



## 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 dose escalation 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<br>(gestational age < 37 wks) | 0        | 0     |  |
| Newborns (0-27 days)                                  | 0        | 0     |  |
| Infants and toddlers (28 days-23<br>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:<br>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 <sup>[1]</sup> |
|-----------------|--|

#### 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. <sup>[2]</sup> |
| End point description:<br>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.

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | 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

|                                  |                 |  |  |  |
|----------------------------------|-----------------|--|--|--|
| <b>End point values</b>          | 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.



|                                       |                 |  |  |  |
|---------------------------------------|-----------------|--|--|--|
| <b>End point values</b>               | 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

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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 %

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

|  |                      |  |  |
|--|----------------------|--|--|
| Confusion<br>subjects affected / exposed<br>occurrences (all)      | 2 / 20 (10.00%)<br>1 |  |  |
| Metabolism and nutrition disorders                                 |                      |  |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 20 (5.00%)<br>1  |  |  |
| Anorexia<br>subjects affected / exposed<br>occurrences (all)       | 6 / 20 (30.00%)<br>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:

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### 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