



## Clinical trial results:

**A randomized, double blind, placebo-controlled, multicenter phase II study to evaluate efficacy and safety of roniciclib in subjects with extensive-stage disease small cell lung cancer (SCLC) who are receiving cisplatin + etoposide or carboplatin + etoposide as first-line therapy**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-004198-28 |
| Trial protocol           | DE BE HU IT PL |
| Global end of trial date | 25 May 2016    |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 24 March 2017 |
| First version publication date | 24 March 2017 |

### Trial information

#### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | BAY1000394/14615 |
|-----------------------|------------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02161419 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                    |
|------------------------------|--------------------------------------------------------------------|
| Sponsor organisation name    | Bayer AG                                                           |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,                 |
| Public contact               | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact           | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |

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                       | 25 May 2016 |
| Is this the analysis of the primary completion data? | No          |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 25 May 2016 |
| Was the trial ended prematurely?                     | Yes         |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to compare roniciclib with placebo in addition to background treatment with chemotherapy (either cisplatin + etoposide or carboplatin + etoposide) in terms of progression free survival (PFS) in small cell lung cancer (SCLC) subjects.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

Subjects received background treatment with chemotherapy (either cisplatin + etoposide or carboplatin + etoposide) in terms of progression free survival in SCLC subjects.

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 30 July 2014 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                                           |
|--------------------------------------|-------------------------------------------|
| Country: Number of subjects enrolled | Poland: 16                                |
| Country: Number of subjects enrolled | Belgium: 6                                |
| Country: Number of subjects enrolled | France: 26                                |
| Country: Number of subjects enrolled | Germany: 21                               |
| Country: Number of subjects enrolled | Hungary: 18                               |
| Country: Number of subjects enrolled | Italy: 14                                 |
| Country: Number of subjects enrolled | Japan: 6                                  |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 9 |
| Country: Number of subjects enrolled | United States: 26                         |
| Worldwide total number of subjects   | 142                                       |
| EEA total number of subjects         | 101                                       |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| 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)                      | 84 |
| From 65 to 84 years                       | 58 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 32 centers, enrolled subjects in 9 countries between 30 July 2014 (first subject first visit) and 07 April 2016 (last subject last visit). Primary completion date of the study was 31 December 2015.

### Pre-assignment

Screening details:

A total of 172 subjects were screened, of these 30 subjects failed screening. The remaining 142 subjects were randomized and 140 subjects received treatment.

### Period 1

|                              |                                        |
|------------------------------|----------------------------------------|
| Period 1 title               | Overall study (overall period)         |
| Is this the baseline period? | Yes                                    |
| Allocation method            | Randomised - controlled                |
| Blinding used                | Double blind                           |
| Roles blinded                | Subject, Investigator, Carer, Assessor |

### Arms

|                              |                               |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes                           |
| <b>Arm title</b>             | Roniciclib (BAY1000394) 10 mg |

Arm description:

Subjects received roniciclib 5 milligram (mg) (2 \* 2.5 mg tablet) orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (carboplatin/etoposide or cisplatin/etoposide) for 6 cycles (21 days each) and continued thereafter with roniciclib monotherapy. Study treatment continued until tumor progression, unacceptable toxicity, death, consent withdrawal, or withdrawal from the study at the discretion of the investigator.

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Roniciclib   |
| Investigational medicinal product code | BAY1000394   |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Subjects received roniciclib 5 mg (2 \* 2.5 mg tablet) orally twice daily for 3 days on / 4 days off schedule for 6 cycles (21 days each) and continued thereafter with roniciclib monotherapy.

|                                        |                       |
|----------------------------------------|-----------------------|
| Investigational medicinal product name | Chemotherapy          |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Cisplatin: Subjects received cisplatin 75 milligram per square meter (mg/m<sup>2</sup>) as infusion for 6 cycles (21 days each).

Etoposide: Subjects received etoposide 100 mg/m<sup>2</sup> as infusion for 3 days for up to 6 cycles (21 days each).

Carboplatin: Subjects received carboplatin as infusion for 6 cycles (21 days each). Carboplatin dose is calculated based on the Calvert's formula = target area under curve (AUC) (5) x (estimated glomerular filtration rate [eGFR] [milliliter/minute] + 25).

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Subjects received placebo matched to roniciclib tablets orally twice daily for 3 days on / 4 days off schedule along with chemotherapy (carboplatin/etoposide or cisplatin/etoposide) for 6 cycles (21 days each).

|                                        |          |
|----------------------------------------|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Subjects received placebo matched to roniciclib tablets orally twice daily for 3 days on / 4 days off schedule for 6 cycles (21 days each).

|                                        |                       |
|----------------------------------------|-----------------------|
| Investigational medicinal product name | Chemotherapy          |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Cisplatin: Subjects received cisplatin 75 mg/m<sup>2</sup> as infusion for 6 cycles (21 days each).

Etoposide: Subjects received etoposide 100 mg/m<sup>2</sup> as infusion for 3 days for up to 6 cycles (21 days each).

Carboplatin: Subjects received carboplatin as infusion for 6 cycles (21 days each). Carboplatin dose is calculated based on the Calvert's formula = target area under curve (AUC) (5) x (estimated glomerular filtration rate [eGFR] [milliliter/minute] + 25).

| <b>Number of subjects in period 1</b>                | Roniciclib<br>(BAY1000394) 10<br>mg | Placebo |
|------------------------------------------------------|-------------------------------------|---------|
| Started                                              | 71                                  | 71      |
| Treated                                              | 70                                  | 70      |
| Completed                                            | 47                                  | 58      |
| Not completed                                        | 24                                  | 13      |
| Physician decision                                   | 4                                   | -       |
| Lost to follow-up                                    | -                                   | 1       |
| Deterioration of general conditions                  | -                                   | 1       |
| Protocol violation                                   | 1                                   | 1       |
| Protocol driven decision point                       | -                                   | 1       |
| Study drug never administered                        | 1                                   | 1       |
| AE unassociated with clinical<br>disease progression | 10                                  | 3       |
| Switching to other therapy                           | 1                                   | 1       |
| Intolerance                                          | 1                                   | -       |
| Withdrawal by subject                                | 6                                   | 4       |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                               | Roniciclib (BAY1000394) 10 mg |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                        |                               |
| Subjects received roniciclib 5 milligram (mg) (2 * 2.5 mg tablet) orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (carboplatin/etoposide or cisplatin/etoposide) for 6 cycles (21 days each) and continued thereafter with roniciclib monotherapy. Study treatment continued until tumor progression, unacceptable toxicity, death, consent withdrawal, or withdrawal from the study at the discretion of the investigator. |                               |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                               | Placebo                       |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                        |                               |
| Subjects received placebo matched to roniciclib tablets orally twice daily for 3 days on / 4 days off schedule along with chemotherapy (carboplatin/etoposide or cisplatin/etoposide) for 6 cycles (21 days each).                                                                                                                                                                                                                                                  |                               |

| Reporting group values                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Roniciclib<br>(BAY1000394) 10<br>mg | Placebo | Total |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|---------|-------|
| Number of subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 71                                  | 71      | 142   |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                     |         |       |
| Age continuous<br>Units: years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                     |         |       |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 62.5                                | 62.4    |       |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | ± 8.9                               | ± 7.5   | -     |
| Gender categorical<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                     |         |       |
| Female                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 28                                  | 27      | 55    |
| Male                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 43                                  | 44      | 87    |
| Eastern cooperative oncology group<br>(ECOG) Performance Status (PS)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                     |         |       |
| ECOG PS was measured in a scale from 0 to grade 5, where 0= Fully active, able to carry on all pre-diseases performance without restriction, 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 2= Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50 percent (%) waking hours, 3= Capable of only limited self-care, confined to bed/chair, more than 50% waking hours, 4= Completely disabled, cannot carry on any self-care, totally confined to bed/chair and 5= dead. |                                     |         |       |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                     |         |       |
| Score 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 25                                  | 20      | 45    |
| Score 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 46                                  | 51      | 97    |
| Type of chemo combination therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                     |         |       |
| Subjects received roniciclib along with chemotherapy (carboplatin/etoposide or cisplatin/etoposide) for 6 cycles (21 days each).                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                     |         |       |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                     |         |       |
| Missing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 1                                   | 1       | 2     |
| Carboplatin / Etoposide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 44                                  | 44      | 88    |
| Cisplatin / Etoposide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 26                                  | 26      | 52    |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Roniciclib (BAY1000394) 10 mg |
| Reporting group description:<br>Subjects received roniciclib 5 milligram (mg) (2 * 2.5 mg tablet) orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (carboplatin/etoposide or cisplatin/etoposide) for 6 cycles (21 days each) and continued thereafter with roniciclib monotherapy. Study treatment continued until tumor progression, unacceptable toxicity, death, consent withdrawal, or withdrawal from the study at the discretion of the investigator. |                               |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Placebo                       |
| Reporting group description:<br>Subjects received placebo matched to roniciclib tablets orally twice daily for 3 days on / 4 days off schedule along with chemotherapy (carboplatin/etoposide or cisplatin/etoposide) for 6 cycles (21 days each).                                                                                                                                                                                                                                                  |                               |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Full Analysis Set (FAS)       |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Full analysis                 |
| Subject analysis set description:<br>FAS (N= 142) included all subjects who were randomized.                                                                                                                                                                                                                                                                                                                                                                                                        |                               |

### Primary: Progression Free Survival (PFS)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Progression Free Survival (PFS) |
| End point description:<br>PFS was defined as the time (days) from the date of randomization to the date of the first observed radiological disease progression or death due to any cause, whichever occurs first. Subjects without progression or death at the time of analysis were censored at their last date of tumor evaluation. PFS for subjects without tumor progression at the time of analysis was censored at their last date of tumor evaluation before the data base cut-off date. Median, percentile and other 95% confidence intervals (CIs) computed using Kaplan-Meier estimates. |                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Primary                         |
| End point timeframe:<br>From date of randomization of the first subject until disease progression or start of new anti-tumor therapy after discontinuation of study drug (assessed every 6 weeks)                                                                                                                                                                                                                                                                                                                                                                                                  |                                 |

| End point values                 | Roniciclib (BAY1000394) 10 mg | Placebo           |  |  |
|----------------------------------|-------------------------------|-------------------|--|--|
| Subject group type               | Reporting group               | Reporting group   |  |  |
| Number of subjects analysed      | 71 <sup>[1]</sup>             | 71 <sup>[2]</sup> |  |  |
| Units: days                      |                               |                   |  |  |
| median (confidence interval 95%) | 149 (129 to 168)              | 166 (139 to 170)  |  |  |

Notes:

[1] - FAS

[2] - FAS

### Statistical analyses

|                                                                                                                                                                                                                                        |                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| Statistical analysis title                                                                                                                                                                                                             | Roniciclib v Placebo: Stratified |
| Statistical analysis description:<br>The two treatment groups (roniciclib plus chemotherapy and placebo plus chemotherapy) were compared using a one-sided stratified log-rank test stratified by gender (female / male). Hazard ratio |                                  |

and 95% CI were based on Cox Regression Model, stratified by gender.

|                                         |                                         |
|-----------------------------------------|-----------------------------------------|
| Comparison groups                       | Roniciclib (BAY1000394) 10 mg v Placebo |
| Number of subjects included in analysis | 142                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority <sup>[3]</sup>              |
| P-value                                 | = 0.8653 <sup>[4]</sup>                 |
| Method                                  | Logrank                                 |
| Parameter estimate                      | Hazard ratio (HR)                       |
| Point estimate                          | 1.242                                   |
| Confidence interval                     |                                         |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 0.82                                    |
| upper limit                             | 1.881                                   |

Notes:

[3] - Hazard ratio < 1 indicates superiority of Roniciclib over Placebo.

[4] - One-sided p-value was calculated from log rank test. P-value was manually rounded.

## Secondary: Overall Survival (OS)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Overall Survival (OS) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                       |
| Overall Survival was defined as the time (days) from the date of randomization to death due to any cause. Subjects alive at the time of analysis were censored at their last contact date. Here, 99999 denotes that data was not calculated as value cannot be estimated due to censored data. Median and 95% confidence interval were computed using Kaplan-Meier estimates. In the below table, '99999' indicates that values were not estimated due to censored data. |                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Secondary             |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                       |
| From start of study treatment until death, assessed every 2 months                                                                                                                                                                                                                                                                                                                                                                                                       |                       |

| End point values                 | Roniciclib (BAY1000394) 10 mg | Placebo            |  |  |
|----------------------------------|-------------------------------|--------------------|--|--|
| Subject group type               | Reporting group               | Reporting group    |  |  |
| Number of subjects analysed      | 71 <sup>[5]</sup>             | 71 <sup>[6]</sup>  |  |  |
| Units: days                      |                               |                    |  |  |
| median (confidence interval 95%) | 324 (240 to 432)              | 323 (287 to 99999) |  |  |

Notes:

[5] - FAS

[6] - FAS

## Statistical analyses

|                                                                                                                                                                                                                                                                         |                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                              | Roniciclib v Placebo: Stratified        |
| Statistical analysis description:                                                                                                                                                                                                                                       |                                         |
| The two treatment groups (ronniciclib plus chemotherapy and placebo plus chemotherapy) were compared using a one-sided stratified log-rank test stratified by gender (female / male). Hazard ratio and 95% CI were based on Cox Regression Model, stratified by gender. |                                         |
| Comparison groups                                                                                                                                                                                                                                                       | Roniciclib (BAY1000394) 10 mg v Placebo |



|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 142                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[7]</sup> |
| P-value                                 | = 0.8691 <sup>[8]</sup>    |
| Method                                  | Logrank                    |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 1.43                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.785                      |
| upper limit                             | 2.606                      |

Notes:

[7] - Hazard ratio < 1 indicates superiority of Roniciclib over Placebo.

[8] - One-sided p-value was calculated from log rank test. P-value was manually rounded.

### Secondary: Time to Progression (TTP)

|                 |                           |
|-----------------|---------------------------|
| End point title | Time to Progression (TTP) |
|-----------------|---------------------------|

End point description:

TTP was defined as the time (days) from date of randomization to date of first observed radiological progression. TTP for subjects without tumor progression at the time of analysis will be censored at their last date of tumor evaluation. Median and 95% confidence interval were computed using Kaplan-Meier estimates.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of randomization of the first subject until disease progression or start of new anti-tumor therapy after discontinuation of study drug (assessed every 6 weeks)

| End point values                 | Roniciclib<br>(BAY1000394)<br>10 mg | Placebo            |  |  |
|----------------------------------|-------------------------------------|--------------------|--|--|
| Subject group type               | Reporting group                     | Reporting group    |  |  |
| Number of subjects analysed      | 71 <sup>[9]</sup>                   | 71 <sup>[10]</sup> |  |  |
| Units: days                      |                                     |                    |  |  |
| median (confidence interval 95%) | 164 (139 to 174)                    | 167 (145 to 171)   |  |  |

Notes:

[9] - FAS

[10] - FAS

### Statistical analyses

|                            |                                  |
|----------------------------|----------------------------------|
| Statistical analysis title | Roniciclib v Placebo: Stratified |
|----------------------------|----------------------------------|

Statistical analysis description:

The two treatment groups (ronniciclib plus chemotherapy and placebo plus chemotherapy) were compared using a one-sided stratified log-rank test stratified by gender (female / male). Hazard ratio and 95% CI were based on Cox Regression Model, stratified by gender.

|                   |                                         |
|-------------------|-----------------------------------------|
| Comparison groups | Placebo v Roniciclib (BAY1000394) 10 mg |
|-------------------|-----------------------------------------|

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Number of subjects included in analysis | 142                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[11]</sup> |
| P-value                                 | = 0.59 <sup>[12]</sup>      |
| Method                                  | Logrank                     |
| Parameter estimate                      | Hazard ratio (HR)           |
| Point estimate                          | 1.047                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.665                       |
| upper limit                             | 1.648                       |

Notes:

[11] - Hazard ratio < 1 indicates superiority of Roniciclib over Placebo.

[12] - One-sided p-value was calculated from log rank test. P-value was manually rounded.

## Secondary: Objective Response Rate (ORR)

|                        |                                                                                                                                                                                                                                                                                                                                                                      |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Objective Response Rate (ORR)                                                                                                                                                                                                                                                                                                                                        |
| End point description: | Objective response of a subject was defined as the best tumor response: complete response or partial response observed during trial period assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v 1.1) criteria. Objective response rate was defined as the percentage of subjects with complete response or partial response. |
| End point type         | Secondary                                                                                                                                                                                                                                                                                                                                                            |
| End point timeframe:   | From date of randomization of the first subject until disease progression or start of new anti-tumor therapy after discontinuation of study drug (assessed every 6 weeks)                                                                                                                                                                                            |

| End point values                 | Roniciclib<br>(BAY1000394)<br>10 mg | Placebo             |  |  |
|----------------------------------|-------------------------------------|---------------------|--|--|
| Subject group type               | Reporting group                     | Reporting group     |  |  |
| Number of subjects analysed      | 71 <sup>[13]</sup>                  | 71 <sup>[14]</sup>  |  |  |
| Units: percentage of subjects    |                                     |                     |  |  |
| number (confidence interval 95%) | 60.6 (48.3 to 72)                   | 74.6 (62.9 to 84.2) |  |  |

Notes:

[13] - FAS

[14] - FAS

## Statistical analyses

|                                   |                                                                                                                                                                                                                                                                                                                                                      |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Statistical analysis title        | Roniciclib v Placebo                                                                                                                                                                                                                                                                                                                                 |
| Statistical analysis description: | Objective response rate was analyzed using the Cochran-Mantel-Haenszel test. The two treatment groups (ronniciclib plus chemotherapy and placebo plus chemotherapy) were compared using a one-sided stratified log-rank test stratified by gender (female / male). Hazard ratio and 95% CI were based on Cox Regression Model, stratified by gender. |
| Comparison groups                 | Roniciclib (BAY1000394) 10 mg v Placebo                                                                                                                                                                                                                                                                                                              |

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 142                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.9685                |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Treatment difference    |
| Point estimate                          | -14.37                  |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | -29.34                  |
| upper limit                             | 0.06                    |

## Secondary: Best Overall Response

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Best Overall Response |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                       |
| Best overall response of a subject was defined as the best tumor response across timepoints: Complete response, Partial response, Stable disease or Progressive disease observed during trial period assessed according to the RECIST version 1.1 criteria. Complete response was defined as disappearance of tumor lesions, Partial response was defined as a decrease of at least 30% in the sum of tumor lesion sizes, Stable disease was defined as steady state of disease and Progressive disease was defined as an increase of at least 20% in the sum of tumor lesions sizes. |                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Secondary             |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                       |
| From date of randomization of the first subject until disease progression or start of new anti-tumor therapy after discontinuation of study drug (assessed every 6 weeks)                                                                                                                                                                                                                                                                                                                                                                                                             |                       |

| End point values                 | Roniciclib<br>(BAY1000394)<br>10 mg | Placebo             |  |  |
|----------------------------------|-------------------------------------|---------------------|--|--|
| Subject group type               | Reporting group                     | Reporting group     |  |  |
| Number of subjects analysed      | 71 <sup>[15]</sup>                  | 71 <sup>[16]</sup>  |  |  |
| Units: percentage of subjects    |                                     |                     |  |  |
| number (confidence interval 95%) |                                     |                     |  |  |
| Complete response                | 1.4 (0 to 7.6)                      | 0 (0 to 0)          |  |  |
| Partial response                 | 59.2 (46.8 to 70.7)                 | 74.6 (62.9 to 84.2) |  |  |
| Stable disease                   | 12.7 (6 to 22.7)                    | 15.5 (8 to 26)      |  |  |
| Progressive disease              | 4.2 (0.9 to 11.9)                   | 5.6 (1.6 to 13.8)   |  |  |
| Not evaluable                    | 22.5 (13.5 to 34)                   | 4.2 (0.9 to 11.9)   |  |  |

Notes:

[15] - FAS

[16] - FAS

## Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to 30 days after the last dose of study treatment

Adverse event reporting additional description:

Survival of subjects after treatment discontinuation for the overall survival efficacy endpoint was noted. Deaths later than 30 days after treatment discontinuation (which cannot be counted as adverse event) was noted. In total 42 and 36 deaths for roniciclib and placebo in the study, but only 9 and 3 due to adverse events.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Roniciclib (BAY1000394) 10 mg |
|-----------------------|-------------------------------|

Reporting group description:

Subjects received roniciclib 5 mg (2 \* 2.5 mg tablets) orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (carboplatin/etoposide or cisplatin/etoposide) for 6 cycles (21 days each) and continued thereafter with roniciclib monotherapy. Study treatment continued until tumor progression, unacceptable toxicity, death, consent withdrawal, or withdrawal from the study at the discretion of the investigator.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received placebo matched to roniciclib tablets orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (carboplatin/etoposide or cisplatin/etoposide) for 6 cycles (21 days each) and continued thereafter with placebo monotherapy. Study treatment continued until tumor progression, unacceptable toxicity, death, consent withdrawal, or withdrawal from the study at the discretion of the investigator.

| Serious adverse events                            | Roniciclib<br>(BAY1000394) 10<br>mg | Placebo          |  |
|---------------------------------------------------|-------------------------------------|------------------|--|
| Total subjects affected by serious adverse events |                                     |                  |  |
| subjects affected / exposed                       | 40 / 70 (57.14%)                    | 27 / 70 (38.57%) |  |
| number of deaths (all causes)                     | 42                                  | 36               |  |
| number of deaths resulting from adverse events    |                                     |                  |  |
| Vascular disorders                                |                                     |                  |  |
| Hypertension                                      |                                     |                  |  |
| subjects affected / exposed                       | 0 / 70 (0.00%)                      | 1 / 70 (1.43%)   |  |
| occurrences causally related to treatment / all   | 0 / 0                               | 0 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0                               | 0 / 0            |  |
| Hypovolaemic shock                                |                                     |                  |  |
| subjects affected / exposed                       | 1 / 70 (1.43%)                      | 0 / 70 (0.00%)   |  |
| occurrences causally related to treatment / all   | 0 / 1                               | 0 / 0            |  |
| deaths causally related to treatment / all        | 0 / 1                               | 0 / 0            |  |

|                                                      |                |                |  |
|------------------------------------------------------|----------------|----------------|--|
| Hypotension                                          |                |                |  |
| subjects affected / exposed                          | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Superior vena cava syndrome                          |                |                |  |
| subjects affected / exposed                          | 0 / 70 (0.00%) | 2 / 70 (2.86%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 3          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 1          |  |
| Thrombosis                                           |                |                |  |
| subjects affected / exposed                          | 2 / 70 (2.86%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Venous thrombosis                                    |                |                |  |
| subjects affected / exposed                          | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Peripheral artery occlusion                          |                |                |  |
| subjects affected / exposed                          | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Deep vein thrombosis                                 |                |                |  |
| subjects affected / exposed                          | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Embolism                                             |                |                |  |
| subjects affected / exposed                          | 0 / 70 (0.00%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| Fatigue                                              |                |                |  |
| subjects affected / exposed                          | 2 / 70 (2.86%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all      | 1 / 2          | 0 / 2          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 1          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Death                                           |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Gait disturbance                                |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pyrexia                                         |                |                |  |
| subjects affected / exposed                     | 2 / 70 (2.86%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Sudden death                                    |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| General physical health deterioration           |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 2 / 70 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Non-cardiac chest pain                          |                |                |  |
| subjects affected / exposed                     | 0 / 70 (0.00%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Multiple organ dysfunction syndrome             |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Chronic obstructive pulmonary disease           |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Dyspnoea                                        |                |                |  |
| subjects affected / exposed                     | 3 / 70 (4.29%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Haemoptysis                                     |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pleural effusion                                |                |                |  |
| subjects affected / exposed                     | 0 / 70 (0.00%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumothorax                                    |                |                |  |
| subjects affected / exposed                     | 0 / 70 (0.00%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pulmonary embolism                              |                |                |  |
| subjects affected / exposed                     | 2 / 70 (2.86%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 3 / 4          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pulmonary haemorrhage                           |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          |  |
| Respiratory failure                             |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 1          |  |
| Psychiatric disorders                           |                |                |  |
| Mental status changes                           |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Investigations                                  |                |                |  |



|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Haemoglobin decreased                           |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Neutrophil count decreased                      |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Platelet count decreased                        |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| White blood cell count decreased                |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| Spinal compression fracture                     |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ulna fracture                                   |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Post procedural haemorrhage                     |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| Atrial fibrillation                             |                |                |  |
| subjects affected / exposed                     | 0 / 70 (0.00%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Atrial flutter                                  |                |                |  |
| subjects affected / exposed                     | 0 / 70 (0.00%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac failure acute                           |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (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                        |                |                |  |
| Cerebrovascular accident                        |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Dysarthria                                      |                |                |  |
| subjects affected / exposed                     | 0 / 70 (0.00%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Haemorrhage intracranial                        |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Seizure                                         |                |                |  |
| subjects affected / exposed                     | 2 / 70 (2.86%) | 2 / 70 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Syncope                                         |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Brain oedema                                    |                |                |  |
| subjects affected / exposed                     | 0 / 70 (0.00%) | 2 / 70 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders            |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Anaemia                                         |                |                |  |
| subjects affected / exposed                     | 6 / 70 (8.57%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 2 / 9          | 0 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Febrile neutropenia                             |                |                |  |
| subjects affected / exposed                     | 5 / 70 (7.14%) | 2 / 70 (2.86%) |  |
| occurrences causally related to treatment / all | 3 / 5          | 1 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Neutropenia                                     |                |                |  |
| subjects affected / exposed                     | 2 / 70 (2.86%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 1 / 3          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Pancytopenia                                    |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Thrombocytopenia                                |                |                |  |
| subjects affected / exposed                     | 2 / 70 (2.86%) | 2 / 70 (2.86%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Ear and labyrinth disorders                     |                |                |  |
| Vertigo                                         |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Abdominal pain                                  |                |                |  |
| subjects affected / exposed                     | 0 / 70 (0.00%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Diarrhoea                                       |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Dyspepsia                                       |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Enterocolitis                                   |                |                |  |
| subjects affected / exposed                     | 0 / 70 (0.00%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastric perforation                             |                |                |  |
| subjects affected / exposed                     | 0 / 70 (0.00%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nausea                                          |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatobiliary disorders                         |                |                |  |
| Hepatic function abnormal                       |                |                |  |
| subjects affected / exposed                     | 0 / 70 (0.00%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Renal failure                                   |                |                |  |
| subjects affected / exposed                     | 2 / 70 (2.86%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Acute kidney injury                             |                |                |  |
| subjects affected / exposed                     | 2 / 70 (2.86%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Back pain                                       |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal pain                            |                |                |  |
| subjects affected / exposed                     | 0 / 70 (0.00%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 2 / 70 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 4          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia pseudomonal                           |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Sepsis                                          |                |                |  |
| subjects affected / exposed                     | 2 / 70 (2.86%) | 1 / 70 (1.43%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Septic shock                                    |                |                |  |
| subjects affected / exposed                     | 3 / 70 (4.29%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3          | 0 / 0          |  |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          |  |
| Lung infection                                  |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 2 / 70 (2.86%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Peritonitis bacterial                           |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (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              |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Dehydration                                     |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypercalcaemia                                  |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hyperglycaemia                                  |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypocalcaemia                                   |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (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 / 70 (1.43%) | 0 / 70 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hyponatraemia                                   |                |                |  |
| subjects affected / exposed                     | 2 / 70 (2.86%) | 4 / 70 (5.71%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 4 / 7          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Decreased appetite                              |                |                |  |
| subjects affected / exposed                     | 1 / 70 (1.43%) | 0 / 70 (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 %

| <b>Non-serious adverse events</b>                        | Roniciclib<br>(BAY1000394) 10<br>mg | Placebo          |  |
|----------------------------------------------------------|-------------------------------------|------------------|--|
| Total subjects affected by non-serious<br>adverse events |                                     |                  |  |
| subjects affected / exposed                              | 70 / 70 (100.00%)                   | 69 / 70 (98.57%) |  |
| Vascular disorders                                       |                                     |                  |  |
| Hypertension                                             |                                     |                  |  |
| subjects affected / exposed                              | 2 / 70 (2.86%)                      | 6 / 70 (8.57%)   |  |
| occurrences (all)                                        | 2                                   | 7                |  |
| Hypotension                                              |                                     |                  |  |
| subjects affected / exposed                              | 10 / 70 (14.29%)                    | 1 / 70 (1.43%)   |  |
| occurrences (all)                                        | 12                                  | 1                |  |
| General disorders and administration<br>site conditions  |                                     |                  |  |
| Asthenia                                                 |                                     |                  |  |
| subjects affected / exposed                              | 13 / 70 (18.57%)                    | 11 / 70 (15.71%) |  |
| occurrences (all)                                        | 27                                  | 17               |  |
| Chest pain                                               |                                     |                  |  |
| subjects affected / exposed                              | 5 / 70 (7.14%)                      | 10 / 70 (14.29%) |  |
| occurrences (all)                                        | 5                                   | 12               |  |
| Oedema peripheral                                        |                                     |                  |  |
| subjects affected / exposed                              | 11 / 70 (15.71%)                    | 2 / 70 (2.86%)   |  |
| occurrences (all)                                        | 15                                  | 2                |  |
| Fatigue                                                  |                                     |                  |  |
| subjects affected / exposed                              | 28 / 70 (40.00%)                    | 17 / 70 (24.29%) |  |
| occurrences (all)                                        | 61                                  | 30               |  |
| Pyrexia                                                  |                                     |                  |  |
| subjects affected / exposed                              | 6 / 70 (8.57%)                      | 11 / 70 (15.71%) |  |
| occurrences (all)                                        | 6                                   | 14               |  |
| Pain                                                     |                                     |                  |  |
| subjects affected / exposed                              | 5 / 70 (7.14%)                      | 4 / 70 (5.71%)   |  |
| occurrences (all)                                        | 5                                   | 4                |  |
| Respiratory, thoracic and mediastinal<br>disorders       |                                     |                  |  |
| Cough                                                    |                                     |                  |  |
| subjects affected / exposed                              | 5 / 70 (7.14%)                      | 2 / 70 (2.86%)   |  |
| occurrences (all)                                        | 5                                   | 2                |  |
| Dyspnoea                                                 |                                     |                  |  |

|                                                                                      |                        |                        |  |
|--------------------------------------------------------------------------------------|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                     | 12 / 70 (17.14%)<br>15 | 4 / 70 (5.71%)<br>7    |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)               | 0 / 70 (0.00%)<br>0    | 4 / 70 (5.71%)<br>4    |  |
| Psychiatric disorders                                                                |                        |                        |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                         | 10 / 70 (14.29%)<br>13 | 2 / 70 (2.86%)<br>2    |  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                          | 5 / 70 (7.14%)<br>8    | 2 / 70 (2.86%)<br>2    |  |
| Investigations                                                                       |                        |                        |  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)       | 6 / 70 (8.57%)<br>10   | 1 / 70 (1.43%)<br>1    |  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)       | 13 / 70 (18.57%)<br>52 | 16 / 70 (22.86%)<br>65 |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)         | 19 / 70 (27.14%)<br>59 | 7 / 70 (10.00%)<br>20  |  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all) | 7 / 70 (10.00%)<br>17  | 3 / 70 (4.29%)<br>5    |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                 | 4 / 70 (5.71%)<br>4    | 5 / 70 (7.14%)<br>5    |  |
| Nervous system disorders                                                             |                        |                        |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                        | 10 / 70 (14.29%)<br>10 | 6 / 70 (8.57%)<br>6    |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                         | 17 / 70 (24.29%)<br>27 | 6 / 70 (8.57%)<br>8    |  |
| Paraesthesia                                                                         |                        |                        |  |



|                                                                                   |                         |                        |  |
|-----------------------------------------------------------------------------------|-------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                  | 7 / 70 (10.00%)<br>11   | 6 / 70 (8.57%)<br>6    |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all) | 4 / 70 (5.71%)<br>11    | 4 / 70 (5.71%)<br>6    |  |
| Blood and lymphatic system disorders                                              |                         |                        |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                       | 31 / 70 (44.29%)<br>84  | 26 / 70 (37.14%)<br>64 |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)              | 16 / 70 (22.86%)<br>42  | 9 / 70 (12.86%)<br>22  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                   | 28 / 70 (40.00%)<br>107 | 30 / 70 (42.86%)<br>69 |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)                    | 6 / 70 (8.57%)<br>12    | 2 / 70 (2.86%)<br>4    |  |
| Ear and labyrinth disorders                                                       |                         |                        |  |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 70 (0.00%)<br>0     | 6 / 70 (8.57%)<br>6    |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                       | 5 / 70 (7.14%)<br>9     | 3 / 70 (4.29%)<br>5    |  |
| Gastrointestinal disorders                                                        |                         |                        |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)          | 8 / 70 (11.43%)<br>10   | 5 / 70 (7.14%)<br>8    |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                     | 30 / 70 (42.86%)<br>79  | 12 / 70 (17.14%)<br>18 |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                  | 9 / 70 (12.86%)<br>17   | 16 / 70 (22.86%)<br>23 |  |
| Vomiting                                                                          |                         |                        |  |

|                                                                                                                  |                         |                        |  |
|------------------------------------------------------------------------------------------------------------------|-------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                 | 44 / 70 (62.86%)<br>118 | 15 / 70 (21.43%)<br>27 |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                                                   | 5 / 70 (7.14%)<br>7     | 5 / 70 (7.14%)<br>6    |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                                       | 46 / 70 (65.71%)<br>173 | 34 / 70 (48.57%)<br>86 |  |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all)           | 20 / 70 (28.57%)<br>25  | 23 / 70 (32.86%)<br>29 |  |
| Renal and urinary disorders<br>Renal failure<br>subjects affected / exposed<br>occurrences (all)                 | 4 / 70 (5.71%)<br>6     | 1 / 70 (1.43%)<br>1    |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 10 / 70 (14.29%)<br>14  | 8 / 70 (11.43%)<br>10  |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                                                   | 3 / 70 (4.29%)<br>4     | 4 / 70 (5.71%)<br>5    |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)                                         | 3 / 70 (4.29%)<br>3     | 4 / 70 (5.71%)<br>4    |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                                            | 7 / 70 (10.00%)<br>8    | 3 / 70 (4.29%)<br>3    |  |
| Infections and infestations<br>Oral candidiasis<br>subjects affected / exposed<br>occurrences (all)              | 0 / 70 (0.00%)<br>0     | 4 / 70 (5.71%)<br>6    |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 70 (1.43%)<br>1     | 5 / 70 (7.14%)<br>7    |  |

|                                    |                  |                  |  |
|------------------------------------|------------------|------------------|--|
| Metabolism and nutrition disorders |                  |                  |  |
| Hypokalaemia                       |                  |                  |  |
| subjects affected / exposed        | 8 / 70 (11.43%)  | 6 / 70 (8.57%)   |  |
| occurrences (all)                  | 19               | 8                |  |
| Hyponatraemia                      |                  |                  |  |
| subjects affected / exposed        | 4 / 70 (5.71%)   | 5 / 70 (7.14%)   |  |
| occurrences (all)                  | 6                | 9                |  |
| Decreased appetite                 |                  |                  |  |
| subjects affected / exposed        | 20 / 70 (28.57%) | 15 / 70 (21.43%) |  |
| occurrences (all)                  | 35               | 16               |  |
| Hypomagnesaemia                    |                  |                  |  |
| subjects affected / exposed        | 23 / 70 (32.86%) | 9 / 70 (12.86%)  |  |
| occurrences (all)                  | 93               | 20               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 26 March 2014     | The following modifications were done in the inclusion criteria regarding contraception. <ul style="list-style-type: none"><li>• Adequate contraception for subjects had to be ensured during chemotherapy treatment and for at least 6 months after end of chemotherapy.</li><li>• The partners of sexually active subjects should have been advised to use adequate contraception during the six cycles of chemotherapy.</li></ul> |
| 03 September 2014 | The following modifications were done: <ul style="list-style-type: none"><li>• Concomitant therapies were revised, and one specification on dose modification was changed.</li><li>• A cautionary provision on the use of strong Cytochrome P450 3A4 (CYP3A4) modifiers was added.</li></ul>                                                                                                                                         |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date             | Interruption                                                      | Restart date |
|------------------|-------------------------------------------------------------------|--------------|
| 24 February 2016 | Study was terminated after evaluation of primary completion data. | -            |

Notes:

### Limitations and caveats

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

Decimal places were automatically truncated if last decimal equals zero. '99999' in the posting indicates that values were not estimated due to censored data.

Notes: