# Clinical trial results:
# Phase Ib/II trial of copanlisib, a selective PI3K inhibitor, in combination with cetuximab in patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) harboring a PI3KCA mutation/amplification and/or a PTEN loss

## Summary

| | |
|---|---|
| EudraCT number | 2015-004340-19 |
| Trial protocol | FR |
| Global end of trial date | 21 February 2020 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 12 March 2022 |
| First version publication date | 12 March 2022 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | UC-0130/1507 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02822482 |
| 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 171936704, n.ait-rahmoune@unicancer.fr |
| Scientific contact | Nourredine AIT RAHMOUNE, UNICANCER, +33 171936704, 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 | 22 April 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 21 February 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 February 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to determine the MTD of copanlisib used in combination with cetuximab and the RP2D in the phase Ib part and to evaluate the efficacy of the combination at the RP2D in the phase II. Determination of the MTD will be based on the occurrence of DLT during cycle 1.

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 | 14 December 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 4 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | France: 11 |
| Worldwide total number of subjects | 11 |
| EEA total number of subjects | 11 |

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) | 8 |
| From 65 to 84 years | 3 |

| | |
|---|---|
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Date of first inclusion: 07-Mar-2017
Date of early study termination date: 22-Mar-2019

### Pre-assignment

Screening details:

Patients with recurrent and/or metastatic HNSCC after failure of platinum-based chemotherapy, not amenable to curative treatment with surgery and/or chemotherapy and/or radiotherapy.

### Period 1

| | |
|---|---|
| Period 1 title | Phase Ib (first step) (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | Phase Ib - Determination of MDT |

Arm description:

The Phase IB is to determine the maximum tolerated dose (MTD) of copanlisib used in combination with cetuximab and the recommended phase II dose (RP2D) in the phase Ib part.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | copanlisib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Infusion |

Dosage and administration details:

The phase Ib was designed as a dose-escalation study. The objective of this phase was to determine the RP2D. The study was conducted using the modified Fibonacci "3+3" method.
-Dose level -1: 3 to 6 patients
- Dose level 1: 3 to 6 patients
- Dose level 2: 3 to 6 patients

30 mg Dose Level # -1
45 mg Dose Level # 1
60 mg Dose Level # 2

| | |
|---|---|
| Investigational medicinal product name | Cetuximab |
| Investigational medicinal product code | |
| Other name | Cetuximab |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Injection |

Dosage and administration details:

Weekly infusion, with a loading dose of 400 mg/m² then 250 mg/m².

| **Number of subjects in period 1** | Phase Ib - Determination of MDT |
|---|---|
| Started | 11 |
| Completed | 11 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Phase Ib - Determination of MDT |
| Reporting group description: | |
| The Phase IB is to determine the maximum tolerated dose (MTD) of copanlisib used in combination with cetuximab and the recommended phase II dose (RP2D) in the phase Ib part. | |

| Reporting group values | Phase Ib - Determination of MDT | Total | |
|---|---|---|---|
| Number of subjects | 11 | 11 | |
| Age categorical<br>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) | 8 | 8 | |
| From 65-84 years | 3 | 3 | |
| 85 years and over | 0 | 0 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 11 | 11 | |

## End points

### End points reporting groups

| Reporting group title | Phase Ib - Determination of MDT |
|---|---|

Reporting group description:

The Phase IB is to determine the maximum tolerated dose (MTD) of copanlisib used in combination with cetuximab and the recommended phase II dose (RP2D) in the phase Ib part.

### Primary: Determination of the MTD

| End point title | Determination of the MTD[1] |
|---|---|

End point description:

| End point type | Primary |
|---|---|

End point timeframe:

DLTs occurence
At least, 3 patients will be treated at each dose level until a DLT is encountered during the first cycle of 29 days (DLT period).

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: Early termination of the study due to poor recruitment and short study treatment duration. Only 11 patients were included during the phase 1b

| **End point values** | Phase Ib - Determination of MDT | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 | | | |
| Units: Nimber of DLT | 2 | | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events occured during all the course of study treatment

Adverse event reporting additional description:

Concerning the adverse event (not serious) the number of "Subjects affected number" and the "Occurrences all number" are not available and are always noted "1" in the section of adverse event.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Phase Ib - Determination of MDT |

Reporting group description: -

| Serious adverse events | Phase Ib - Determination of MDT | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 11 (72.73%) | | |
| number of deaths (all causes) | 9 | | |
| number of deaths resulting from adverse events | 1 | | |
| Investigations | | | |
| Weight loss | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oral hemorrhage | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Ulcero-necrotic skin lesion | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Shoulder pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septicemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular access related infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| HYPOKALEMIA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Phase Ib - Determination of MDT | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 11 (100.00%) | | |
| Investigations | | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| GGT increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Potassium increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Weight loss | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Creatinine increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Eosinophil count increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|---|---|---|
| Vascular disorders | | | |
| Bleeding | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Oedema | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Oedema lower limb | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Oedema upper limb | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Face oedema | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Inflammation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Neck oedema | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Thoracic pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Xerosis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| HYPOCHONDRIUM PAIN RIGHT | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|---|---|---|
| Oral haemorrhage<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | |
| Oral lesion<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | |
| Vomiting<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | |
| Hepatobiliary disorders<br>Cholestasis<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | |
| Respiratory, thoracic and mediastinal disorders<br>Vasovagal attack<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | |
| Interstitial pneumonitis<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | |
| Sputum bloody<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | |
| Skin and subcutaneous tissue disorders<br>Localised skin reaction<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | |
| Skin erythema<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | |

| | | | |
|---|---|---|---|
| Unspecified nail disease | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Erythema periorbital | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Rash acneiform | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Cervical pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Cervicalgia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Shoulder pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Bronchopulmonary infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Medical device site pustule | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Septicaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Tracheostomy infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Folliculitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Paronychia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Cytolysis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Hypoalbuminemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|---|---|---|
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 13 May 2016 | -Update of IB, IMP labelling<br>-The protocol was clarify concerning the flow-chart, the definition of DLT. Addition of new criteria for IMP discontinuation, modification of inclusion criterai (protection of patients). Clarification of rules related to management of hyperglycemia due to IMP. Introduction of rules in case of hypertension due to IMP.<br>-information ans consent were updated |
| 23 March 2017 | - Patients without PI3KCA mutation/amplification and/or a PTEN loss can be included<br>-update of adverses rections due to IMP |
| 27 February 2018 | -Adition of Metformine (premedication) for the IMP administration<br>- Extension of the inclusion period<br>- Update of adverse reaction due to IMP |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 01 April 2019 | Early termination of study due to poor recruitment and short study treatment duration | - |

Notes:

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| Early termination of study due to poor recruitment and short study treatment duration.<br>Only 11 patients were included during the phase 1b of the study(determination of MTD). |

Notes: