



## Clinical trial results:

**A Phase III, Open Label, Randomized Study of AZD9291 versus Platinum-Based Doublet Chemotherapy for Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and whose Tumours harbour a T790M mutation within the Epidermal Growth Factor Receptor Gene (AURA3).**

### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2014-000594-39          |
| Trial protocol           | DE GB SE IT NL FR NO HU |
| Global end of trial date | 15 December 2023        |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 28 December 2024 |
| First version publication date | 28 December 2024 |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | D5160C00003 |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02151981 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | AstraZeneca Clinical Study Information Center  |
| Sponsor organisation address | Melbourn Science Park, Royston, United Kingdom, SG8 6EE  |
| Public contact               | Global Clinical Lead, AstraZeneca Clinical Study Information Center, +1 8772409479, information.center@astrazeneca.com |
| Scientific contact           | Global Clinical Lead, AstraZeneca Clinical Study Information Center, +1 8772409479, information.center@astrazeneca.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                                       | Interim          |
| Date of interim/final analysis                       | 15 March 2019    |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 15 December 2023 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of Osimertinib compared with platinum-based doublet chemotherapy by assessment of Progression Free Survival using investigator assessment according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1)

Protection of trial subjects:

Patients given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 04 August 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 | Korea, Republic of: 72 |
| Country: Number of subjects enrolled | Japan: 63              |
| Country: Number of subjects enrolled | China: 48              |
| Country: Number of subjects enrolled | Taiwan: 48             |
| Country: Number of subjects enrolled | Italy: 25              |
| Country: Number of subjects enrolled | United States: 21      |
| Country: Number of subjects enrolled | Canada: 20             |
| Country: Number of subjects enrolled | Australia: 16          |
| Country: Number of subjects enrolled | Russian Federation: 16 |
| Country: Number of subjects enrolled | Germany: 15            |
| Country: Number of subjects enrolled | United Kingdom: 15     |
| Country: Number of subjects enrolled | Netherlands: 14        |
| Country: Number of subjects enrolled | Spain: 14              |
| Country: Number of subjects enrolled | Hong Kong: 12          |
| Country: Number of subjects enrolled | France: 10             |
| Country: Number of subjects enrolled | Mexico: 5              |
| Country: Number of subjects enrolled | Sweden: 4              |
| Country: Number of subjects enrolled | Hungary: 1             |
| Worldwide total number of subjects   | 419                    |
| EEA total number of subjects         | 83                     |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 242 |
| From 65 to 84 years                       | 174 |
| 85 years and over                         | 3   |

## Subject disposition

### Recruitment

Recruitment details:

First patient dosed: 20 August 2014. Data cut off: 15 March 2019. Open for enrolment at 145 study centres, 126 centres in 17 countries randomised patients to treatment. Following the final OS analysis, patients were permitted to continue to receive treatment if, in the investigator's opinion, they were continuing to receive benefit from treatment

### Pre-assignment

Screening details:

Consenting subjects were assessed to ensure they met eligibility criteria. Confirmation of T790M mutation assessment was determined by the central laboratory.

### 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               |
| <b>Arm title</b>             | Osimertinib 80 mg |

Arm description:

Daily single dose of Osimertinib 80mg

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Osimertinib  |
| Investigational medicinal product code |              |
| Other name                             | AZD9291      |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

40 mg

|  |             |
|--|-------------|
| Investigational medicinal product name | Osimertinib |
| Investigational medicinal product code |             |
| Other name                             | AZD9291     |
| Pharmaceutical forms                   | Tablet      |
| Routes of administration               | Oral use    |

Dosage and administration details:

80 mg

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

Arm description:

Platinum-based doublet chemotherapy

|  |                          |
|--|--------------------------|
| Arm type                               | Active comparator        |
| Investigational medicinal product name | Pemetrexed + Carboplatin |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Injection                |
| Routes of administration               | Intravenous use          |

Dosage and administration details:

Pemetrexed 500 mg/m<sup>2</sup> on Day 1 of every 21-day cycle

Carboplatin AUC5 on Day 1 of every 21-day cycle

|   |                                    |
|---|------------------------------------|
| Investigational medicinal product name                          | Pemetrexed maintenance monotherapy |
| Investigational medicinal product code                          |                                    |
| Other name  |                                    |
| Pharmaceutical forms  | Injection                          |
| Routes of administration  | Intravenous use                    |
| Dosage and administration details:                              |                                    |
| 500 mg/m <sup>2</sup> on Day 1 of every 21-day cycle            |                                    |
| Investigational medicinal product name                          | Pemetrexed + Cisplatin             |
| Investigational medicinal product code                          |                                    |
| Other name  |                                    |
| Pharmaceutical forms  | Injection                          |
| Routes of administration  | Intravenous use                    |
| Dosage and administration details:                              |                                    |
| Pemetrexed 500 mg/m <sup>2</sup> on Day 1 of every 21-day cycle |                                    |
| Cisplatin 75 mg/m <sup>2</sup> on Day 1 of every 21-day cycle   |                                    |

| Number of subjects in period 1     | Osimertinib 80 mg | Chemotherapy     |
|------------------------------------|-------------------|------------------|
| Started                            | 279               | 140              |
| Received randomised treatment only | 279               | 136              |
| Did not receive treatment          | 0 <sup>[1]</sup>  | 4 <sup>[2]</sup> |
| Crossed over Osimertinib           | 0 <sup>[3]</sup>  | 99               |
| Completed                          | 60                | 27               |
| Not completed                      | 219               | 113              |
| Adverse event, serious fatal       | 184               | 88               |
| Consent withdrawn by subject       | 27                | 21               |
| Eligibility criteria not fulfilled | -                 | 1                |
| Other reasons                      | 1                 | 2                |
| Lost to follow-up                  | 7                 | 1                |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Out of the 136 subjects randomised to the chemotherapy arm, 4 subjects did not receive the study treatment.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only subjects randomised to the chemotherapy arm had the opportunity to cross-over and begin treatment with Osimertinib 80 mg once daily

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Confirms that all 279 subjects randomised to the osimertinib arm received treatment.

## Baseline characteristics

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Osimertinib 80 mg |
|-----------------------|-------------------|

Reporting group description:

Daily single dose of Osimertinib 80mg

|                       |              |
|-----------------------|--------------|
| Reporting group title | Chemotherapy |
|-----------------------|--------------|

Reporting group description:

Platinum-based doublet chemotherapy

| Reporting group values                                | Osimertinib 80 mg | Chemotherapy | Total |
|---|-------------------|--------------|-------|
| Number of subjects                                    | 279               | 140          | 419   |
| Age categorical<br>Units: Subjects                    |                   |              |       |
| In utero  | 0                 | 0            | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                 | 0            | 0     |
| Newborns (0-27 days)                                  | 0                 | 0            | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0                 | 0            | 0     |
| Children (2-11 years)                                 | 0                 | 0            | 0     |
| Adolescents (12-17 years)                             | 0                 | 0            | 0     |
| Adults (18-64 years)                                  | 165               | 77           | 242   |
| From 65-84 years                                      | 113               | 61           | 174   |
| 85 years and over                                     | 1                 | 2            | 3     |
| Age Continuous<br>Units: Years                        |                   |              |       |
| arithmetic mean                                       | 61.5              | 62.0         |       |
| standard deviation                                    | ± 11.64           | ± 11.91      | -     |
| Gender, Male/Female<br>Units: Subjects                |                   |              |       |
| Female  | 172               | 97           | 269   |
| Male  | 107               | 43           | 150   |
| Race/Ethnicity, Customized<br>Units: Subjects         |                   |              |       |
| Asian   | 182               | 92           | 274   |
| Black Or African American                             | 4                 | 1            | 5     |
| Other   | 4                 | 1            | 5     |
| White   | 89                | 45           | 134   |
| American Indian or Alaska Native                      | 0                 | 1            | 1     |

## End points

### End points reporting groups

|   |                   |
|---|-------------------|
| Reporting group title   | Osimertinib 80 mg |
| Reporting group description:<br>Daily single dose of Osimertinib 80mg |                   |
| Reporting group title   | Chemotherapy      |
| Reporting group description:<br>Platinum-based doublet chemotherapy   |                   |

### Primary: Progression Free Survival (PFS) by investigator assessment

|   |  |
|---|--|
| End point title   | Progression Free Survival (PFS) by investigator assessment |
| End point description:<br>Per Response Evaluation Criteria in Solid Tumours (RECIST v1.1) assessed by MRI or CT: Progressive Disease (PD): $\geq 20\%$ increase in the sum of diameters of TLs and an absolute increase in sum of diameters of $\geq 5\text{mm}$ (compared to the previous minimum sum) or progression of NTLs or a new lesion. PFS is the time from date of randomisation until the date of PD (by investigator assessment) or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy prior to progression. Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. |  |
| End point type  | Primary  |
| End point timeframe:<br>RECIST tumour assessments every 6 weeks from randomisation until objective disease progression up to 19 months (at the time of the primary PFS analysis).   |  |

| End point values                 | Osimertinib 80 mg  | Chemotherapy       |  |  |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type               | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed      | 279 <sup>[1]</sup> | 140 <sup>[2]</sup> |  |  |
| Units: Months                    |                    |                    |  |  |
| median (confidence interval 95%) | 10.1 (8.3 to 12.3) | 4.4 (4.2 to 5.6)   |  |  |

Notes:

[1] - 140 events analyzed

[2] - 110 events analyzed

### Statistical analyses

|   |                                  |
|---|----------------------------------|
| Statistical analysis title  | Primary Analysis                 |
| Statistical analysis description:<br>Progression Free Survival (PFS) by investigator assessment |                                  |
| Comparison groups   | Osimertinib 80 mg v Chemotherapy |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 419                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[3]</sup> |
| P-value                                 | < 0.001                    |
| Method                                  | Logrank                    |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 0.3                        |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.23                       |
| upper limit                             | 0.41                       |

Notes:

[3] - A hazard ratio <1 favours Osimertinib 80mg

## Secondary: Objective Response Rate (ORR) by investigator assessment

|                        |  |
|------------------------|--|
| End point title        | Objective Response Rate (ORR) by investigator assessment   |
| End point description: | Per Response Evaluation Criteria in Solid Tumours (RECIST v1.1) assessed by MRI or CT: Complete Response (CR): Disappearance of all target and non-target lesions and no new lesions; Partial Response (PR): $\geq 30\%$ decrease in the sum of diameters of Target Lesions (compared to baseline) and no new lesions. ORR is the percentage of patients with at least 1 visit response of CR or PR prior to progression or any further therapy. |
| End point type         | Secondary  |
| End point timeframe:   | RECIST tumour assessments every 6 weeks from randomisation until objective disease progression up to 19 months (at the time of the primary PFS analysis).  |

| End point values            | Osimertinib 80 mg | Chemotherapy    |  |  |
|-----------------------------|-------------------|-----------------|--|--|
| Subject group type          | Reporting group   | Reporting group |  |  |
| Number of subjects analysed | 279               | 140             |  |  |
| Units: % of participants    |                   |                 |  |  |
| number (not applicable)     | 70.6              | 31.4            |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Secondary Analysis                                       |
| Statistical analysis description:       | Objective Response Rate (ORR) by investigator assessment |
| Comparison groups                       | Osimertinib 80 mg v Chemotherapy                         |
| Number of subjects included in analysis | 419  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority <sup>[4]</sup>                               |
| P-value                                 | < 0.001  |
| Method                                  | Regression, Logistic                                     |
| Parameter estimate                      | Odds ratio (OR)  |
| Point estimate                          | 5.39   |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 3.47    |
| upper limit         | 8.48    |

Notes:

[4] - Adjusted for ethnicity (Asian/non-Asian).

Adjusted response rate: Osimertinib 72.8, Chemo 33.1

## Secondary: Duration of Response (DoR) by investigator assessment

|                 |   |
|-----------------|---|
| End point title | Duration of Response (DoR) by investigator assessment |
|-----------------|---|

End point description:

Per Response Evaluation Criteria in Solid Tumours (RECIST v1.1) assessed by MRI or CT: Complete Response (CR): Disappearance of all target and non-target lesions and no new lesions; Partial Response (PR):  $\geq 30\%$  decrease in the sum of diameters of Target Lesions (compared to baseline) and no new lesions. DoR is the time from the date of first documented response until the date of documented progression or death in the absence of disease progression.

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

End point timeframe:

RECIST tumour assessments every 6 weeks from randomisation until objective disease progression up to 19 months (at the time of the primary PFS analysis).

| End point values                 | Osimertinib 80 mg | Chemotherapy     |  |  |
|----------------------------------|-------------------|------------------|--|--|
| Subject group type               | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed      | 279               | 140              |  |  |
| Units: months                    |                   |                  |  |  |
| median (confidence interval 95%) | 9.7 (8.3 to 11.6) | 4.1 (3.0 to 5.6) |  |  |

## Statistical analyses

|                            |                    |
|----------------------------|--------------------|
| Statistical analysis title | Secondary Analysis |
|----------------------------|--------------------|

Statistical analysis description:

Duration of Response (DoR) by investigator assessment

|   |   |
|---|---|
| Comparison groups                       | Osimertinib 80 mg v Chemotherapy        |
| Number of subjects included in analysis | 419                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           |   |
| P-value                                 | < 0.001                                 |
| Method                                  | formulae provided in Ellis S et al 2008 |
| Parameter estimate                      | Ratio of Expected (DoR)                 |
| Point estimate                          | 6.22                                    |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 4.04                                    |
| upper limit                             | 9.57                                    |

## Secondary: Disease Control Rate (DCR) by investigator assessment

|                 |   |
|-----------------|---|
| End point title | Disease Control Rate (DCR) by investigator assessment |
|-----------------|---|

End point description:

Per Response Evaluation Criteria in Solid Tumours (RECIST v1.1) assessed by MRI or CT: Complete Response (CR): Disappearance of all target and non-target lesions and no new lesions; Partial Response (PR):  $\geq 30\%$  decrease in the sum of diameters of Target Lesions (compared to baseline) and no new lesions; Stable disease (SD): Neither sufficient shrinkage to qualify as a response nor sufficient growth to qualify as progression; Progressive Disease (PD):  $\geq 20\%$  increase in the sum of diameters of TLs and an absolute increase in sum of diameters of  $\geq 5\text{mm}$  (compared to the previous minimum sum) or progression of NTLs or a new lesion. DCR is the percentage of patients with best response of CR, PR or SD at  $\geq 6$  weeks, prior to any progressive disease (PD).

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

End point timeframe:

RECIST tumour assessments every 6 weeks from randomisation until objective disease progression up to 19 months (at the time of the primary PFS analysis).

| End point values            | Osimertinib 80 mg | Chemotherapy    |  |  |
|-----------------------------|-------------------|-----------------|--|--|
| Subject group type          | Reporting group   | Reporting group |  |  |
| Number of subjects analysed | 279               | 140             |  |  |
| Units: % of participants    |                   |                 |  |  |
| number (not applicable)     | 93.2              | 74.3            |  |  |

## Statistical analyses

|                            |                    |
|----------------------------|--------------------|
| Statistical analysis title | Secondary Analysis |
|----------------------------|--------------------|

Statistical analysis description:

Disease Control Rate (DCR) by investigator assessment

|                   |                                  |
|-------------------|----------------------------------|
| Comparison groups | Osimertinib 80 mg v Chemotherapy |
|-------------------|----------------------------------|

|   |     |
|---|-----|
| Number of subjects included in analysis | 419 |
|---|-----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |                            |
|---------------|----------------------------|
| Analysis type | superiority <sup>[5]</sup> |
|---------------|----------------------------|

|         |         |
|---------|---------|
| P-value | < 0.001 |
|---------|---------|

|        |                      |
|--------|----------------------|
| Method | Regression, Logistic |
|--------|----------------------|

|                    |                 |
|--------------------|-----------------|
| Parameter estimate | Odds ratio (OR) |
|--------------------|-----------------|

|                |      |
|----------------|------|
| Point estimate | 4.76 |
|----------------|------|

Confidence interval

|       |      |
|-------|------|
| level | 95 % |
|-------|------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|             |      |
|-------------|------|
| lower limit | 2.64 |
|-------------|------|

|             |      |
|-------------|------|
| upper limit | 8.84 |
|-------------|------|

Notes:

[5] - Adjusted response rate: Osimertinib 93.7, Chemo 75.7

## Secondary: Tumour Shrinkage by investigator assessment

|  |   |
|--|---|
| End point title  | Tumour Shrinkage by investigator assessment |
| End point description:<br>Per Response Evaluation Criteria in Solid Tumours (RECIST v1.1) assessed by MRI or CT: Tumour size was calculated as the sum of the longest diameters (SLD) of the Target Lesions. Tumour shrinkage is percentage change in tumour size from baseline using RECIST v1.1 tumour response. |   |
| End point type   | Secondary                                   |
| End point timeframe:<br>RECIST tumour assessments every 6 weeks from randomisation until objective disease progression up to 19 months (at the time of the primary PFS analysis).  |   |

|                                      |                   |                 |  |  |
|--------------------------------------|-------------------|-----------------|--|--|
| <b>End point values</b>              | Osimertinib 80 mg | Chemotherapy    |  |  |
| Subject group type                   | Reporting group   | Reporting group |  |  |
| Number of subjects analysed          | 278               | 131             |  |  |
| Units: % change from baseline        |                   |                 |  |  |
| arithmetic mean (standard deviation) | -46.1 (± 29.50)   | -24.4 (± 29.27) |  |  |

## Statistical analyses

|  |                                  |
|--|----------------------------------|
| <b>Statistical analysis title</b>  | Secondary Analysis               |
| Statistical analysis description:<br>Tumour Shrinkage by investigator assessment |                                  |
| Comparison groups  | Osimertinib 80 mg v Chemotherapy |
| Number of subjects included in analysis  | 409                              |
| Analysis specification   | Pre-specified                    |
| Analysis type  | superiority <sup>[6]</sup>       |
| P-value  | < 0.001                          |
| Method   | ANCOVA                           |
| Parameter estimate   | Difference in LS means           |
| Point estimate   | -21.62                           |
| Confidence interval  |                                  |
| level  | 95 %                             |
| sides  | 2-sided                          |
| lower limit  | -27.71                           |
| upper limit  | -15.52                           |

Notes:

[6] - Covariates for ethnicity (Asian, non-Asian) and the baseline sum of diameters of target lesions.  
LS Mean: Osimertinib -46.93, Chemo -25.3 A difference in LS means <0 favours Osimertinib 80mg.

## Secondary: Overall Survival (OS)

|   |                       |
|---|-----------------------|
| End point title   | Overall Survival (OS) |
| End point description:<br>Time between the date of randomisation and the date of death due to any cause             |                       |
| End point type  | Secondary             |
| End point timeframe:<br>From date of randomisation until time of final OS analysis, a median follow-up of 43 months |                       |

| End point values            | Osimertinib 80 mg  | Chemotherapy       |  |  |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type          | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed | 279 <sup>[7]</sup> | 140 <sup>[8]</sup> |  |  |
| Units: Participants         |                    |                    |  |  |
| Died                        | 188                | 93                 |  |  |
| Still in survival follow-up | 58                 | 27                 |  |  |
| Terminated prior to death   | 30                 | 17                 |  |  |
| Other                       | 3                  | 3                  |  |  |

Notes:

[7] - 188 events analyzed

[8] - 93 events analyzed

### Statistical analyses

| Statistical analysis title              | Secondary Analysis               |
|---|----------------------------------|
| Statistical analysis description:       |                                  |
| Overall Survival (OS)                   |                                  |
| Comparison groups                       | Osimertinib 80 mg v Chemotherapy |
| Number of subjects included in analysis | 419                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority <sup>[9]</sup>       |
| P-value                                 | = 0.277                          |
| Method                                  | Logrank                          |
| Parameter estimate                      | Hazard ratio (HR)                |
| Point estimate                          | 0.87                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 0.67                             |
| upper limit                             | 1.13                             |

Notes:

[9] - A hazard ratio <1 favours Osimertinib 80 mg

### Other pre-specified: Time to first subsequent therapy (TFST)

|  |   |
|--|---|
| End point title  | Time to first subsequent therapy (TFST) |
| End point description:   |   |
| Time from randomisation to first subsequent anti-cancer therapy (FST) following randomised treatment discontinuation, or death if no FST administered. Any patient not known to have died nor received any subsequent anti-cancer therapy (ST) was censored at the last time known not to have received ST, ie, the last follow-up visit this was confirmed. |   |
| End point type   | Other pre-specified                     |
| End point timeframe:   |   |
| From date of randomisation until time of final OS analysis   |   |

|  |                     |                     |  |  |
|--|---------------------|---------------------|--|--|
| <b>End point values</b>                            | Osimertinib 80 mg   | Chemotherapy        |  |  |
| Subject group type                                 | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                        | 279 <sup>[10]</sup> | 140 <sup>[11]</sup> |  |  |
| Units: Participants                                |                     |                     |  |  |
| Started 1st subsequent cancer therapy              | 165                 | 114                 |  |  |
| Did not start 1st subsequent cancer therapy (died) | 65                  | 14                  |  |  |

Notes:

[10] - 230 events analyzed

[11] - 128 events analyzed

## Statistical analyses

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | Other                            |
| Statistical analysis description:       |                                  |
| Time to first subsequent therapy (TFST) |                                  |
| Comparison groups                       | Osimertinib 80 mg v Chemotherapy |
| Number of subjects included in analysis | 419                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority <sup>[12]</sup>      |
| P-value                                 | < 0.001                          |
| Method                                  | Logrank                          |
| Parameter estimate                      | Hazard ratio (HR)                |
| Point estimate                          | 0.21                             |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 0.16                             |
| upper limit                             | 0.28                             |

Notes:

[12] - A hazard ratio <1 favours Osimertinib 80 mg

## Other pre-specified: Time to second subsequent therapy (TSST)

|  |  |
|--|--|
| End point title  | Time to second subsequent therapy (TSST) |
| End point description:   |  |
| Time from randomisation to second subsequent anti-cancer therapy (SST) following randomised treatment discontinuation, or death if no SST administered. Any patient not known to have died nor received any SST was censored at the last time known not to have received SST, ie, the last follow-up visit this was confirmed. |  |
| End point type   | Other pre-specified                      |
| End point timeframe:   |  |
| From date of randomisation until time of final OS analysis   |  |

| End point values                                   | Osimertinib 80 mg   | Chemotherapy        |  |  |
|--|---------------------|---------------------|--|--|
| Subject group type                                 | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                        | 279 <sup>[13]</sup> | 140 <sup>[14]</sup> |  |  |
| Units: Participants                                |                     |                     |  |  |
| Started 2nd subsequent cancer therapy              | 108                 | 52                  |  |  |
| Did not start 2nd subsequent cancer therapy (died) | 106                 | 53                  |  |  |

Notes:

[13] - 214 events analyzed

[14] - 105 events analyzed

## Statistical analyses

| Statistical analysis title               | Other                            |
|--|----------------------------------|
| Statistical analysis description:        |                                  |
| Time to second subsequent therapy (TSST) |                                  |
| Comparison groups                        | Osimertinib 80 mg v Chemotherapy |
| Number of subjects included in analysis  | 419                              |
| Analysis specification                   | Pre-specified                    |
| Analysis type                            | superiority <sup>[15]</sup>      |
| P-value                                  | < 0.001                          |
| Method                                   | Logrank                          |
| Parameter estimate                       | Hazard ratio (HR)                |
| Point estimate                           | 0.87                             |
| Confidence interval                      |                                  |
| level                                    | 95 %                             |
| sides                                    | 2-sided                          |
| lower limit                              | 0.69                             |
| upper limit                              | 1.11                             |

Notes:

[15] - A hazard ratio <1 favours Osimertinib 80 mg

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs from start of study drug until 28 days post treatment discontinuation up to 4 years and 7 months (at the time of analysis)

Adverse event reporting additional description:

Systematic assessment due to regular investigator assessment at study visits.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Chemotherapy |
|-----------------------|--------------|

Reporting group description:

Platinum-based doublet chemotherapy

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Osimertinib 80 mg |
|-----------------------|-------------------|

Reporting group description:

Daily single dose of Osimertinib 80mg

| Serious adverse events  | Chemotherapy      | Osimertinib 80 mg |  |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                   |                   |  |
| subjects affected / exposed   | 36 / 136 (26.47%) | 84 / 279 (30.11%) |  |
| number of deaths (all causes)                                       | 93                | 188               |  |
| number of deaths resulting from adverse events                      | 2                 | 12                |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Basal cell carcinoma  |                   |                   |  |
| subjects affected / exposed   | 0 / 136 (0.00%)   | 1 / 279 (0.36%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Invasive breast carcinoma   |                   |                   |  |
| subjects affected / exposed   | 0 / 136 (0.00%)   | 1 / 279 (0.36%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Vascular disorders  |                   |                   |  |
| Deep vein thrombosis  |                   |                   |  |
| subjects affected / exposed   | 4 / 136 (2.94%)   | 1 / 279 (0.36%)   |  |
| occurrences causally related to treatment / all                     | 0 / 4             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Hypovolaemic shock                                   |                 |                 |  |
| subjects affected / exposed                          | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 1 / 1           | 0 / 0           |  |
| Peripheral arterial occlusive disease                |                 |                 |  |
| subjects affected / exposed                          | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Non-cardiac chest pain                               |                 |                 |  |
| subjects affected / exposed                          | 2 / 136 (1.47%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Asthenia   |                 |                 |  |
| subjects affected / exposed                          | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Chest discomfort                                     |                 |                 |  |
| subjects affected / exposed                          | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pyrexia  |                 |                 |  |
| subjects affected / exposed                          | 2 / 136 (1.47%) | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General physical health deterioration                |                 |                 |  |
| subjects affected / exposed                          | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           |  |
| Immune system disorders                              |                 |                 |  |
| Contrast media allergy                               |                 |                 |  |
| subjects affected / exposed                          | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Reproductive system and breast disorders        |                 |                 |  |
| Uterine cyst                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Lung consolidation                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 2 / 2           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 4 / 279 (1.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Interstitial lung disease                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 136 (1.47%) | 8 / 279 (2.87%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 3 / 279 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 3           |  |
| Dyspnoea exertional                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Bipolar disorder                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric decompensation                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Organic brain syndrome                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anxiety   |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Electrocardiogram QT prolonged                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fibrin D dimer increased                        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemoglobin decreased                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood bilirubin increased                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gamma-glutamyltransferase increased             |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Hip fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Road traffic accident                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subdural haematoma                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pharynx radiation injury                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pericardial effusion                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial thrombosis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac tamponade                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Epilepsy  |                 |                 |  |
| subjects affected / exposed                     | 3 / 136 (2.21%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure   |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral infarction                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 136 (0.74%) | 3 / 279 (1.08%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 3           |  |
| Embolitic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Spinal cord compression                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sciatica  |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 136 (2.21%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Disseminated intravascular coagulation          |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile neutropenia                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Leukopenia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Leukocytosis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Vertigo   |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Intestinal ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Ascites   |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorder                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 2 / 136 (1.47%) | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 4 / 279 (1.43%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Dental caries                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus   |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestine polyp                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatitis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Flank pain                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscular weakness                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Musculoskeletal chest pain                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteonecrosis of jaw                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 6 / 279 (2.15%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchiolitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterocolitis infectious                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatitis B                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumocystis jirovecii pneumonia                |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia bacterial                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tuberculosis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacterial infection                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis viral                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Periodontitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory tract infection                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 279 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 136 (1.47%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus inadequate control            |                 |                 |  |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 279 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperuricaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 279 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Chemotherapy       | Osimertinib 80 mg  |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 134 / 136 (98.53%) | 275 / 279 (98.57%) |  |
| Vascular disorders                                    |                    |                    |  |
| Hypertension  |                    |                    |  |
| subjects affected / exposed                           | 10 / 136 (7.35%)   | 9 / 279 (3.23%)    |  |
| occurrences (all)                                     | 11                 | 10                 |  |
| General disorders and administration site conditions  |                    |                    |  |
| Oedema peripheral                                     |                    |                    |  |
| subjects affected / exposed                           | 16 / 136 (11.76%)  | 16 / 279 (5.73%)   |  |
| occurrences (all)                                     | 23                 | 21                 |  |
| Pyrexia   |                    |                    |  |
| subjects affected / exposed                           | 13 / 136 (9.56%)   | 29 / 279 (10.39%)  |  |
| occurrences (all)                                     | 15                 | 36                 |  |
| Non-cardiac chest pain                                |                    |                    |  |

|  |                         |                         |  |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 6 / 136 (4.41%)<br>6    | 23 / 279 (8.24%)<br>24  |  |
| Malaise<br>subjects affected / exposed<br>occurrences (all)  | 14 / 136 (10.29%)<br>21 | 12 / 279 (4.30%)<br>14  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)  | 40 / 136 (29.41%)<br>60 | 54 / 279 (19.35%)<br>66 |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)   | 19 / 136 (13.97%)<br>25 | 23 / 279 (8.24%)<br>29  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 20 / 136 (14.71%)<br>21 | 60 / 279 (21.51%)<br>72 |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 18 / 136 (13.24%)<br>20 | 35 / 279 (12.54%)<br>40 |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)  | 3 / 136 (2.21%)<br>3    | 20 / 279 (7.17%)<br>21  |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)  | 2 / 136 (1.47%)<br>2    | 14 / 279 (5.02%)<br>18  |  |
| Productive cough<br>subjects affected / exposed<br>occurrences (all)   | 3 / 136 (2.21%)<br>3    | 18 / 279 (6.45%)<br>20  |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                        | 14 / 136 (10.29%)<br>16 | 26 / 279 (9.32%)<br>28  |  |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)     | 17 / 136 (12.50%)<br>25 | 23 / 279 (8.24%)<br>34  |  |
| Aspartate aminotransferase increased   |                         |                         |  |

|                                      |                   |                   |  |
|--------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed          | 16 / 136 (11.76%) | 21 / 279 (7.53%)  |  |
| occurrences (all)                    | 23                | 33                |  |
| Blood creatinine increased           |                   |                   |  |
| subjects affected / exposed          | 9 / 136 (6.62%)   | 16 / 279 (5.73%)  |  |
| occurrences (all)                    | 15                | 20                |  |
| Neutrophil count decreased           |                   |                   |  |
| subjects affected / exposed          | 16 / 136 (11.76%) | 17 / 279 (6.09%)  |  |
| occurrences (all)                    | 38                | 31                |  |
| Platelet count decreased             |                   |                   |  |
| subjects affected / exposed          | 21 / 136 (15.44%) | 20 / 279 (7.17%)  |  |
| occurrences (all)                    | 34                | 32                |  |
| Weight decreased                     |                   |                   |  |
| subjects affected / exposed          | 7 / 136 (5.15%)   | 16 / 279 (5.73%)  |  |
| occurrences (all)                    | 7                 | 17                |  |
| White blood cell count decreased     |                   |                   |  |
| subjects affected / exposed          | 12 / 136 (8.82%)  | 22 / 279 (7.89%)  |  |
| occurrences (all)                    | 36                | 38                |  |
| Nervous system disorders             |                   |                   |  |
| Dizziness                            |                   |                   |  |
| subjects affected / exposed          | 12 / 136 (8.82%)  | 22 / 279 (7.89%)  |  |
| occurrences (all)                    | 16                | 26                |  |
| Dysgeusia                            |                   |                   |  |
| subjects affected / exposed          | 12 / 136 (8.82%)  | 9 / 279 (3.23%)   |  |
| occurrences (all)                    | 13                | 9                 |  |
| Headache                             |                   |                   |  |
| subjects affected / exposed          | 16 / 136 (11.76%) | 33 / 279 (11.83%) |  |
| occurrences (all)                    | 19                | 44                |  |
| Blood and lymphatic system disorders |                   |                   |  |
| Anaemia                              |                   |                   |  |
| subjects affected / exposed          | 35 / 136 (25.74%) | 32 / 279 (11.47%) |  |
| occurrences (all)                    | 45                | 38                |  |
| Neutropenia                          |                   |                   |  |
| subjects affected / exposed          | 17 / 136 (12.50%) | 14 / 279 (5.02%)  |  |
| occurrences (all)                    | 26                | 24                |  |
| Thrombocytopenia                     |                   |                   |  |

|                             |                   |                    |  |
|-----------------------------|-------------------|--------------------|--|
| subjects affected / exposed | 10 / 136 (7.35%)  | 18 / 279 (6.45%)   |  |
| occurrences (all)           | 15                | 30                 |  |
| Leukopenia                  |                   |                    |  |
| subjects affected / exposed | 7 / 136 (5.15%)   | 14 / 279 (5.02%)   |  |
| occurrences (all)           | 12                | 33                 |  |
| Ear and labyrinth disorders |                   |                    |  |
| Tinnitus                    |                   |                    |  |
| subjects affected / exposed | 7 / 136 (5.15%)   | 2 / 279 (0.72%)    |  |
| occurrences (all)           | 7                 | 2                  |  |
| Eye disorders               |                   |                    |  |
| Lacrimation increased       |                   |                    |  |
| subjects affected / exposed | 8 / 136 (5.88%)   | 1 / 279 (0.36%)    |  |
| occurrences (all)           | 10                | 1                  |  |
| Gastrointestinal disorders  |                   |                    |  |
| Constipation                |                   |                    |  |
| subjects affected / exposed | 48 / 136 (35.29%) | 50 / 279 (17.92%)  |  |
| occurrences (all)           | 94                | 56                 |  |
| Abdominal pain upper        |                   |                    |  |
| subjects affected / exposed | 11 / 136 (8.09%)  | 10 / 279 (3.58%)   |  |
| occurrences (all)           | 11                | 13                 |  |
| Diarrhoea                   |                   |                    |  |
| subjects affected / exposed | 14 / 136 (10.29%) | 123 / 279 (44.09%) |  |
| occurrences (all)           | 21                | 226                |  |
| Vomiting                    |                   |                    |  |
| subjects affected / exposed | 27 / 136 (19.85%) | 42 / 279 (15.05%)  |  |
| occurrences (all)           | 49                | 53                 |  |
| Stomatitis                  |                   |                    |  |
| subjects affected / exposed | 22 / 136 (16.18%) | 48 / 279 (17.20%)  |  |
| occurrences (all)           | 26                | 70                 |  |
| Nausea                      |                   |                    |  |
| subjects affected / exposed | 66 / 136 (48.53%) | 64 / 279 (22.94%)  |  |
| occurrences (all)           | 144               | 75                 |  |
| Mouth ulceration            |                   |                    |  |
| subjects affected / exposed | 0 / 136 (0.00%)   | 16 / 279 (5.73%)   |  |
| occurrences (all)           | 0                 | 26                 |  |
| Abdominal pain              |                   |                    |  |

|  |                         |                         |  |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                               | 6 / 136 (4.41%)<br>9    | 20 / 279 (7.17%)<br>22  |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 136 (1.47%)<br>2    | 15 / 279 (5.38%)<br>18  |  |
| Skin and subcutaneous tissue disorders   |                         |                         |  |
| Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all)        | 3 / 136 (2.21%)<br>3    | 19 / 279 (6.81%)<br>25  |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)                   | 7 / 136 (5.15%)<br>9    | 42 / 279 (15.05%)<br>55 |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)                   | 6 / 136 (4.41%)<br>6    | 54 / 279 (19.35%)<br>66 |  |
| Dermatitis acneiform<br>subjects affected / exposed<br>occurrences (all)       | 3 / 136 (2.21%)<br>3    | 41 / 279 (14.70%)<br>70 |  |
| Skin fissures<br>subjects affected / exposed<br>occurrences (all)              | 1 / 136 (0.74%)<br>1    | 16 / 279 (5.73%)<br>18  |  |
| Musculoskeletal and connective tissue disorders                                |                         |                         |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                 | 7 / 136 (5.15%)<br>8    | 25 / 279 (8.96%)<br>30  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                  | 14 / 136 (10.29%)<br>20 | 42 / 279 (15.05%)<br>52 |  |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all) | 8 / 136 (5.88%)<br>8    | 21 / 279 (7.53%)<br>25  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)          | 6 / 136 (4.41%)<br>11   | 25 / 279 (8.96%)<br>31  |  |
| Musculoskeletal pain   |                         |                         |  |



|                                    |                   |                   |  |
|------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed        | 4 / 136 (2.94%)   | 21 / 279 (7.53%)  |  |
| occurrences (all)                  | 4                 | 27                |  |
| Muscle spasms                      |                   |                   |  |
| subjects affected / exposed        | 2 / 136 (1.47%)   | 19 / 279 (6.81%)  |  |
| occurrences (all)                  | 2                 | 22                |  |
| Infections and infestations        |                   |                   |  |
| Nasopharyngitis                    |                   |                   |  |
| subjects affected / exposed        | 7 / 136 (5.15%)   | 34 / 279 (12.19%) |  |
| occurrences (all)                  | 7                 | 45                |  |
| Paronychia                         |                   |                   |  |
| subjects affected / exposed        | 2 / 136 (1.47%)   | 58 / 279 (20.79%) |  |
| occurrences (all)                  | 2                 | 72                |  |
| Upper respiratory tract infection  |                   |                   |  |
| subjects affected / exposed        | 10 / 136 (7.35%)  | 36 / 279 (12.90%) |  |
| occurrences (all)                  | 10                | 61                |  |
| Urinary tract infection            |                   |                   |  |
| subjects affected / exposed        | 6 / 136 (4.41%)   | 24 / 279 (8.60%)  |  |
| occurrences (all)                  | 9                 | 32                |  |
| Conjunctivitis                     |                   |                   |  |
| subjects affected / exposed        | 5 / 136 (3.68%)   | 14 / 279 (5.02%)  |  |
| occurrences (all)                  | 6                 | 17                |  |
| Metabolism and nutrition disorders |                   |                   |  |
| Decreased appetite                 |                   |                   |  |
| subjects affected / exposed        | 49 / 136 (36.03%) | 67 / 279 (24.01%) |  |
| occurrences (all)                  | 87                | 78                |  |
| Hypoalbuminaemia                   |                   |                   |  |
| subjects affected / exposed        | 7 / 136 (5.15%)   | 4 / 279 (1.43%)   |  |
| occurrences (all)                  | 9                 | 6                 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 22 December 2014 | V2. Addition post-progression open label Osimertinib for subjects on chemotherapy.   |
| 06 May 2015      | V3. Change the power to detect a statistically significant difference for the primary analysis of progression-free survival (PFS) from 90% to 80%. |
| 21 March 2016    | V4. Additional OS analysis, based on a data cut-off 4 months after the data cut-off for the primary analysis of PFS.                               |
| 10 January 2017  | V5. Post primary PFS analysis data collection schedule reduced. Patient management post final OS analysis outlined.                                |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported