



Clinical trial results:

Phase Ib / II study of BAY 1000394 in combination with cisplatin / etoposide or carboplatin / etoposide as first-line therapy in subjects with extensive disease small cell lung cancer

Summary

EudraCT number	2011-004155-39
Trial protocol	FR
Global end of trial date	08 March 2016

Results information

Result version number	v1 (current)
This version publication date	19 March 2017
First version publication date	19 March 2017

Trial information

Trial identification

Sponsor protocol code	BAY1000394/14858
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01573338
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	08 March 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 March 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the Phase Ib part of this study was to determine the safety, tolerability, pharmacokinetics, and maximum tolerated dose (MTD) dose of roniciclib (BAY1000394) in combination with cisplatin / etoposide or carboplatin / etoposide chemotherapy in 2 separate cohorts in parallel; The primary objective of the Phase II part of this study was to evaluate the response rate in subjects with extensive disease small cell lung cancer (SCLC) receiving first-line cisplatin / etoposide or carboplatin / etoposide chemotherapy in combination with roniciclib. Tumor response was evaluated based on Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1). Tumor measurements were made at baseline and then every 2 cycles, id est (i.e.) every 6 weeks based on 21-day cycles, until progressive disease occurred.

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 carboplatin 5 milligram per milliliter per minute (mg/mL/min) intravenous (IV) on Day 1 and Etoposide 100 milligram per meter square (mg/m²) IV on Days 1-3 of a 21-day treatment cycle or Cisplatin 75mg/m² IV on Day 1 and Etoposide 100 mg/m² IV on Days 1-3 of a 21-day treatment cycle. A maximum of 6 cycles of carboplatin / etoposide or cisplatin / etoposide was administered unless there was tumor progression, unacceptable toxicity, consent withdrawal, or withdrawal from the study at the discretion of the investigator or his/her designated associate(s).

Evidence for comparator: -

Actual start date of recruitment	25 February 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Korea, Republic of: 20
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	43
EEA total number of subjects	11

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	26
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at multiple study centers in France, South Korea and United States, between 25 February 2013 (first subject first visit) and 25 March 2016 (last subject last visit).

Pre-assignment

Screening details:

A total of 58 subjects were screened, of these 15 subjects failed screening. Forty three (43) subjects were assigned to treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Roniciclib 2.5 mg bid / Carboplatin / Etoposide

Arm description:

Subjects received roniciclib 2.5 mg tablets orally twice daily (bid) for 3 days on / 4 days off schedule in combination with chemotherapy (carboplatin / 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 2.5 mg orally twice daily for 3 days on / 4 days off schedule for 6 cycles (21 days each) in combination with chemotherapy 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:

Carboplatin: Subjects received carboplatin 5 mg/mL/min IV on Day 1 of a 21-day treatment cycle.

Carboplatin dose was calculated based on the Calvert's formula = target area under curve (AUC) (5) * (estimated glomerular filtration rate [eGFR] [milliliter/minute] + 25).

Etoposide: Subjects received etoposide 100 mg/m² as infusion for 3 days for 21-day treatment cycle (for 6 cycles).

Arm title	Roniciclib 2.5 mg bid / Cisplatin / Etoposide
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Arm description:

Subjects received roniciclib 2.5 mg tablets orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (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
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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 2.5 mg orally twice daily for 3 days on / 4 days off schedule for 6 cycles (21 days each) in combination with chemotherapy 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 mg/m² as infusion on Day 1 of 21-days treatment cycle (for 6 cycles).

Etoposide: Subjects received etoposide 100 mg/m² as infusion for 3 days for 21-day treatment cycle (for 6 cycles).

Arm title	Roniciclib 5 mg bid / Carboplatin / Etoposide
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Arm description:

Subjects received roniciclib 5 mg tablets orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (carboplatin / 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 orally twice daily for 3 days on / 4 days off schedule for 6 cycles (21 days each) in combination with chemotherapy 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:

Carboplatin: Subjects received carboplatin 5 mg/mL/min IV on Day 1 of a 21-day treatment cycle. Carboplatin dose was calculated based on the Calvert's formula = target AUC (5) * (eGFR [milliliter/minute] + 25).

Etoposide: Subjects received etoposide 100 mg/m² as infusion for 3 days for 21-day treatment cycle (for 6 cycles).

Arm title	Roniciclib 5 mg bid / Cisplatin / Etoposide
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Arm description:

Subjects received roniciclib 5 mg tablets orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (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
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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 orally twice daily for 3 days on / 4 days off schedule for 6 cycles (21 days each) in combination with chemotherapy 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 mg/m² as infusion on Day 1 of 21-days treatment cycle (for 6 cycles).

Etoposide: Subjects received etoposide 100 mg/m² as infusion for 3 days for 21-day treatment cycle (for 6 cycles).

Number of subjects in period 1	Roniciclib 2.5 mg bid / Carboplatin / Etoposide	Roniciclib 2.5 mg bid / Cisplatin / Etoposide	Roniciclib 5 mg bid / Carboplatin / Etoposide
Started	4	3	24
Completed	0	0	0
Not completed	4	3	24
AE associated with clinical disease progression	-	-	2
Physician decision	-	-	1
Progressive disease- radiological progression	1	2	15
Progressive disease- clinical progression	1	-	1
Death	-	-	2
Switching to other therapy	1	-	-
AE un-associated with clinical disease progression	1	-	1
Withdrawal by subject	-	1	2

Number of subjects in period 1	Roniciclib 5 mg bid / Cisplatin / Etoposide
Started	12
Completed	0
Not completed	12
AE associated with clinical disease progression	-
Physician decision	1
Progressive disease- radiological progression	9
Progressive disease- clinical progression	-
Death	-

Switching to other therapy	-
AE un-associated with clinical disease progression	1
Withdrawal by subject	1

Baseline characteristics

Reporting groups

Reporting group title	Roniciclib 2.5 mg bid / Carboplatin / Etoposide
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Reporting group description:

Subjects received roniciclib 2.5 mg tablets orally twice daily (bid) for 3 days on / 4 days off schedule in combination with chemotherapy (carboplatin / 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	Roniciclib 2.5 mg bid / Cisplatin / Etoposide
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Reporting group description:

Subjects received roniciclib 2.5 mg tablets orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (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	Roniciclib 5 mg bid / Carboplatin / Etoposide
-----------------------	---

Reporting group description:

Subjects received roniciclib 5 mg tablets orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (carboplatin / 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	Roniciclib 5 mg bid / Cisplatin / Etoposide
-----------------------	---

Reporting group description:

Subjects received roniciclib 5 mg tablets orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (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 values	Roniciclib 2.5 mg bid / Carboplatin / Etoposide	Roniciclib 2.5 mg bid / Cisplatin / Etoposide	Roniciclib 5 mg bid / Carboplatin / Etoposide
Number of subjects	4	3	24
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	68 ± 8	59.3 ± 5.1	60.6 ± 8.5
Gender categorical Units: Subjects			
Female	2	2	5
Male	2	1	19

Reporting group values	Roniciclib 5 mg bid / Cisplatin / Etoposide	Total	
Number of subjects	12	43	
Age categorical Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	59.3		
standard deviation	± 8.4	-	
Gender categorical			
Units: Subjects			
Female	5	14	
Male	7	29	

End points

End points reporting groups

Reporting group title	Roniciclib 2.5 mg bid / Carboplatin / Etoposide
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Reporting group description:

Subjects received roniciclib 2.5 mg tablets orally twice daily (bid) for 3 days on / 4 days off schedule in combination with chemotherapy (carboplatin / 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	Roniciclib 2.5 mg bid / Cisplatin / Etoposide
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Reporting group description:

Subjects received roniciclib 2.5 mg tablets orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (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	Roniciclib 5 mg bid / Carboplatin / Etoposide
-----------------------	---

Reporting group description:

Subjects received roniciclib 5 mg tablets orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (carboplatin / 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	Roniciclib 5 mg bid / Cisplatin / Etoposide
-----------------------	---

Reporting group description:

Subjects received roniciclib 5 mg tablets orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (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.

Subject analysis set title	Safety analysis set SAF (SAF)
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Subject analysis set type	Safety analysis
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Subject analysis set description:

SAF (N=43) included all subjects who received at least one dose of roniciclib.

Subject analysis set title	Pharmacokinetic (PK) analysis set (PKS)
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

PKS (N=18) included subjects treated with at least one dose of active study medication who had valid PK data.

Subject analysis set title	Roniciclib, dose escalation 2.5 mg, 5 mg bid
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

All subjects (N=43) who received roniciclib 2.5 or 5 mg twice daily for 3 days on / 4 days off schedule in combination with chemotherapy.

Primary: Response Rate

End point title	Response Rate ^[1]
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End point description:

Response rate was defined as the percentage (%) of subjects with the best tumor response (confirmed partial response [PR] or confirmed complete response [CR]) that was achieved during or within 30 days after end of therapy. The total number of subjects with CR or PR divided by the total numbers of subjects in the safety population (included all subjects who received at least one dose of roniciclib) was ORR. CR = Disappearance of all clinical and radiological evidence of tumor (both target and non-target). Any pathological lymph nodes (whether target or non-target) must have a reduction in shortaxis to greater than (<) 10 millimeter (mm). PR = At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non target lesions and no appearance of new lesions.

