Clinical trial results:
TIGER-3: A Phase 3, Open-label, Multicenter, Randomized Study of Oral Rociletinib (CO-1686) Monotherapy Versus Single-agent Cytotoxic Chemotherapy in Patients with Mutant EGFR Non-small Cell Lung Cancer (NSCLC) After Failure of at Least 1 Previous EGFR-directed Tyrosine Kinase Inhibitor (TKI) and Platinum-doublet Chemotherapy

Summary

EudraCT number	2014-003437-26
Trial protocol	GB DE NL ES IT
Global end of trial date	29 March 2018

Results information

Result version number	v2 (current)
This version publication date	25 September 2019
First version publication date	02 June 2019
Version creation reason	• New data added to full data set Adding the following 2 secondary outcomes: Overall Survival (OS) and PK

Trial information

Trial identification

Sponsor protocol code	CO-1686-020

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02322281
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Clovis Oncology UK Ltd
Sponsor organisation address	Sheraton House, Castle Park, Cambridge, United Kingdom, CB3 0AX
Public contact	Dr Lindsey Rolfe, Clovis Oncology UK Ltd, +44 1223 370037, info@clovisoncology.com
Scientific contact	Dr Lindsey Rolfe, Clovis Oncology UK Ltd, +44 1223 370037, info@clovisoncology.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	29 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 March 2018
Global end of trial reached?	Yes
Global end of trial date	29 March 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the anti-tumor efficacy of oral single-agent rociletinib, as measured by investigator assessment of the PFS, with that of single-agent cytotoxic chemotherapy in patients with EGFR-mutated, advanced/metastatic NSCLC after failure of at least 1 previous EGFR-directed TKI and at least 1 line of platinum-containing doublet chemotherapy

Protection of trial subjects:

A data monitoring committee consisting of 3 of the clinical trial investigators and sponsor personnel met every 3 to 6 months to review and assess the safety and efficacy data, and provide recommendations regarding study continuation/discontinuation and protocol modifications.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 December 2014
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	Netherlands: 12
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Korea, Republic of: 17
Country: Number of subjects enrolled	Taiwan: 25
Country: Number of subjects enrolled	United States: 49
Worldwide total number of subjects	149
EEA total number of subjects	55

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)	88
From 65 to 84 years	58
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

149 subjects recruited from 83 sites in 10 countries and randomized (1:1) to treatment with rociletinib or single-agent cytotoxic chemotherapy (investigator's choice of pemetrexed, gemcitabine, docetaxel, or paclitaxel). Crossover to rociletinib treatment, permitted for comparator chemotherapy treated subjects but only after eligibility confirmed.

Pre-assignment

Screening details:

Eligible patients were ≥ 18 years of age with advanced/metastatic NSCLC that had evidence of a tumor with 1 or more activating EGFR mutations (excluding exon 20 insertion) and had undergone a biopsy or surgical resection of either primary or metastatic tumor tissue within 60 days of the first day of treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Rociletinib 500 mg BID

Arm description:

Starting dose of 500mg. Taken orally twice daily (continuous 21 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

Arm type	Experimental
Investigational medicinal product name	Rociletinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Starting dose of 500mg. Taken orally twice daily (continuous 21 day treatment cycle).

Arm title	Rociletinib 625 mg BID

Arm description:

Starting dose of 625mg. Taken orally twice daily (continuous 21 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

Arm type	Experimental
Investigational medicinal product name	Rociletinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Starting dose of 625mg. Taken orally twice daily (continuous 21 day treatment cycle).

Arm title	Chemotherapy

Arm description:

Investigator's choice -
Pemetrexed 500 mg/m2 given intravenously on Day 1 of each 21-day cycle.
Gemcitabine 1250 mg/m2 given intravenously on Day 1 and 8 of each 21-day cycle.
Paclitaxel 80 mg/m2 given intravenously on a weekly basis as part of a continuous 21-day cycle; i.e. dosing will be on Days 1, 8, and 15 of each 21-day cycle.

Docetaxel 75 mg/m2 (60 mg/m2 for patients residing in East-Asian territories) given intravenously on Day 1 of each 21-day cycle, OR
35 mg/m2 docetaxel given intravenously on a weekly basis as part of a continuous 21-day cycle; i.e. dosing will be on Days 1, 8, and 15 of each 21-day cycle.
Treatment duration until radiographically confirmed disease progression.

Arm type	Active comparator
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed administered at 500 mg/m2 intravenously (IV) on Day 1 of each 21-day cycle.

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

Dosage and administration details:

Gemcitabine administered at 1,250 mg/m2 IV on Days 1 and 8 of each 21-day cycle.

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

Dosage and administration details:

Paclitaxel administered at 80 mg/m2 IV weekly as part of a continuous 21-day cycle (Days 1, 8, and 15 of each 21-day cycle).

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

Dosage and administration details:

Docetaxel administered at 75 mg/m2 (60 mg/m2 in Asian patients) IV on Day 1 of each 21-day cycle, or 35 mg/m2 docetaxel IV weekly as part of a continuous 21-day cycle (Days 1, 8, and 15 of each 21-day cycle)

Number of subjects in period 1	Rociletinib 500 mg BID	Rociletinib 625 mg BID	Chemotherapy
Started	53	22	74
Crossed Over to Rociletinib 500 mg BID	0	0	36
Crossed Over to Rociletinib 625 mg BID	0	0	3
Completed	0	0	0
Not completed	53	22	74
Physician decision	2	-	5
Adverse Event	3	4	6
Death	3	3	3
Progressive Disease	42	14	49

Miscellaneous	-	-	4
Withdrawal by Subject	1	1	6
Study Terminated by Sponsor	2	-	-
Missing	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Rociletinib 500 mg BID
Reporting group description:	
Starting dose of 500mg. Taken orally twice daily (continuous 21 day treatment cycle). Treatment duration until radiographically confirmed disease progression.	
Reporting group title	Rociletinib 625 mg BID
Reporting group description:	
Starting dose of 625mg. Taken orally twice daily (continuous 21 day treatment cycle). Treatment duration until radiographically confirmed disease progression.	
Reporting group title	Chemotherapy
Reporting group description:	
Investigator's choice - Pemetrexed 500 mg/m2 given intravenously on Day 1 of each 21-day cycle. Gemcitabine 1250 mg/m2 given intravenously on Day 1 and 8 of each 21-day cycle. Paclitaxel 80 mg/m2 given intravenously on a weekly basis as part of a continuous 21-day cycle; i.e. dosing will be on Days 1, 8, and 15 of each 21-day cycle. Docetaxel 75 mg/m2 (60 mg/m2 for patients residing in East-Asian territories) given intravenously on Day 1 of each 21-day cycle, OR 35 mg/m2 docetaxel given intravenously on a weekly basis as part of a continuous 21-day cycle; i.e. dosing will be on Days 1, 8, and 15 of each 21-day cycle. Treatment duration until radiographically confirmed disease progression.	

Reporting group values	Rociletinib 500 mg BID	Rociletinib 625 mg BID	Chemotherapy
Number of subjects	53	22	74
Age categorical Units: Subjects			
18-64	31	12	45
65-84	21	9	28
>=85	1	1	1
Age continuous Units: years			
arithmetic mean	61.6	63.4	61.4
standard deviation	± 11.66	± 12.30	± 9.84
Gender categorical Units: Subjects			
Female	35	13	39
Male	18	9	35
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	0	3
Not Hispanic or Latino	46	22	68
Unknown or Not Reported	3	0	3
Race/Ethnicity, Customized 1 Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	23	6	30
Black or African American	2	0	3
Native Hawaiian or Other Pacific Islander	0	0	1
White	24	15	38

Other	0	1	1
Missing	4	0	1
Race/Ethnicity, Customized 2 Units: Subjects			
White	24	15	38
Asian	23	6	30
Non-White, Non-Asian	6	1	6
Number of Previous Therapies Units: number			
median	3.0	3.0	3.0
full range (min-max)	1.0 to 8.0	2.0 to 6.0	0.0 to 13.0
Time Since Diagnosis of NSCLC [1]			
[1] Measure Analysis Population Description: Information missing for one patient in the Chemotherapy treatment group.			
Units: Months			
arithmetic mean	42.6	37.5	39.0
standard deviation	± 35.54	± 16.92	± 25.10

Reporting group values	Total		
Number of subjects	149		
Age categorical Units: Subjects			
18-64	88		
65-84	58		
>=85	3		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	87		
Male	62		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7		
Not Hispanic or Latino	136		
Unknown or Not Reported	6		
Race/Ethnicity, Customized 1 Units: Subjects			
American Indian or Alaska Native	0		
Asian	59		
Black or African American	5		
Native Hawaiian or Other Pacific Islander	1		
White	77		
Other	2		
Missing	5		
Race/Ethnicity, Customized 2 Units: Subjects			
White	77		
Asian	59		

Non-White, Non-Asian	13		

Number of Previous Therapies Units: number median full range (min-max)	- -		
Time Since Diagnosis of NSCLC [1]			
[1] Measure Analysis Population Description: Information missing for one patient in the Chemotherapy treatment group.			
Units: Months arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Rociletinib 500 mg BID
Reporting group description:	
Starting dose of 500mg. Taken orally twice daily (continuous 21 day treatment cycle). Treatment duration until radiographically confirmed disease progression.	
Reporting group title	Rociletinib 625 mg BID
Reporting group description:	
Starting dose of 625mg. Taken orally twice daily (continuous 21 day treatment cycle). Treatment duration until radiographically confirmed disease progression.	
Reporting group title	Chemotherapy
Reporting group description:	
Investigator's choice - Pemetrexed 500 mg/m2 given intravenously on Day 1 of each 21-day cycle. Gemcitabine 1250 mg/m2 given intravenously on Day 1 and 8 of each 21-day cycle. Paclitaxel 80 mg/m2 given intravenously on a weekly basis as part of a continuous 21-day cycle; i.e. dosing will be on Days 1, 8, and 15 of each 21-day cycle. Docetaxel 75 mg/m2 (60 mg/m2 for patients residing in East-Asian territories) given intravenously on Day 1 of each 21-day cycle, OR 35 mg/m2 docetaxel given intravenously on a weekly basis as part of a continuous 21-day cycle; i.e. dosing will be on Days 1, 8, and 15 of each 21-day cycle. Treatment duration until radiographically confirmed disease progression.	

Primary: Progression Free Survival (PFS) According to RECIST Version 1.1 as Determined by Investigator Review (invPFS)

End point title	Progression Free Survival (PFS) According to RECIST Version 1.1 as Determined by Investigator Review (invPFS)[1]
End point description:	
Median InvPFS was calculated as 1+ the number of days from the date of randomization to documented radiographic progression as determined by the investigator, or death due to any cause, whichever occurs first. Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression. 1 patient in the Chemotherapy treatment group was not included in the analysis, due to discontinuation of study shortly after randomization and prior to first dose of study drug.	
End point type	Primary
End point timeframe:	
Cycle 1 Day 1 to End of Treatment, up to approximately 35 months. This Time Frame includes the cross-over period, however, participants who crossed over to rociletinib were not analyzed for PFS.	
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: Per EMA feedback, the statistical analyses section can not accommodate the end point results for this study. Therefore, for each end point, all statistical analyses details are provided in the End point values sections.	

End point values	Rociletinib 500 mg BID	Rociletinib 625 mg BID	Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53[2]	22[3]	73[4]	
Units: PFS Days	125	166	77	

Notes:

[2] - PFS Days - Confidence interval: level 95%, 2-sided, lower limit 79, upper limit 165

[3] - PFS Days - Confidence interval: level 95%, 2-sided, lower limit 56, upper limit 246

[4] - PFS Days - Confidence interval: level 95%, 2-sided, lower limit 42, upper limit 88

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With Confirmed Response

End point title	Percentage of Patients With Confirmed Response

End point description:

Percentage of patients with best overall confirmed response of partial response (PR) or complete response (CR) recorded from the start of the treatment until disease progression or recurrence. Per RECIST v1.1 for target lesions: CR is disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR is at least 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of longest diameter. Overall Response (OR) is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment was dependent on the achievement of both measurement and confirmation criteria. 1 patient in the Chemotherapy group was not included in analysis due to discontinuation after randomization and prior to 1st dose.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 to End of Treatment, up to approximately 35 months. This Time Frame includes the cross-over period, however, participants who crossed over to rociletinib were not analyzed for best overall confirmed response.

End point values	Rociletinib 500 mg BID	Rociletinib 625 mg BID	Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53[5]	22[6]	73[7]	
Units: Percentage of participants	17	18	8	

Notes:

[5] - Percentage of Patients - Confidence interval: level 95%, 2-sided, lower limit 8.1, upper limit 29.8

[6] - Percentage of Patients - Confidence interval: level 95%, 2-sided, lower limit 5.2, upper limit 40.3

[7] - Percentage of Patients - Confidence interval: level 95%, 2-sided, lower limit 3.1, upper limit 17

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) According to RECIST Version 1.1 as Determined by Investigator Assessment

End point title	Duration of Response (DOR) According to RECIST Version 1.1 as Determined by Investigator Assessment

End point description:

Median Duration of Response in patients with confirmed response (CR or PR) per investigator. The DOR was measured from date best response is first recorded until first date that progressive disease is objectively documented. For patients who continue treatment post-progression, first date of progression was used for the analysis. Per RECIST v1.1 for target lesions: CR is disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to

<10mm. PR is at least a 30% decrease in sum of the longest diameter of target lesions, taking as reference the baseline sum of longest diameter. Overall Response is the best response from start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The overall number of patients in the Chemotherapy arm does not include those who crossed over into the Rociletinib treatment groups

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 to End of Treatment, up to approximately 35 months

End point values	Rociletinib 500 mg BID	Rociletinib 625 mg BID	Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9[8]	4[9]	6[10]	
Units: Days	335	275	206	

Notes:

[8] - DOR Days - Confidence interval: level 95%, 2-sided, lower limit 77, upper limit 418

[9] - DOR Days - Confidence interval: level 95%, 2-sided, lower limit 167, upper limit 375

[10] - DOR Days - Confidence interval: level 95%, 2-sided, lower limit 136, upper limit not available

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Median OS was calculated as 1+ the number of days from randomization to death due to any cause. Patients without a documented date of death were censored on the date the patient was last known to be alive. One patient in the Rociletinib 500 and 2 patients in the Chemotherapy treatment group were not included in the analysis because their OS data was not collected. One additional patient in the Chemotherapy group was not included due to discontinuation from study shortly after randomization and prior to first dose of study drug.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 to date of death, assessed up to 3 years

End point values	Rociletinib 500 mg BID	Rociletinib 625 mg BID	Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52[11]	22[12]	71[13]	
Units: Median Days	665	541	348	

Notes:

[11] - Confidence interval: level 95%, 2-sided, lower limit 232, upper limit not available

[12] - Confidence interval: level 95%, 2-sided, lower limit 173, upper limit not available

[13] - Confidence interval: level 95%, 2-sided, lower limit 231, upper limit 522

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma PK for Patients Treated with Rociletinib Based on Sparse Sampling

End point title	Plasma PK for Patients Treated with Rociletinib Based on Sparse Sampling[14]

End point description:

Blood samples were drawn for PK analysis at 21 ± 3 day intervals for the first 6 months (Day 1 of Cycles 2 to 7 inclusive). The sample could be taken predose or postdose. Plasma concentrations are presented for Rociletinib and 3 metabolites (M460, M502, M544). Population Description: A small subset of patients treated with rociletinib (ie, patients randomized to receive rociletinib or who crossed over to receive rociletinib following treatment with single agent cytotoxic chemotherapy). Note: 1 sample was analyzed in the 500mg treatment group and 33 samples were analyzed in the 625mg treatment group. 2 patients in the 625mg treatment group had M502 values at upper limit of quantification (ULOQ) which were set as missing values.

End point type	Secondary

End point timeframe:

Cycles 2 Day 1 to Cycle 7 Day 1, or approximately 6 months

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per EMA feedback, the statistical analyses section can not accommodate the end point results for this study. Therefore, for each end point, all statistical analyses details are provided in the End point values sections

End point values	Rociletinib 500 mg BID	Rociletinib 625 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[15]	10[16]		
Units: Rociletinib plasma concentration (ng/mL)	80	207		

Notes:

[15] - Metabolite ng/mL: M460=20, M502=573, M544=765

[16] - Metabolite ng/mL (range): M460=555 (144-1200), M502=3260 (98.4-4880), M544=525 (20-3640)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the date of first dose of study drug and until 28 days after last dose of study drug, an average of 6 months.

Adverse event reporting additional description:

If subject experiences the same preferred term (system organ class) multiple times, the subject was counted only once for that preferred term. Treatment Arm/Groups for subjects who crossed over to Rociletinib from Chemotherapy are included. 1 subject in Chemo group was not included due to discontinuation after randomization and prior to first dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Rociletinib 500 mg BID

Reporting group description:

Starting dose of 500mg. Taken orally twice daily (continuous 21 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

Reporting group title	Rociletinib 625 mg BID

Reporting group description:

Starting dose of 625mg. Taken orally twice daily (continuous 21 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

Reporting group title	Chemotherapy

Reporting group description:

Investigator's choice -
Pemetrexed 500 mg/m2 given intravenously on Day 1 of each 21-day cycle.
Gemcitabine 1250 mg/m2 given intravenously on Day 1 and 8 of each 21day cycle.
Paclitaxel 80 mg/m2 given intravenously on a weekly basis as part of a continuous 21-day cycle; i.e. dosing will be on Days 1, 8, and 15 of each 21-day cycle.
Docetaxel 75 mg/m2 (60 mg/m2 for patients residing in East-Asian territories) given intravenously on Day 1 of each 21-day cycle, OR
35 mg/m2 docetaxel given intravenously on a weekly basis as part of a continuous 21-day cycle; i.e. dosing will be on Days 1, 8, and 15 of each 21-day cycle.
Treatment duration until radiographically confirmed disease progression.

Reporting group title	Crossover from Chemotherapy to Rociletinib 500 mg BID

Reporting group description:

Patients initially randomized to comparator chemotherapy had the option to cross over to rociletinib following disease progression per RECIST Version 1.1. Rociletinib starting dose of 500 mg taken orally twice daily (continuous 21 day treatment cycle). Treatment duration until radiographically confirmed disease progression.

Reporting group title	Crossover From Chemotherapy to Rociletinib 625 mg BID

Reporting group description:

Patients initially randomized to comparator chemotherapy had the option to cross over to rociletinib following disease progression per RECIST Version 1.1. Rociletinib starting dose of 625 mg taken orally twice daily (continuous 21 day treatment cycle). Treatment duration until radiographically confirmed disease progression

Serious adverse events	Rociletinib 500 mg BID	Rociletinib 625 mg BID	Chemotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 53 (43.40%)	7 / 22 (31.82%)	23 / 73 (31.51%)

number of deaths (all causes)	10	3	3
number of deaths resulting from adverse events	10	3	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	5 / 53 (9.43%)	1 / 22 (4.55%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 5	0 / 1	0 / 2
Metastases to meninges			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metastatic pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 53 (1.89%)	1 / 22 (4.55%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General oedema			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothermia			

subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 22 (4.55%)	0 / 73 (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
Sudden death			
subjects affected / exposed	0 / 53 (0.00%)	1 / 22 (4.55%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (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
Reproductive system and breast disorders			
Prostatic obstruction			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 53 (3.77%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pleural effusion			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 53 (0.00%)	1 / 22 (4.55%)	0 / 73 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Subdural haematoma			

subjects affected / exposed	0 / 53 (0.00%)	1 / 22 (4.55%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-pulmonary arrest			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nodal arrhythmia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (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
Ventricular fibrillation			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (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			

Complex partial seizures			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 53 (0.00%)	1 / 22 (4.55%)	0 / 73 (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
Sciatica			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 53 (0.00%)	1 / 22 (4.55%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 53 (0.00%)	1 / 22 (4.55%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 53 (0.00%)	1 / 22 (4.55%)	0 / 73 (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
Anal fistula			

subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (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
Pancreatitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (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
Pancreatitis acute			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (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
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 53 (0.00%)	1 / 22 (4.55%)	0 / 73 (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
Bile duct stone			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (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
Cholecystitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (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			
Back pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertabral disc protrusion			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Flank pain			
subjects affected / exposed	0 / 53 (0.00%)	1 / 22 (4.55%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility decreased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (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
Pain in extremity			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (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			
Gastroenteritis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Influenza			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 53 (5.66%)	1 / 22 (4.55%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal bacteraemia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (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
Peritonitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (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
Sepsis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	3 / 53 (5.66%)	1 / 22 (4.55%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	4 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			

subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 22 (4.55%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Crossover from Chemotherapy to Rociletinib 500 mg BID	Crossover From Chemotherapy to Rociletinib 625 mg BID	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 36 (50.00%)	1 / 3 (33.33%)	
number of deaths (all causes)	6	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			

subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 36 (8.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General oedema			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatic obstruction			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 36 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-pulmonary arrest			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nodal arrhythmia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
Complex partial seizures			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Cataract			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	3 / 36 (8.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertabral disc protrusion			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Rociletinib 500 mg BID	Rociletinib 625 mg BID	Chemotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 53 (100.00%)	21 / 22 (95.45%)	71 / 73 (97.26%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	7 / 53 (13.21%)	1 / 22 (4.55%)	2 / 73 (2.74%)
occurrences (all)	7	1	2
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 53 (11.32%)	0 / 22 (0.00%)	2 / 73 (2.74%)
occurrences (all)	10	0	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 53 (18.87%)	1 / 22 (4.55%)	10 / 73 (13.70%)
occurrences (all)	16	1	10
Chest discomfort			
subjects affected / exposed	3 / 53 (5.66%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences (all)	3	0	0
Chest pain			

subjects affected / exposed	2 / 53 (3.77%)	2 / 22 (9.09%)	2 / 73 (2.74%)
occurrences (all)	7	2	4
Fatigue			
subjects affected / exposed	16 / 53 (30.19%)	12 / 22 (54.55%)	18 / 73 (24.66%)
occurrences (all)	23	21	37
Non-cardiac chest pain			
subjects affected / exposed	3 / 53 (5.66%)	0 / 22 (0.00%)	5 / 73 (6.85%)
occurrences (all)	3	0	5
Oedema peripheral			
subjects affected / exposed	5 / 53 (9.43%)	1 / 22 (4.55%)	6 / 73 (8.22%)
occurrences (all)	6	1	9
Pyrexia			
subjects affected / exposed	5 / 53 (9.43%)	2 / 22 (9.09%)	7 / 73 (9.59%)
occurrences (all)	6	2	7
General physical health deterioration			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 53 (28.30%)	6 / 22 (27.27%)	14 / 73 (19.18%)
occurrences (all)	19	7	17
Dyspnoea			
subjects affected / exposed	8 / 53 (15.09%)	5 / 22 (22.73%)	10 / 73 (13.70%)
occurrences (all)	13	7	13
Oropharyngeal pain			
subjects affected / exposed	6 / 53 (11.32%)	1 / 22 (4.55%)	2 / 73 (2.74%)
occurrences (all)	7	1	4
Pleural effusion			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	4 / 73 (5.48%)
occurrences (all)	0	0	6
Pneumonitis			
subjects affected / exposed	4 / 53 (7.55%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences (all)	5	0	0
Pulmonary embolism			

subjects affected / exposed	0 / 53 (0.00%)	2 / 22 (9.09%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Epistaxis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Sputum increased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 53 (1.89%)	1 / 22 (4.55%)	4 / 73 (5.48%)
occurrences (all)	1	3	4
Insomnia			
subjects affected / exposed	8 / 53 (15.09%)	1 / 22 (4.55%)	10 / 73 (13.70%)
occurrences (all)	10	2	13
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 53 (7.55%)	2 / 22 (9.09%)	4 / 73 (5.48%)
occurrences (all)	13	2	4
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 53 (9.43%)	1 / 22 (4.55%)	5 / 73 (6.85%)
occurrences (all)	16	1	7
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 53 (5.66%)	0 / 22 (0.00%)	3 / 73 (4.11%)
occurrences (all)	6	0	3
Blood bilirubin increased			
subjects affected / exposed	4 / 53 (7.55%)	4 / 22 (18.18%)	1 / 73 (1.37%)
occurrences (all)	6	4	1
Blood creatinine increased			
subjects affected / exposed	4 / 53 (7.55%)	1 / 22 (4.55%)	3 / 73 (4.11%)
occurrences (all)	6	2	4
Electrocardiogram QT prolonged			

subjects affected / exposed	10 / 53 (18.87%)	10 / 22 (45.45%)	0 / 73 (0.00%)
occurrences (all)	24	24	0
Lymphocyte count decreased			
subjects affected / exposed	2 / 53 (3.77%)	1 / 22 (4.55%)	4 / 73 (5.48%)
occurrences (all)	4	2	12
Neutrophil count decreased			
subjects affected / exposed	2 / 53 (3.77%)	0 / 22 (0.00%)	10 / 73 (13.70%)
occurrences (all)	2	0	22
Platelet count decreased			
subjects affected / exposed	3 / 53 (5.66%)	1 / 22 (4.55%)	4 / 73 (5.48%)
occurrences (all)	4	1	7
Weight decreased			
subjects affected / exposed	10 / 53 (18.87%)	4 / 22 (18.18%)	4 / 73 (5.48%)
occurrences (all)	10	6	4
White blood cell count decreased			
subjects affected / exposed	2 / 53 (3.77%)	3 / 22 (13.64%)	9 / 73 (12.33%)
occurrences (all)	4	3	22
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 53 (7.55%)	3 / 22 (13.64%)	2 / 73 (2.74%)
occurrences (all)	4	3	2
Headache			
subjects affected / exposed	6 / 53 (11.32%)	5 / 22 (22.73%)	5 / 73 (6.85%)
occurrences (all)	8	6	5
Migraine			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 53 (13.21%)	2 / 22 (9.09%)	18 / 73 (24.66%)
occurrences (all)	9	7	28
Leukopenia			

subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	5 / 73 (6.85%)
occurrences (all)	1	0	10
Neutropenia			
subjects affected / exposed	0 / 53 (0.00%)	2 / 22 (9.09%)	9 / 73 (12.33%)
occurrences (all)	0	3	21
Thrombocytopenia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	5 / 73 (6.85%)
occurrences (all)	1	0	6
Eye disorders			
Cataract			
subjects affected / exposed	5 / 53 (9.43%)	3 / 22 (13.64%)	1 / 73 (1.37%)
occurrences (all)	7	6	1
Vision blurred			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 53 (11.32%)	0 / 22 (0.00%)	3 / 73 (4.11%)
occurrences (all)	9	0	4
Constipation			
subjects affected / exposed	6 / 53 (11.32%)	2 / 22 (9.09%)	10 / 73 (13.70%)
occurrences (all)	7	2	10
Diarrhoea			
subjects affected / exposed	33 / 53 (62.26%)	15 / 22 (68.18%)	12 / 73 (16.44%)
occurrences (all)	54	23	12
Dry mouth			
subjects affected / exposed	3 / 53 (5.66%)	1 / 22 (4.55%)	2 / 73 (2.74%)
occurrences (all)	4	1	2
Dyspepsia			
subjects affected / exposed	3 / 53 (5.66%)	5 / 22 (22.73%)	1 / 73 (1.37%)
occurrences (all)	6	5	1
Gastroesophageal reflux disease			
subjects affected / exposed	3 / 53 (5.66%)	2 / 22 (9.09%)	2 / 73 (2.74%)
occurrences (all)	4	2	2
Nausea			

subjects affected / exposed	19 / 53 (35.85%)	9 / 22 (40.91%)	20 / 73 (27.40%)
occurrences (all)	27	14	29
Vomiting			
subjects affected / exposed	10 / 53 (18.87%)	8 / 22 (36.36%)	6 / 73 (8.22%)
occurrences (all)	14	11	7
Stomatitis			
subjects affected / exposed	3 / 53 (5.66%)	1 / 22 (4.55%)	4 / 73 (5.48%)
occurrences (all)	3	1	4
Pancreatitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 53 (5.66%)	0 / 22 (0.00%)	8 / 73 (10.96%)
occurrences (all)	3	0	8
Rash			
subjects affected / exposed	5 / 53 (9.43%)	0 / 22 (0.00%)	4 / 73 (5.48%)
occurrences (all)	6	0	4
Dry skin			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	4 / 73 (5.48%)
occurrences (all)	0	0	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 53 (9.43%)	0 / 22 (0.00%)	6 / 73 (8.22%)
occurrences (all)	5	0	10
Back pain			
subjects affected / exposed	6 / 53 (11.32%)	3 / 22 (13.64%)	10 / 73 (13.70%)
occurrences (all)	7	4	14
Bone pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 22 (0.00%)	4 / 73 (5.48%)
occurrences (all)	0	0	4
Flank pain			

subjects affected / exposed	0 / 53 (0.00%)	2 / 22 (9.09%)	1 / 73 (1.37%)
occurrences (all)	0	5	1
Muscle spasms			
subjects affected / exposed	8 / 53 (15.09%)	3 / 22 (13.64%)	0 / 73 (0.00%)
occurrences (all)	9	3	0
Muscular weakness			
subjects affected / exposed	1 / 53 (1.89%)	2 / 22 (9.09%)	2 / 73 (2.74%)
occurrences (all)	1	2	3
Musculoskeletal chest pain			
subjects affected / exposed	3 / 53 (5.66%)	2 / 22 (9.09%)	6 / 73 (8.22%)
occurrences (all)	3	3	9
Musculoskeletal pain			
subjects affected / exposed	6 / 53 (11.32%)	2 / 22 (9.09%)	3 / 73 (4.11%)
occurrences (all)	4	8	2
Myalgia			
subjects affected / exposed	7 / 53 (13.21%)	3 / 22 (13.64%)	2 / 73 (2.74%)
occurrences (all)	8	5	3
Pain in extremity			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	4 / 73 (5.48%)
occurrences (all)	1	0	6
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 53 (5.66%)	0 / 22 (0.00%)	0 / 73 (0.00%)
occurrences (all)	4	0	0
Pneumonia			
subjects affected / exposed	4 / 53 (7.55%)	2 / 22 (9.09%)	0 / 73 (0.00%)
occurrences (all)	4	2	0
Upper respiratory tract infection			
subjects affected / exposed	4 / 53 (7.55%)	2 / 22 (9.09%)	3 / 73 (4.11%)
occurrences (all)	5	2	3
Urinary tract infection			
subjects affected / exposed	4 / 53 (7.55%)	1 / 22 (4.55%)	2 / 73 (2.74%)
occurrences (all)	8	2	3
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	19 / 53 (35.85%)	9 / 22 (40.91%)	10 / 73 (13.70%)
occurrences (all)	30	12	12
Hyperglycaemia			
subjects affected / exposed	30 / 53 (56.60%)	14 / 22 (63.64%)	6 / 73 (8.22%)
occurrences (all)	84	33	8
Hypokalaemia			
subjects affected / exposed	7 / 53 (13.21%)	6 / 22 (27.27%)	3 / 73 (4.11%)
occurrences (all)	9	9	3
Hypomagnesaemia			
subjects affected / exposed	4 / 53 (7.55%)	2 / 22 (9.09%)	4 / 73 (5.48%)
occurrences (all)	4	2	4
Hyponatraemia			
subjects affected / exposed	1 / 53 (1.89%)	3 / 22 (13.64%)	2 / 73 (2.74%)
occurrences (all)	1	3	2
Hyperkalaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 22 (0.00%)	1 / 73 (1.37%)
occurrences (all)	1	0	1

Non-serious adverse events	Crossover from Chemotherapy to Rociletinib 500 mg BID	Crossover From Chemotherapy to Rociletinib 625 mg BID	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 36 (97.22%)	3 / 3 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	2 / 36 (5.56%)	1 / 3 (33.33%)	
occurrences (all)	2	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 36 (8.33%)	0 / 3 (0.00%)	
occurrences (all)	6	0	
Chest discomfort			

subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Chest pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	4 / 36 (11.11%)	1 / 3 (33.33%)	
occurrences (all)	6	1	
Non-cardiac chest pain			
subjects affected / exposed	3 / 36 (8.33%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Oedema peripheral			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
General physical health deterioration			
subjects affected / exposed	3 / 36 (8.33%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 36 (8.33%)	0 / 3 (0.00%)	
occurrences (all)	8	0	
Dyspnoea			
subjects affected / exposed	6 / 36 (16.67%)	0 / 3 (0.00%)	
occurrences (all)	8	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Pleural effusion			
subjects affected / exposed	0 / 36 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Pneumonitis			

subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pulmonary embolism			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Epistaxis			
subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Haemoptysis			
subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Sputum increased			
subjects affected / exposed	0 / 36 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Blood bilirubin increased			
subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Blood creatinine increased			

subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Electrocardiogram QT prolonged			
subjects affected / exposed	7 / 36 (19.44%)	1 / 3 (33.33%)	
occurrences (all)	16	1	
Lymphocyte count decreased			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Platelet count decreased			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Weight decreased			
subjects affected / exposed	1 / 36 (2.78%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
White blood cell count decreased			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	1 / 36 (2.78%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Migraine			
subjects affected / exposed	0 / 36 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	5 / 36 (13.89%)	1 / 3 (33.33%)	
occurrences (all)	6	1	
Leukopenia			
subjects affected / exposed	4 / 36 (11.11%)	0 / 3 (0.00%)	
occurrences (all)	10	0	
Neutropenia			
subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	7	0	
Thrombocytopenia			
subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
Cataract			
subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Vision blurred			
subjects affected / exposed	0 / 36 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	3 / 36 (8.33%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			
subjects affected / exposed	13 / 36 (36.11%)	1 / 3 (33.33%)	
occurrences (all)	22	1	
Dry mouth			
subjects affected / exposed	3 / 36 (8.33%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Dyspepsia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Gastroesophageal reflux disease			

subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	7 / 36 (19.44%)	1 / 3 (33.33%)	
occurrences (all)	8	1	
Vomiting			
subjects affected / exposed	6 / 36 (16.67%)	2 / 3 (66.67%)	
occurrences (all)	10	4	
Stomatitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Pancreatitis			
subjects affected / exposed	3 / 36 (8.33%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Dry skin			
subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 36 (8.33%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Back pain			
subjects affected / exposed	1 / 36 (2.78%)	2 / 3 (66.67%)	
occurrences (all)	2	2	
Bone pain			

subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Flank pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	3 / 36 (8.33%)	1 / 3 (33.33%)	
occurrences (all)	4	1	
Muscular weakness			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal pain			
subjects affected / exposed	4 / 36 (11.11%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Myalgia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	4 / 36 (11.11%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Pneumonia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 36 (22.22%)	1 / 3 (33.33%)	
occurrences (all)	11	1	
Hyperglycaemia			
subjects affected / exposed	12 / 36 (33.33%)	2 / 3 (66.67%)	
occurrences (all)	41	4	
Hypokalaemia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Hypomagnesaemia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Hyponatraemia			
subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Hyperkalaemia			
subjects affected / exposed	2 / 36 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2014	In global Amendment 1, the planned enrollment was increased to approximately 600 patients, which increased the number of targeted PFS events from 350 to 400 events to strengthen the statistical analyses. Other revisions included clarification/revision of inclusion and exclusion criteria and updates to safety management, such as requiring a follow-up scan to confirm that treated brain metastasis remain controlled without evidence of new lesions, and updated guidance on the management of hyperglycemia.
27 April 2015	Global Amendment 2 included decreasing the starting dose of rociletinib from 625 mg BID to 500 mg BID and specifying that a dose reduction for patients initially treated at 625 mg BID was allowed only if necessitated by unacceptable toxicity. Supportive analysis of Independent radiology review of PFS (irrPFS) and stratification subgroups to the statistical analyses were added. Additional information was provided on the management of prolonged QTC and hyperglycemia, and tumor assessments were revised to minimize scan parameters if not necessary, including exception for scans following discontinuation without progression, to allow for local variations in scan requirements. This global amendment also specified that creatinine clearance ≥ 45 ml/min be used instead of plasma creatinine in the inclusion criteria and single-agent cytotoxic medication sections. Fasting serum glucose within normal ranges was incorporated into the global protocol amendment as an inclusion criterion.
07 September 2016	Extension Phase and Early Termination of the Study -- Clovis announced on 05 May 2016 that enrollment would be terminated due to a decision to halt the clinical development of rociletinib. The purpose of Protocol Amendment 4 was to add a new Extension Phase to allow patients who continued to derive clinical benefit from study treatment to remain on-study, at the discretion of the Principal Investigator, but to avoid unnecessary collection of data that would no longer be analyzed or required for regulatory purposes whilst maintaining an appropriate level of safety monitoring. Patients were administered rociletinib daily at 500 mg BID (or 625 mg BID under Protocol Amendment 1). A new schedule of assessments for the Extension Phase, as well as a complete description of procedures, was provided, which replaced all prior assessment schedules. Treatment could continue until disease progression or intolerable toxicity; for patients who wished to continue rociletinib treatment post-progression or for patients who wished to cross over to rociletinib treatment following progression on chemotherapy, a full exploration of alternative treatment options between patients and their treating physicians took place prior to making that decision.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 May 2016	Due to an internal corporate decision announced on 05 May 2016 to suspend the development of rociletinib, no new patients were permitted to enter screening for enrollment into any ongoing Clovis-sponsored rociletinib clinical study. Patients who were in screening as of that date could enroll on or before 12 May 2016 if they met eligibility requirements. At this time, there were 149 patients randomized.	-

Notes:

Limitations and caveats

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

Due to early study termination, only 149 of 600 planned patients were randomized.

Notes: