



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 | 15 | 9 | |
| Male | 36 | 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 subjects affected / exposed occurrences (all) Fever subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Limbs edema 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 | | |
| | 0 / 49 (0.00%) 0 | 1 / 24 (4.17%) 1 | |
| | Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported | | |
| | 12 / 49 (24.49%) 12 | 5 / 24 (20.83%) 5 | |
| | Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported | | |
| | 32 / 49 (65.31%) 32 | 16 / 24 (66.67%) 16 | |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Dyspnea 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 | 4 / 24 (16.67%) 4 | |
| | Additional description: Only subjects affected number is available. in the table of value for non serious AE only subjects affected number is reported | | |
| | 3 / 49 (6.12%) 3 | 4 / 24 (16.67%) 4 | |
| | 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 | 4 / 24 (16.67%) 4 | |
| Psychiatric disorders Anxiety 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 | | |
| | 3 / 49 (6.12%) 3 | 2 / 24 (8.33%) 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 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 | 1 / 49 (2.04%) |
| | occurrences (all) | 1 |
| | | 0 / 24 (0.00%) |
| 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%) |
| | occurrences (all) | 3 |
| | | 1 / 24 (4.17%) |
| 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%) |
| | occurrences (all) | 2 |
| | | 1 / 24 (4.17%) |
| 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%) |
| | occurrences (all) | 2 |
| | | 1 / 24 (4.17%) |
| 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%) |
| | occurrences (all) | 3 |
| | | 0 / 24 (0.00%) |
| 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%) |
| | occurrences (all) | 6 |
| | | 2 / 24 (8.33%) |
| 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%) |
| | occurrences (all) | 3 |
| | | 1 / 24 (4.17%) |
| 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%) |
| | occurrences (all) | 16 |
| | | 4 / 24 (16.67%) |
| 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%) |
| | occurrences (all) | 12 |
| | | 5 / 24 (20.83%) |
| 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%) |
| | occurrences (all) | 24 |
| | | 10 / 24 (41.67%) |
| 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 | |
| Services | 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 | 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 |
| 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 occurrences (all) | 4 / 49 (8.16%) 4 | 2 / 24 (8.33%) 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 occurrences (all) | 11 / 49 (22.45%) 11 | 2 / 24 (8.33%) 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 occurrences (all) | 18 / 49 (36.73%) 18 | 6 / 24 (25.00%) 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 occurrences (all) | 10 / 49 (20.41%) 10 | 6 / 24 (25.00%) 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 occurrences (all) | 21 / 49 (42.86%) 21 | 8 / 24 (33.33%) 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 occurrences (all) | 2 / 49 (4.08%) 2 | 3 / 24 (12.50%) 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 occurrences (all) | 17 / 49 (34.69%) 17 | 7 / 24 (29.17%) 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 occurrences (all) | 5 / 49 (10.20%) 5 | 0 / 24 (0.00%) 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 occurrences (all) | 25 / 49 (51.02%) 25 | 10 / 24 (41.67%) 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 | <ul style="list-style-type: none">•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 | <ul style="list-style-type: none">•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 inclusion 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 | <ul style="list-style-type: none">•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 | <ul style="list-style-type: none">•Presentation of the modified IB to the regulatory agency |
| 28 November 2014 | <ul style="list-style-type: none">•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 | <ul style="list-style-type: none">•Modification of the investigators list. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported