Clinical trial results:
A single arm, multicenter, phase II study of BEZ235 as monotherapy in patients with locally advanced or metastatic Transitional Cell Carcinoma (TCC) after failure of platinum based chemotherapy.

Summary

EudraCT number	2012-004123-20
Trial protocol	BE
Global end of trial date	16 June 2015

Results information

Result version number	v1 (current)
This version publication date	13 March 2021
First version publication date	13 March 2021

Trial information

Trial identification

Sponsor protocol code	UCL-ONCO2012-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01856101
WHO universal trial number (UTN)	-
Other trial identifiers	CBEZ235ZBE01T: UCL-ONCO2012-01

Notes:

Sponsors

Sponsor organisation name	Cliniques universitaires Saint-Luc- Université Catholique de Louvain
Sponsor organisation address	Avenue Hippocrate 10, Brussels, Belgium, 1200
Public contact	Jean-Pascal Machiels, Centre du Cancer, Cliniques universitaires Saint-Luc, 0032 27645457, jean-pascal.machiels@uclouvain.be
Scientific contact	Jean-Pascal Machiels, Centre du Cancer, Cliniques universitaires Saint-Luc, 0032 27645457, jean-pascal.machiels@uclouvain.be

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	16 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess, in a multicentre phase II trial, the safety and efficacy of BEZ235, an oral pan-class I phosphoinositol-3- kinase (PI3K) and mammalian target of rapamycin (mTOR) complex1/2 inhibitor, in locally advanced or metastatic transitional cell carcinoma (TCC) after failure of platinumbased therapy.

Protection of trial subjects:

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) were reported.
For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to the study coordinator or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality.

Background therapy:

BEZ235 was administered orally and continuously at a starting dose of 300 mg twice daily. Although it was not a doseescalation study, at day 15, based on a clinical evaluation of adverse events, the dose was adjusted for the rest of study.

Evidence for comparator:

Not applicable

Actual start date of recruitment	15 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?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Luxembourg: 2
Country: Number of subjects enrolled	Belgium: 18
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	9
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between March 2013 and October 2013, 20 patients from 10 centers including 9 in Belgium and 1 in Luxembourg were included. All patients had locally advanced or metastatic TBI and were previously exposed to platinum-based chemotherapy in the (neo) adjuvant and / or metastatic setting. Out of the 20 patients, only two exhibited PI3K/Akt/mTORpathway.

Pre-assignment

Screening details:

Initially, patients were stratified into two groups according to activation of the PI3K / Akt / mTOR pathway (loss of PTEN expression and / or PIK3CA activation vs no loss of PTEN expression and no PIK3CA activation). After Novartis' decision to stop the development of BEZ235, the study design was reviewed and the two groups were merged.

Period 1

Period 1 title	BEZ235 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	BEZ235

Arm description:

BEZ235 was administered orally and continuously at a starting dose of 300 mg twice daily. Although it was not a doseescalation study, at day 15, based on a clinical evaluation of adverse events, the dose was adjusted for the rest of study.

Arm type	Experimental
Investigational medicinal product name	BEZ235
Investigational medicinal product code	BEZ235
Other name	
Pharmaceutical forms	Powder for oral solution in sachet
Routes of administration	Oral use

Dosage and administration details:

BEZ235, supplied in sachets of 200 mg, 300 mg and 400 mg. The starting dose is 300 mg PO bid. It is administered orally on the same day on a continuous basis twice a day and should be taken immediately after a meal (e.g. breakfast / dinner), 12 ± 2 hours apart (dinner in the evening), at about the same time every day, except cycle 1, day 1. The full cycle is 28 days. Patients were treated until progression or until criteria for discontinuation were met.

Number of subjects in period 1	BEZ235
Started	20
Completed	11
Not completed	9
Consent withdrawn by subject	1
Adverse event, non-fatal	6
rapid clinical deterioration	2

Baseline characteristics

Reporting groups	
Reporting group title	BEZ235

Reporting group description:

BEZ235 was administered orally and continuously at a starting dose of 300 mg twice daily. Although it was not a doseescalation study, at day 15, based on a clinical evaluation of adverse events, the dose was adjusted for the rest of study.

Reporting group values	BEZ235	Total	
Number of subjects	20	20	
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)	9	9	
From 65-84 years	11	11	
85 years and over	0	0	
Age continuous Units: years			
median	66.5		
inter-quartile range (Q1-Q3)	41 to 78	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	17	17	

End points

End points reporting groups

Reporting group title	BEZ235

Reporting group description:

BEZ235 was administered orally and continuously at a starting dose of 300 mg twice daily. Although it was not a doseescalation study, at day 15, based on a clinical evaluation of adverse events, the dose was adjusted for the rest of study.

Primary: Determine the efficacy of BEZ235 in patients with palliative TCC in term of progression free survival rate (PFSR) at 16 weeks in one group of patients with PI3K/Akt/mTOR pathway deregulations and in one group of patients without PI3K/Akt/mTOR pathway dere

End point title	Determine the efficacy of BEZ235 in patients with palliative TCC in term of progression free survival rate (PFSR) at 16 weeks in one group of patients with PI3K/Akt/mTOR pathway deregulations and in one group of patients without PI3K/Akt/mTOR pathway dere[1]

End point description:

The PFS rate was defined as the proportion of patients alive and progression-free at 16 weeks. Patients who did not progress were considered as having stable disease, a partial response or a complete response at 16 weeks, according to RECIST 1.1. Patients who were unable to be evaluated at 16 weeks, because of rapid clinical deterioration or death from any cause, or the start of an additional anti-tumour therapy, were considered as having progressive disease.

End point type	Primary

End point timeframe:

16 weeks

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: No formal statistical tests were performed on the primary and secondary endpoints. Efficacy analyses were reported overall. The reported results are mainly descriptive (median and range for continuous variables, frequencies and percentages for categorical variables).

End point values	BEZ235			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Percentage	10			

Statistical analyses

No statistical analyses for this end point

Primary: Progression-free survival rate at 8 weeks.

End point title	Progression-free survival rate at 8 weeks.[2]

End point description:

The definition used for PFS was the time interval between the date of inclusion and the date of progressive disease or death from any cause.

End point type	Primary

End point timeframe:

8 weeks

Notes:

[2] - 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: The reported results are mainly descriptive.

End point values	BEZ235			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Percentage	15			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

End point type	Secondary

End point timeframe:

Progression free survival (PFS) will be measured from the date of registration to the date of progression or death, whatever the cause. Patients who are still alive and without progression at the time of the analyse will be censored at the date of last fo

End point values	BEZ235			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: days				
median (confidence interval 95%)	62 (38 to 588)			

Statistical analyses

No statistical analyses for this end point

Secondary: overall survival

End point title	overall survival

End point description:

End point type	Secondary

End point timeframe:

Overall survival (OS) is defined as the time from the date of registration to the date of death from any cause.

End point values	BEZ235			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: days				
median (inter-quartile range (Q1-Q3))	127 (41 to 734)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All patients will have a follow-up visit scheduled 28 days after the last dose of the study drug to follow for AEs and SAEs that may have occurred after discontinuation from the study.

Adverse event reporting additional description:

For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and the study coordinator concurs with that assessment.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE GRADE
Dictionary version	4.03

Reporting groups

Reporting group title	BEZ235

Reporting group description:

BEZ235 was administered orally and continuously at a starting dose of 300 mg twice daily.

Serious adverse events	BEZ235		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 20 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhea			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Cutaneous disorder			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Stomatitis			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BEZ235		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 20 (90.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all) Fever subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Weight loss subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all)	8 / 20 (40.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 4 / 20 (20.00%) 1 1 / 20 (5.00%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Pyrosis/gastritis subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	 6 / 20 (30.00%) 1 4 / 20 (20.00%) 1 3 / 20 (15.00%) 1 1 / 20 (5.00%) 1		
Skin and subcutaneous tissue disorders Rash/pruritus subjects affected / exposed occurrences (all)	 7 / 20 (35.00%) 1		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Psychiatric disorders			

Confusion subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 1		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all) Anorexia subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 6 / 20 (30.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2013	amend 1
20 October 2013	amend 2

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 October 2013	This study was, however, closed prematurely because BEZ235 was withdrawn from further development.	-

Notes:

Limitations and caveats

None reported