End point type	Primary
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End point timeframe:

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

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Roniciclib 2.5 mg bid / Carboplatin / Etoposide	Roniciclib 2.5 mg bid / Cisplatin / Etoposide	Roniciclib 5 mg bid / Carboplatin / Etoposide	Roniciclib 5 mg bid / Cisplatin / Etoposide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[2]	3 ^[3]	24 ^[4]	12 ^[5]
Units: Percentage of subjects				
number (confidence interval 95%)	75 (19.4 to 99.4)	33.3 (0.8 to 90.6)	87.5 (67.6 to 97.3)	83.3 (51.6 to 97.9)

Notes:

[2] - SAF

[3] - SAF

[4] - SAF

[5] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs) ^[6]
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End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly and another medical important serious event as judged by the investigator. Treatment-emergent adverse events (TEAEs) and Treatment-emergent serious adverse events (TESAEs) were defined as adverse events that started or worsened after the start of study drug administration up to 30 days after last administration of the study medication.

End point type	Primary
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End point timeframe:

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

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Roniciclib 2.5 mg bid / Carboplatin / Etoposide	Roniciclib 2.5 mg bid / Cisplatin / Etoposide	Roniciclib 5 mg bid / Carboplatin / Etoposide	Roniciclib 5 mg bid / Cisplatin / Etoposide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[7]	3 ^[8]	24 ^[9]	12 ^[10]
Units: Subjects				
TEAE	4	3	24	12

TESAE	0	2	13	6
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Notes:

- [7] - SAF
- [8] - SAF
- [9] - SAF
- [10] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Tolerated Dose (MTD)

End point title	Maximum Tolerated Dose (MTD) ^[11]
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End point description:

MTD reflects highest dose of drug that did not cause an unacceptable side effect (= Dose limiting toxicity [DLT] in more than 30% of subjects). The MTD was the dose started at Level 1 and a modified 3+3 dose-escalation / de-escalation design was employed. Initially, 3 subjects were treated at Level 1. If 1 of the first 3 subjects experienced a DLT, another 3 subjects were added to this cohort. If none of 3 or up to 1 of 6 subjects experienced any DLT in Cycle 1 of Level 1, subsequent subjects would be treated at Level 2. If a DLT occurred in 2 subjects of one cohort, dose escalation would stop. Six subjects were to be treated at Level 2. If up to 1 of 6 subjects experienced any DLT in Cycle 1 of Level 2, Level 2 would be the MTD.

End point type	Primary
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End point timeframe:

From start of treatment up to first three weeks therapy

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Roniciclib, dose escalation 2.5 mg, 5 mg bid			
Subject group type	Subject analysis set			
Number of subjects analysed	43 ^[12]			
Units: Milligram (mg)				
number (not applicable)	5			

Notes:

- [12] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration Versus Time Curve From Zero to the Last Data Point Greater Than Lower Limit of Quantitation (LLOQ) of BAY1000394 in Plasma (AUC[0-tlast]) After Single Oral Dose

End point title	Area Under the Concentration Versus Time Curve From Zero to the Last Data Point Greater Than Lower Limit of Quantitation (LLOQ) of BAY1000394 in Plasma (AUC[0-tlast]) After Single Oral Dose ^[13]
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End point description:

Area under the concentration versus time curve from zero to the last data point greater than (>) LLOQ (AUC[0-tlast]) after single dose of BAY1000394 were measured. Geometric mean and percentage geometric coefficient of variation (%CV) were reported.

End point type	Primary
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End point timeframe:

Plasma samples were collected at pre-dose; 0.5, 1, 2, 4, 6, and 8 hours post-dose on Cycle 1, Day 8 (C1D8) and Cycle 2, Day 1 (C2D1)

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: EudraCT database does not allow to report only one treatment group in statistical analyses section (as here, data were evaluated between different time point C1D8 and C2D1; not between different reporting groups). Due to this format constraint, charts have been uploaded with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

End point values	Roniciclib 2.5 mg bid / Carboplatin / Etoposide	Roniciclib 2.5 mg bid / Cisplatin / Etoposide	Roniciclib 5 mg bid / Carboplatin / Etoposide	Roniciclib 5 mg bid / Cisplatin / Etoposide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[14]	3 ^[15]	6 ^[16]	5 ^[17]
Units: Microgram*hour per liter (mcg*h/L)				
geometric mean (geometric coefficient of variation)				
C1D8	96.6 (± 20.3)	114 (± 32.8)	247 (± 51)	191 (± 19.8)
C2D1	67.6 (± 18.5)	78.1 (± 47.3)	148 (± 38.4)	183 (± 20.2)

Notes:

[14] - PKS

[15] - PKS

[16] - PKS with evaluable subjects for this endpoint.

[17] - PKS with evaluable subjects for this endpoint.

Attachments (see zip file)	Statistical Analyses_Primary_ AUC,0-tlast.DOCX
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Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Concentration (Cmax) of BAY1000394 in Plasma After Single Doses

End point title	Maximum Observed Concentration (Cmax) of BAY1000394 in Plasma After Single Doses ^[18]
End point description:	Maximum concentration of BAY1000394 in plasma after single dose administration. Geometric mean and percentage geometric coefficient of variation (%CV) were reported.
End point type	Primary
End point timeframe:	Plasma samples were collected at pre-dose, 0.5, 1, 2, 4, 6, and 8 hours post-dose on C1D8 and C2D1

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: EudraCT database does not allow to report only one treatment group in statistical analyses section (as here, data were evaluated between different time point C1D8 and C2D1; not between different reporting groups). Due to this format constraint, charts have been uploaded with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

End point values	Roniciclib 2.5 mg bid / Carboplatin / Etoposide	Roniciclib 2.5 mg bid / Cisplatin / Etoposide	Roniciclib 5 mg bid / Carboplatin / Etoposide	Roniciclib 5 mg bid / Cisplatin / Etoposide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[19]	3 ^[20]	6 ^[21]	5 ^[22]
Units: Microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)				
C1D8	23.2 (± 31)	29.1 (± 71.5)	60.2 (± 51)	65.6 (± 40)
C2D1	14.5 (± 26.9)	20.7 (± 64.2)	38.7 (± 75.9)	44.8 (± 18.2)

Notes:

[19] - PKS

[20] - PKS

[21] - PKS with evaluable subjects for this endpoint.

[22] - PKS with evaluable subjects for this endpoint.

Attachments (see zip file)	Statistical Analyses_Primary_ Cmax.DOCX
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Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

End point title	Disease Control Rate
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End point description:

Disease control rate (DCR) was defined as the percentage of subjects who had a best response rating over the whole duration of the study of CR, PR, or SD according to RECIST 1.1. CR = Disappearance of all clinical and radiological evidence of tumor (both target and non-target). Any pathological lymph nodes (whether target or non-target) must have a reduction in shortaxis to < 10 mm. PR = At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non target lesions and no appearance of new lesions. SD = Steady state of disease. Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, no unequivocal progression of existing non-target lesions, and no appearance of new lesions.

End point type	Secondary
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End point timeframe:

From start of treatment of the first subject until 3 years later, assessed every 6 weeks

End point values	Roniciclib 2.5 mg bid / Carboplatin / Etoposide	Roniciclib 2.5 mg bid / Cisplatin / Etoposide	Roniciclib 5 mg bid / Carboplatin / Etoposide	Roniciclib 5 mg bid / Cisplatin / Etoposide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[23]	2 ^[24]	23 ^[25]	11 ^[26]
Units: Percentage of subjects				
number (confidence interval 95%)	100 (47.3 to 100)	66.7 (13.5 to 98.3)	95.8 (81.7 to 99.8)	91.7 (66.1 to 99.6)

Notes:

[23] - SAF

[24] - SAF with evaluable subjects for this endpoint.

[25] - SAF with evaluable subjects for this endpoint.

[26] - SAF with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

Overall survival (OS) was defined as the time (days) from the date of first dose of study drug to death due to any cause. Subjects alive at the time of analysis were censored at their last contact date. Overall survival for subjects without any contact after first dose of study drug was censored at 1 day. In the below table, '99999' indicates that data were not estimable due to censored data.

End point type	Secondary
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End point timeframe:

From start of treatment until death (approximately up to 3 years), assessed every 3 months

End point values	Roniciclib 2.5 mg bid / Carboplatin / Etoposide	Roniciclib 2.5 mg bid / Cisplatin / Etoposide	Roniciclib 5 mg bid / Carboplatin / Etoposide	Roniciclib 5 mg bid / Cisplatin / Etoposide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[27]	3 ^[28]	24 ^[29]	12 ^[30]
Units: Days				
median (confidence interval 95%)	381.5 (238 to 99999)	347 (195 to 99999)	428 (281 to 734)	341.5 (175 to 583)

Notes:

[27] - SAF

[28] - SAF

[29] - SAF

[30] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression

End point title	Time to Progression
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End point description:

Time to progression (TTP) was defined as the time (days) from the date of the first dose of study drug to the date of the first observed radiological disease progression. Time to progression for subjects without tumor progression at the time of analysis were censored at their last date of tumor evaluation. In the below table, '99999' indicates that data were not estimable due to censored data.

End point type	Secondary
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End point timeframe:

From start of treatment of the first subject until 3 years later, assessed every 6 weeks

End point values	Roniciclib 2.5 mg bid / Carboplatin / Etoposide	Roniciclib 2.5 mg bid / Cisplatin / Etoposide	Roniciclib 5 mg bid / Carboplatin / Etoposide	Roniciclib 5 mg bid / Cisplatin / Etoposide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[31]	3 ^[32]	24 ^[33]	12 ^[34]
Units: Days				
median (confidence interval 95%)	203 (157 to 241)	164 (47 to 99999)	227 (164 to 259)	173 (145 to 217)

Notes:

[31] - SAF

[32] - SAF

[33] - SAF

[34] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival
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End point description:

Progression-free survival (PFS) was defined as the time (days) from the date of the first dose of study drug to the date of the first observed radiological disease progression or death, whichever came first. Progression-free survival for subjects without tumor progression at the time of analysis were censored at their last date of tumor evaluation. In the below table, '99999' indicates that data were not estimable due to censored data.

End point type	Secondary
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End point timeframe:

From start of treatment of the first subject until 3 years later, assessed every 6 weeks

End point values	Roniciclib 2.5 mg bid / Carboplatin / Etoposide	Roniciclib 2.5 mg bid / Cisplatin / Etoposide	Roniciclib 5 mg bid / Carboplatin / Etoposide	Roniciclib 5 mg bid / Cisplatin / Etoposide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4 ^[35]	3 ^[36]	24 ^[37]	12 ^[38]
Units: Days				
median (confidence interval 95%)	203 (157 to 241)	164 (47 to 99999)	218.5 (165 to 259)	188 (145 to 217)

Notes:

[35] - SAF

[36] - SAF

[37] - SAF

[38] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title | Duration of Response

End point description:

Duration of response (DOR) was defined as the time (days) from the date of first objective radiological response to the date that progressive disease was first objectively (radiologically) documented or death (if death occurred earlier than disease progression). DOR was evaluated only for subjects who achieved their confirmed best response as complete response or partial response. For subjects who had not progressed or died at the time of analysis, DOR was censored at their last date of evaluable scan. '99999' indicates that data were not estimable due to censored data.

End point type | Secondary

End point timeframe:

From start of treatment of the first subject until 3 years later, assessed every 6 weeks

End point values	Roniciclib 2.5 mg bid / Carboplatin / Etoposide	Roniciclib 2.5 mg bid / Cisplatin / Etoposide	Roniciclib 5 mg bid / Carboplatin / Etoposide	Roniciclib 5 mg bid / Cisplatin / Etoposide
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3 ^[39]	1 ^[40]	21 ^[41]	10 ^[42]
Units: Days				
median (confidence interval 95%)	169 (121 to 206)	128 (0 to 99999)	193 (131 to 224)	154 (64 to 183)

Notes:

[39] - SAF with evaluable subjects for this endpoint.

[40] - SAF with evaluable subjects for this endpoint.

[41] - SAF with evaluable subjects for this endpoint.

[42] - SAF with evaluable subjects for this endpoint.

Statistical analyses

No statistical analyses for this end point

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

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 2.5 mg bid / Carboplatin / Etoposide
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Reporting group description:

Subjects received roniciclib 2.5 mg tablets orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (carboplatin / 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	Roniciclib 2.5 mg bid / Cisplatin / Etoposide
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Reporting group description:

Subjects received roniciclib 2.5 mg tablets orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (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	Roniciclib 5 mg bid / Carboplatin / Etoposide
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Reporting group description:

Subjects received roniciclib 5 mg tablets orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (carboplatin / 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	Roniciclib 5 mg bid / Cisplatin / Etoposide
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Reporting group description:

Subjects received roniciclib 5 mg tablets orally twice daily for 3 days on / 4 days off schedule in combination with chemotherapy (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.

Serious adverse events	Roniciclib 2.5 mg bid / Carboplatin / Etoposide	Roniciclib 2.5 mg bid / Cisplatin / Etoposide	Roniciclib 5 mg bid / Carboplatin / Etoposide
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	2 / 3 (66.67%)	13 / 24 (54.17%)
number of deaths (all causes)	3	2	17
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent claudication			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet count decreased			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	3 / 24 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Roniciclib 5 mg bid / Cisplatin / Etoposide		
Total subjects affected by serious adverse events			

subjects affected / exposed	6 / 12 (50.00%)		
number of deaths (all causes)	12		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intermittent claudication			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Rash maculo-papular subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 12 (0.00%) 0 / 0 0 / 0		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 12 (8.33%) 0 / 1 0 / 0		
Musculoskeletal and connective tissue disorders Muscular weakness subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 12 (8.33%) 0 / 2 0 / 0		
Infections and infestations Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 12 (8.33%) 0 / 1 0 / 0		
Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 12 (8.33%) 1 / 1 0 / 0		
Urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 12 (0.00%) 0 / 0 0 / 0		
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 12 (0.00%) 0 / 0 0 / 0		
Hyponatraemia			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Roniciclib 2.5 mg bid / Carboplatin / Etoposide	Roniciclib 2.5 mg bid / Cisplatin / Etoposide	Roniciclib 5 mg bid / Carboplatin / Etoposide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	3 / 3 (100.00%)	24 / 24 (100.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Haematoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	2
Jugular vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Pelvic venous thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Vascular pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	6 / 24 (25.00%)
occurrences (all)	7	3	13
Chest discomfort			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Discomfort			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	6 / 24 (25.00%)
occurrences (all)	1	1	21
Injection site extravasation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Oedema peripheral			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	1	0	4
Pain			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 24 (4.17%) 1
Pyrexia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	4 / 24 (16.67%) 6
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 3 (33.33%) 1	0 / 24 (0.00%) 0
Vulvovaginal pruritus subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 24 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Aspiration subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 24 (4.17%) 1
Cough subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 3 (33.33%) 1	5 / 24 (20.83%) 5
Dysphonia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	3 / 24 (12.50%) 3
Dyspnoea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	6 / 24 (25.00%) 6
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	2 / 24 (8.33%) 2
Epistaxis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 24 (0.00%) 0
Haemoptysis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 24 (4.17%) 1
Hiccups			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Laryngeal inflammation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	3
Pleuritic pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Rhinitis allergic			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	1	0	3
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1

Confusional state			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Depressed mood			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hallucination			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	6 / 24 (25.00%)
occurrences (all)	0	1	6
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	3 / 24 (12.50%)
occurrences (all)	1	4	3
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	2 / 24 (8.33%)
occurrences (all)	1	2	2
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	3
Blood creatinine increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Blood magnesium decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 3 (33.33%) 3	1 / 24 (4.17%) 5
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 24 (0.00%) 0
Lipase increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	1 / 3 (33.33%) 1	0 / 24 (0.00%) 0
Lymphocyte count decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 3 (33.33%) 1	1 / 24 (4.17%) 1
Neutrophil count decreased subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 15	1 / 3 (33.33%) 14	13 / 24 (54.17%) 74
Platelet count decreased subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 12	1 / 3 (33.33%) 3	12 / 24 (50.00%) 56
Weight decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 24 (4.17%) 1
Weight increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 24 (0.00%) 0
White blood cell count decreased subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 11	1 / 3 (33.33%) 6	5 / 24 (20.83%) 7
Injury, poisoning and procedural complications			
Allergic transfusion reaction subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 24 (4.17%) 1
Burns second degree subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 24 (4.17%) 1
Epicondylitis			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 24 (4.17%) 1
Fall subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 24 (0.00%) 0
Incision site pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 24 (4.17%) 1
Ligament sprain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 3 (33.33%) 1	0 / 24 (0.00%) 0
Radiation skin injury subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 24 (4.17%) 1
Rib fracture subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 24 (0.00%) 0
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 24 (0.00%) 0
Tachycardia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 24 (0.00%) 0
Nervous system disorders Amnesia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 24 (4.17%) 1
Aphasia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 24 (0.00%) 0
Ataxia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 24 (4.17%) 1
Cerebellar syndrome			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	2 / 4 (50.00%)	2 / 3 (66.67%)	3 / 24 (12.50%)
occurrences (all)	3	2	4
Dysgeusia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	5	0	0
Head discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	12 / 24 (50.00%)
occurrences (all)	1	0	36
Hemiparesis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Hypersomnia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Motor dysfunction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Myoclonus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Neuropathy peripheral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	2
Peripheral motor neuropathy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Presyncope			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	1 / 24 (4.17%)
occurrences (all)	3	1	1
Sciatica			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Visual field defect			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 4 (100.00%)	2 / 3 (66.67%)	15 / 24 (62.50%)
occurrences (all)	12	8	44
Leukocytosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Leukopenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	3 / 24 (12.50%)
occurrences (all)	0	1	3
Lymphopenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0

Neutropenia			
subjects affected / exposed	3 / 4 (75.00%)	2 / 3 (66.67%)	3 / 24 (12.50%)
occurrences (all)	4	4	11
Thrombocytopenia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	6 / 24 (25.00%)
occurrences (all)	2	8	43
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hypoacusis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Ototoxicity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Vertigo			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Vertigo positional			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Eye disorders			
Photopsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Visual impairment			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	1	0	4
Constipation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	7 / 24 (29.17%)
occurrences (all)	1	0	10
Diarrhoea			
subjects affected / exposed	3 / 4 (75.00%)	1 / 3 (33.33%)	13 / 24 (54.17%)
occurrences (all)	5	18	40
Dry mouth			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Eructation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Gastrointestinal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	3
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Gingival pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1

Haemorrhoids			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	3 / 24 (12.50%)
occurrences (all)	1	0	4
Nausea			
subjects affected / exposed	3 / 4 (75.00%)	2 / 3 (66.67%)	23 / 24 (95.83%)
occurrences (all)	17	9	162
Oral pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Periodontal disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Retching			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Salivary hypersecretion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Vomiting			
subjects affected / exposed	4 / 4 (100.00%)	1 / 3 (33.33%)	15 / 24 (62.50%)
occurrences (all)	12	7	52
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 4 (100.00%)	2 / 3 (66.67%)	12 / 24 (50.00%)
occurrences (all)	5	4	20
Blister			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	1 / 24 (4.17%)
occurrences (all)	1	1	2
Dry skin			

subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	1	0	2
Nail disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Pain of skin			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	3 / 24 (12.50%)
occurrences (all)	0	0	6
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	4 / 24 (16.67%)
occurrences (all)	0	0	5
Rash maculo-papular			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	3 / 24 (12.50%)
occurrences (all)	0	0	6
Skin disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Skin exfoliation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Skin hyperpigmentation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Skin ulcer			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	6
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Chronic kidney disease			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	3	0	1
Dysuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Incontinence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Nephropathy toxic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Proteinuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Renal impairment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

Renal vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	2 / 24 (8.33%)
occurrences (all)	0	1	6
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Bone pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Joint stiffness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Musculoskeletal stiffness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	5 / 24 (20.83%)
occurrences (all)	0	1	7
Neck pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	3 / 24 (12.50%)
occurrences (all)	0	1	4
Rhabdomyolysis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	3
Spinal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Candida infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Clostridium difficile infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Folliculitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Gingivitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	3
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1

Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Rash pustular			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Tracheitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	7 / 24 (29.17%)
occurrences (all)	0	0	10
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	2 / 24 (8.33%)
occurrences (all)	0	2	2
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			

subjects affected / exposed	1 / 4 (25.00%)	2 / 3 (66.67%)	10 / 24 (41.67%)
occurrences (all)	2	2	18
Dehydration			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Hyperglycaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	2 / 24 (8.33%)
occurrences (all)	1	0	2
Hyperkalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	3 / 24 (12.50%)
occurrences (all)	0	1	7
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	2 / 24 (8.33%)
occurrences (all)	0	2	2
Hypoglycaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Hypokalaemia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	7 / 24 (29.17%)
occurrences (all)	1	3	18
Hypomagnesaemia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	7 / 24 (29.17%)
occurrences (all)	4	20	53
Hyponatraemia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	6 / 24 (25.00%)
occurrences (all)	2	4	15
Hypophagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	2 / 24 (8.33%)
occurrences (all)	0	1	3

Non-serious adverse events	Roniciclib 5 mg bid / Cisplatin / Etoposide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Haematoma			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Jugular vein thrombosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pelvic venous thrombosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Vascular pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	14		
Chest discomfort			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Chest pain			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Chills			
subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Discomfort			
subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Fatigue			
subjects affected / exposed occurrences (all)	6 / 12 (50.00%) 20		
Injection site extravasation			
subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Malaise			
subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 6		
Mucosal inflammation			
subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 3		
Non-cardiac chest pain			
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Oedema			
subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 3		
Oedema peripheral			
subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 3		
Pain			
subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3		
Pyrexia			
subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Reproductive system and breast			

disorders			
Breast pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Vulvovaginal pruritus			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	7		
Dysphonia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	6		
Dyspnoea exertional			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Haemoptysis			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Hiccups			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Laryngeal inflammation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Nasal congestion			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Pleuritic pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Productive cough subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Pulmonary embolism subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Pulmonary haemorrhage subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Wheezing subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Confusional state subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Depressed mood subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		

Hallucination			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood magnesium decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	3		
Lipase increased			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Neutrophil count decreased subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 3		
Platelet count decreased subjects affected / exposed occurrences (all)	5 / 12 (41.67%) 14		
Weight decreased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 3		
Weight increased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
White blood cell count decreased subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 3		
Injury, poisoning and procedural complications			
Allergic transfusion reaction subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Burns second degree subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Epicondylitis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Fall subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 4		
Incision site pain			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Ligament sprain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Radiation skin injury subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Rib fracture subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Tachycardia subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 4		
Nervous system disorders Amnesia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Aphasia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Ataxia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Cerebellar syndrome subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Disturbance in attention subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Dizziness			

subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	12		
Dysgeusia			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	7		
Head discomfort			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	9		
Hemiparesis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypersomnia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Motor dysfunction			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Myoclonus			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Neuropathy peripheral			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Peripheral motor neuropathy			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Peripheral sensory neuropathy			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Visual field defect			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	33		
Leukocytosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Leukopenia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Lymphopenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	14		
Thrombocytopenia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	8		

<p>Ear and labyrinth disorders</p> <p>Ear discomfort</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 12 (8.33%)</p> <p>1</p>		
<p>Ear pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 12 (8.33%)</p> <p>1</p>		
<p>Hypoacusis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 12 (0.00%)</p> <p>0</p>		
<p>Ototoxicity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 12 (8.33%)</p> <p>1</p>		
<p>Tinnitus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 12 (33.33%)</p> <p>6</p>		
<p>Vertigo</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 12 (8.33%)</p> <p>1</p>		
<p>Vertigo positional</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 12 (0.00%)</p> <p>0</p>		
<p>Eye disorders</p> <p>Photopsia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 12 (8.33%)</p> <p>1</p>		
<p>Vision blurred</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 12 (0.00%)</p> <p>0</p>		
<p>Visual impairment</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 12 (8.33%)</p> <p>1</p>		
<p>Gastrointestinal disorders</p> <p>Abdominal distension</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 12 (0.00%)</p> <p>0</p>		
<p>Abdominal pain</p>			

subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	10 / 12 (83.33%)		
occurrences (all)	19		
Dry mouth			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Eructation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gastrointestinal pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gingival pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	11 / 12 (91.67%)		
occurrences (all)	56		
Oral pain			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Periodontal disease			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Retching			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Salivary hypersecretion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Stomatitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	10 / 12 (83.33%)		
occurrences (all)	42		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	13		
Blister			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dermatitis acneiform			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	4		
Hyperhidrosis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Nail disorder			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Night sweats			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pain of skin			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Rash maculo-papular			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Skin disorder			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Skin exfoliation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Skin hyperpigmentation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Chronic kidney disease			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dysuria			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Haematuria			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Incontinence			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Nephropathy toxic			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pollakiuria			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Proteinuria			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Renal failure			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Renal impairment			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Renal vein thrombosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Back pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Bone pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Joint stiffness subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Joint swelling subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Muscular weakness subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Myalgia subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 4		
Neck pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Pain in extremity subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Rhabdomyolysis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Spinal pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Infections and infestations			

Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Candida infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Clostridium difficile colitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Clostridium difficile infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Herpes zoster			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Rash pustular			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

Rhinitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Tonsillitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tracheitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	10 / 12 (83.33%)		
occurrences (all)	19		
Dehydration			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Hypercalcaemia			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Hyperkalaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	5		
Hypocalcaemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Hypoglycaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	5		
Hypomagnesaemia			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	18		
Hyponatraemia			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	6		
Hypophagia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2012	Changed the roniciclib starting dose and dose levels, as well as dose modifications of roniciclib based on the updated results of first-in-man; clarified language concerning study design, sample size, dosing.
28 February 2013	Excluded anticoagulation therapy, clarified procedures for biomarker analysis, dose delays, and PK parameters.
04 September 2013	Reported the change of the Coordinating Investigator.
22 April 2014	Updated adequate contraceptive guidance to continue for 6 months after chemotherapy.
11 November 2014	Updated to include new clinical pharmacology data regarding involvement of Cytochrome P450 3A4 (CYP3A4) in roniciclib biotransformation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 March 2016	The results of preliminary Phase 2 study (14615, 2013-004198-28) suggested that treatment with roniciclib in combination with chemotherapy had an unfavorable benefit-risk balance. Therefore, due to safety reasons it was decided to discontinue and terminate the roniciclib (14858, 2011-004155-39) project.	-

Notes:

Limitations and caveats

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

Occurrence of "±" in relation with geometric CV is auto-generated and cannot be deleted. Decimal places were automatically truncated if last decimal equals zero. '99999' indicates that data were not estimable due to censored data.

Notes: