

**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 | v1 |
| This version publication date | 02 June 2019 |
| First version publication date | 02 June 2019 |

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 | 0 |

| | |
|--|----|
| wk | |
| 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/m ² given intravenously on Day 1 of each 21-day cycle. Gemcitabine 1250 mg/m ² given intravenously on Day 1 and 8 of each 21-day cycle. Paclitaxel 80 mg/m ² 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/m ² (60 mg/m ² for patients residing in East-Asian territories) given intravenously on Day 1 of each 21-day cycle, OR 35 mg/m ² 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. | |

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] | 72 ^[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 a 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 Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1) for target lesions, defined by and assessed as: Complete Response (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. Partial Response (PR), at least a 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. | |
| 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. | |

| 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 per investigator. The DOR for complete response (CR) and partial response (PR) was measured from the date that any of these best responses is first recorded until the first date that progressive disease (PD) is objectively documented. For patients who continue treatment post-progression, the first date of progression was used for the analysis. | |
| 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

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 |
| Intervertebral 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 | |

| | | | |
|---|----------------|---------------|--|
| Intervertebral 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 occurrences (all) | 10 / 53 (18.87%) 24 | 10 / 22 (45.45%) 24 | 0 / 73 (0.00%) 0 |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 2 / 53 (3.77%) 4 | 1 / 22 (4.55%) 2 | 4 / 73 (5.48%) 12 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 2 / 53 (3.77%) 2 | 0 / 22 (0.00%) 0 | 10 / 73 (13.70%) 22 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 4 | 1 / 22 (4.55%) 1 | 4 / 73 (5.48%) 7 |
| Weight decreased subjects affected / exposed occurrences (all) | 10 / 53 (18.87%) 10 | 4 / 22 (18.18%) 6 | 4 / 73 (5.48%) 4 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 2 / 53 (3.77%) 4 | 3 / 22 (13.64%) 3 | 9 / 73 (12.33%) 22 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 4 / 53 (7.55%) 4 | 3 / 22 (13.64%) 3 | 2 / 73 (2.74%) 2 |
| Headache subjects affected / exposed occurrences (all) | 6 / 53 (11.32%) 8 | 5 / 22 (22.73%) 6 | 5 / 73 (6.85%) 5 |
| Migraine subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 22 (0.00%) 0 | 0 / 73 (0.00%) 0 |
| Paraesthesia subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 22 (0.00%) 0 | 0 / 73 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 7 / 53 (13.21%) 9 | 2 / 22 (9.09%) 7 | 18 / 73 (24.66%) 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 occurrences (all) | 19 / 53 (35.85%) 27 | 9 / 22 (40.91%) 14 | 20 / 73 (27.40%) 29 |
| Vomiting subjects affected / exposed occurrences (all) | 10 / 53 (18.87%) 14 | 8 / 22 (36.36%) 11 | 6 / 73 (8.22%) 7 |
| Stomatitis subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 3 | 1 / 22 (4.55%) 1 | 4 / 73 (5.48%) 4 |
| Pancreatitis subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 22 (0.00%) 0 | 0 / 73 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 3 / 53 (5.66%) 3 | 0 / 22 (0.00%) 0 | 8 / 73 (10.96%) 8 |
| Rash subjects affected / exposed occurrences (all) | 5 / 53 (9.43%) 6 | 0 / 22 (0.00%) 0 | 4 / 73 (5.48%) 4 |
| Dry skin subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 22 (0.00%) 0 | 0 / 73 (0.00%) 0 |
| Renal and urinary disorders | | | |
| Dysuria subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 22 (0.00%) 0 | 4 / 73 (5.48%) 4 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 5 / 53 (9.43%) 5 | 0 / 22 (0.00%) 0 | 6 / 73 (8.22%) 10 |
| Back pain subjects affected / exposed occurrences (all) | 6 / 53 (11.32%) 7 | 3 / 22 (13.64%) 4 | 10 / 73 (13.70%) 14 |
| Bone pain subjects affected / exposed occurrences (all) | 0 / 53 (0.00%) 0 | 0 / 22 (0.00%) 0 | 4 / 73 (5.48%) 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 occurrences (all) | 5 / 36 (13.89%) 6 | 1 / 3 (33.33%) 1 | |
| Leukopenia subjects affected / exposed occurrences (all) | 4 / 36 (11.11%) 10 | 0 / 3 (0.00%) 0 | |
| Neutropenia subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 7 | 0 / 3 (0.00%) 0 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 3 | 0 / 3 (0.00%) 0 | |
| Eye disorders | | | |
| Cataract subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 3 | 0 / 3 (0.00%) 0 | |
| Vision blurred subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 1 / 3 (33.33%) 1 | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 0 / 3 (0.00%) 0 | |
| Constipation subjects affected / exposed occurrences (all) | 3 / 36 (8.33%) 3 | 0 / 3 (0.00%) 0 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 13 / 36 (36.11%) 22 | 1 / 3 (33.33%) 1 | |
| Dry mouth subjects affected / exposed occurrences (all) | 3 / 36 (8.33%) 3 | 0 / 3 (0.00%) 0 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 0 / 3 (0.00%) 0 | |
| Gastroesophageal reflux disease | | | |

| | | | |
|---|-----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | 0 / 3 (0.00%) 0 | |
| Nausea subjects affected / exposed occurrences (all) | 7 / 36 (19.44%) 8 | 1 / 3 (33.33%) 1 | |
| Vomiting subjects affected / exposed occurrences (all) | 6 / 36 (16.67%) 10 | 2 / 3 (66.67%) 4 | |
| Stomatitis subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 0 / 3 (0.00%) 0 | |
| Pancreatitis subjects affected / exposed occurrences (all) | 3 / 36 (8.33%) 3 | 0 / 3 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 0 / 3 (0.00%) 0 | |
| Rash subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 0 / 3 (0.00%) 0 | |
| Dry skin subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | 0 / 3 (0.00%) 0 | |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 1 / 36 (2.78%) 3 | 0 / 3 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 3 / 36 (8.33%) 3 | 0 / 3 (0.00%) 0 | |
| Back pain subjects affected / exposed occurrences (all) | 1 / 36 (2.78%) 2 | 2 / 3 (66.67%) 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. OS and PK endpoints were not analyzed. |
|--|

Notes: