



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
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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:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	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
Arm title	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/m²) as infusion for 6 cycles (21 days each).

Etoposide: Subjects received etoposide 100 mg/m² 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).

Arm title	Placebo
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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/m² as infusion for 6 cycles (21 days each).

Etoposide: Subjects received etoposide 100 mg/m² 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).

Number of subjects in period 1	Roniciclib (BAY1000394) 10 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 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 (BAY1000394) 10 mg	Placebo	Total
Number of subjects	71	71	142
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.5	62.4	
standard deviation	± 8.9	± 7.5	-
Gender categorical Units: Subjects			
Female	28	27	55
Male	43	44	87
Eastern cooperative oncology group (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: 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).	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: FAS (N= 142) included all subjects who were randomized.	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description: 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: 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 ^[1]	71 ^[2]		
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: 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 ^[3]
P-value	= 0.8653 ^[4]
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 ^[5]	71 ^[6]		
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 (ronaciclib 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 ^[7]
P-value	= 0.8691 ^[8]
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)
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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
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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 (BAY1000394) 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71 ^[9]	71 ^[10]		
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
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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
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Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.59 ^[12]
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 (BAY1000394) 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71 ^[13]	71 ^[14]		
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 (BAY1000394) 10 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71 ^[15]	71 ^[16]		
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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Roniciclib (BAY1000394) 10 mg
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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
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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 (BAY1000394) 10 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 %

Non-serious adverse events	Roniciclib (BAY1000394) 10 mg	Placebo	
Total subjects affected by non-serious 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 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 disorders			
Cough			
subjects affected / exposed	5 / 70 (7.14%)	2 / 70 (2.86%)	
occurrences (all)	5	2	
Dyspnoea			

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

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

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

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

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: