1 / 49 (2.04%) 1	0 / 24 (0.00%) 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 occurrences (all)	7 / 49 (14.29%) 7	2 / 24 (8.33%) 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 occurrences (all)	8 / 49 (16.33%) 8	2 / 24 (8.33%) 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 occurrences (all)	1 / 49 (2.04%) 1	3 / 24 (12.50%) 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 occurrences (all)	23 / 49 (46.94%) 23	11 / 24 (45.83%) 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 occurrences (all)	12 / 49 (24.49%) 12	5 / 24 (20.83%) 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 occurrences (all)	8 / 49 (16.33%) 8	3 / 24 (12.50%) 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 occurrences (all)	9 / 49 (18.37%) 9	3 / 24 (12.50%) 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 occurrences (all)	1 / 49 (2.04%) 1	0 / 24 (0.00%) 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 occurrences (all)	4 / 49 (8.16%) 4	1 / 24 (4.17%) 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 occurrences (all)	9 / 49 (18.37%) 9	4 / 24 (16.67%) 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 occurrences (all)	2 / 49 (4.08%) 2	0 / 24 (0.00%) 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 occurrences (all)	12 / 49 (24.49%) 12	4 / 24 (16.67%) 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 occurrences (all)	17 / 49 (34.69%) 17	3 / 24 (12.50%) 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 occurrences (all)	9 / 49 (18.37%) 9	3 / 24 (12.50%) 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 occurrences (all)	31 / 49 (63.27%) 31	10 / 24 (41.67%) 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 occurrences (all)	14 / 49 (28.57%) 14	4 / 24 (16.67%) 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 occurrences (all)	8 / 49 (16.33%) 8	5 / 24 (20.83%) 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 occurrences (all)	3 / 49 (6.12%) 3	1 / 24 (4.17%) 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 occurrences (all)	5 / 49 (10.20%) 5	2 / 24 (8.33%) 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 occurrences (all)	1 / 49 (2.04%) 1	0 / 24 (0.00%) 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 occurrences (all)	3 / 49 (6.12%) 3	1 / 24 (4.17%) 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 occurrences (all)	2 / 49 (4.08%) 2	1 / 24 (4.17%) 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 occurrences (all)	2 / 49 (4.08%) 2	1 / 24 (4.17%) 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 occurrences (all)	3 / 49 (6.12%) 3	0 / 24 (0.00%) 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 occurrences (all)	6 / 49 (12.24%) 6	2 / 24 (8.33%) 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 occurrences (all)	3 / 49 (6.12%) 3	1 / 24 (4.17%) 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 occurrences (all)	16 / 49 (32.65%) 16	4 / 24 (16.67%) 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 occurrences (all)	12 / 49 (24.49%) 12	5 / 24 (20.83%) 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 occurrences (all)	24 / 49 (48.98%) 24	10 / 24 (41.67%) 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 occurrences (all)	32 / 49 (65.31%) 32	18 / 24 (75.00%) 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 occurrences (all)	15 / 49 (30.61%) 15	4 / 24 (16.67%) 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 occurrences (all)	4 / 49 (8.16%) 4	3 / 24 (12.50%) 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 occurrences (all)	3 / 49 (6.12%) 3	3 / 24 (12.50%) 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 occurrences (all)	9 / 49 (18.37%) 9	6 / 24 (25.00%) 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 occurrences (all)	3 / 49 (6.12%) 3	1 / 24 (4.17%) 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 occurrences (all)	2 / 49 (4.08%) 2	1 / 24 (4.17%) 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 occurrences (all)	6 / 49 (12.24%) 6	4 / 24 (16.67%) 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 occurrences (all)	3 / 49 (6.12%) 3	4 / 24 (16.67%) 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 occurrences (all)	15 / 49 (30.61%) 15	5 / 24 (20.83%) 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 occurrences (all)	1 / 49 (2.04%) 1	0 / 24 (0.00%) 0	

Nocturia subjects affected / exposed occurrences (all)	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
	1 / 49 (2.04%) 1	0 / 24 (0.00%) 0	
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
	4 / 49 (8.16%) 4	2 / 24 (8.33%) 2	
Infections and infestations Paronychia subjects affected / exposed occurrences (all)	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
	11 / 49 (22.45%) 11	2 / 24 (8.33%) 2	
Metabolism and nutrition disorders Hypokalemia subjects affected / exposed occurrences (all)	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
	18 / 49 (36.73%) 18	6 / 24 (25.00%) 6	
Hyperkalemia subjects affected / exposed occurrences (all)	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
	10 / 49 (20.41%) 10	6 / 24 (25.00%) 6	
Hyponatremia subjects affected / exposed occurrences (all)	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
	21 / 49 (42.86%) 21	8 / 24 (33.33%) 8	
Hypernatremia subjects affected / exposed occurrences (all)	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
	2 / 49 (4.08%) 2	3 / 24 (12.50%) 3	
Hypocalcemia subjects affected / exposed occurrences (all)	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
	17 / 49 (34.69%) 17	7 / 24 (29.17%) 7	
Hypercalcemia subjects affected / exposed occurrences (all)	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
	5 / 49 (10.20%) 5	0 / 24 (0.00%) 0	
Hypomagnesemia subjects affected / exposed occurrences (all)	Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported		
	25 / 49 (51.02%) 25	10 / 24 (41.67%) 10	
Hyper magnesemia	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 occurrences (all)	3 / 49 (6.12%) 3	3 / 24 (12.50%) 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 occurrences (all)	7 / 49 (14.29%) 7	2 / 24 (8.33%) 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 occurrences (all)	2 / 49 (4.08%) 2	0 / 24 (0.00%) 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 occurrences (all)	15 / 49 (30.61%) 15	7 / 24 (29.17%) 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 occurrences (all)	14 / 49 (28.57%) 14	8 / 24 (33.33%) 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 occurrences (all)	15 / 49 (30.61%) 15	8 / 24 (33.33%) 8	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2012	<ul style="list-style-type: none"><li>•Modification of stratification factors.</li><li>•Eliminate screening visit (#0) which was similar to visit baseline visit (#1).</li><li>•Add optional ancillary study before randomization.</li><li>•Eliminate end of study test already performed before each treatment cycle.</li><li>•Specify patient follow-up after progression in each arm.</li><li>•Description of the discontinuation of treatment parameters.</li><li>•Correction of typographic and numbering errors within the protocol.</li><li>•Correction of the publication rules section.</li><li>•Modification of the investigators list.</li><li>•Modification of the consent form.</li></ul>
22 February 2013	<ul style="list-style-type: none"><li>•Update protocol and consent form with respect to the new IB.</li><li>•Addition of non inclusion criteria #17: "Previous history of keratitis, ulcerative keratitis or severe dry eye".</li><li>•Modification of the inclusion criteria #10: the sentence "GammaGT &lt;3 x ULN (&lt;5 x ULN in case of liver involvement)" was removed.</li><li>•Modification of the investigators list.</li><li>•Modification of the regulatory agency name (Afssaps became ANSM) in the protocol</li></ul>
05 February 2014	<ul style="list-style-type: none"><li>•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.</li><li>•Reevaluation of the AE and AESI list.</li><li>•Modification of the test used to assess cardiac evaluation.</li><li>•Modification of the volume of whole blood sampling.</li><li>•Modification of the investigators list.</li><li>•Update of the IB</li><li>•Update of the insurance certificate</li><li>•Update of the consent form (blood and tumor sampling).</li></ul>
22 April 2014	<ul style="list-style-type: none"><li>•Presentation of the modified IB to the regulatory agency</li></ul>
28 November 2014	<ul style="list-style-type: none"><li>•Extension of the recruitment period by 24 months.</li><li>•Update the safety section of the consent form.</li><li>•Update of the insurance certificate.</li><li>•Modification of the investigators list.</li></ul>
06 May 2015	<ul style="list-style-type: none"><li>•Modification of the investigators list.</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported