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 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 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 subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Oral lesion subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Vomiting subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Hepatobiliary disorders Cholestasis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Respiratory, thoracic and mediastinal disorders Vasovagal attack subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Dyspnoea subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Interstitial pneumonitis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Sputum bloody subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Skin and subcutaneous tissue disorders Localised skin reaction subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Skin erythema subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 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 subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 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 -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. -information ans consent were updated
23 March 2017	- Patients without PI3KCA mutation/amplification and/or a PTEN loss can be included -update of adverses rections due to IMP
27 February 2018	-Adition of Metformine (premedication) for the IMP administration - Extension of the inclusion period - 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. Only 11 patients were included during the phase 1b of the study(determination of MTD).

Notes: