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:

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

Arm title	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/m2 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/m2 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/m2 on Day 1 of every 21-day cycle
Cisplatin 75 mg/m2 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 [1]	4 [2]
Crossed over Osimertinib	0 [3]	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 Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 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 Units: Years			
arithmetic mean	61.5	62.0	
standard deviation	± 11.64	± 11.91	-
Gender, Male/Female Units: Subjects			
Female	172	97	269
Male	107	43	150
Race/Ethnicity, Customized 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: Daily single dose of Osimertinib 80mg	
Reporting group title	Chemotherapy
Reporting group description: 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:

Per Response Evaluation Criteria in Solid Tumours (RECIST v1.1) assessed by MRI or CT: Progressive Disease (PD): >= 20% increase in the sum of diameters of TLs and an absolute increase in sum of diameters of >=5mm (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:

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[1]	140[2]		
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: 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[3]
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: 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): >= 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: 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): >= 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[4]
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: 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): >= 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): >= 20% increase in the sum of diameters of TLs and an absolute increase in sum of diameters of >=5mm (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 >=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[5]
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:

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:

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	278	131		
Units: % change from baseline				
arithmetic mean (standard deviation)	-46.1 (± 29.50)	-24.4 (± 29.27)		

Statistical analyses

Statistical analysis title	Secondary Analysis

Statistical analysis description:

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[6]
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:

Time between the date of randomisation and the date of death due to any cause

End point type	Secondary

End point timeframe:

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[7]	140[8]		
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[9]
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

End point values	Osimertinib 80 mg	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	279[10]	140[11]		
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

Statistical analysis title	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[12]
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[13]	140[14]		
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[15]
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 deterioratio			
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	
Embolic 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 %

Non-serious adverse events	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	6 / 136 (4.41%)	23 / 279 (8.24%)	
occurrences (all)	6	24	
Malaise			
subjects affected / exposed	14 / 136 (10.29%)	12 / 279 (4.30%)	
occurrences (all)	21	14	
Fatigue			
subjects affected / exposed	40 / 136 (29.41%)	54 / 279 (19.35%)	
occurrences (all)	60	66	
Asthenia			
subjects affected / exposed	19 / 136 (13.97%)	23 / 279 (8.24%)	
occurrences (all)	25	29	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 136 (14.71%)	60 / 279 (21.51%)	
occurrences (all)	21	72	
Dyspnoea			
subjects affected / exposed	18 / 136 (13.24%)	35 / 279 (12.54%)	
occurrences (all)	20	40	
Epistaxis			
subjects affected / exposed	3 / 136 (2.21%)	20 / 279 (7.17%)	
occurrences (all)	3	21	
Rhinorrhoea			
subjects affected / exposed	2 / 136 (1.47%)	14 / 279 (5.02%)	
occurrences (all)	2	18	
Productive cough			
subjects affected / exposed	3 / 136 (2.21%)	18 / 279 (6.45%)	
occurrences (all)	3	20	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 136 (10.29%)	26 / 279 (9.32%)	
occurrences (all)	16	28	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	17 / 136 (12.50%)	23 / 279 (8.24%)	
occurrences (all)	25	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	6 / 136 (4.41%)	20 / 279 (7.17%)	
occurrences (all)	9	22	
Dyspepsia			
subjects affected / exposed	2 / 136 (1.47%)	15 / 279 (5.38%)	
occurrences (all)	2	18	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	3 / 136 (2.21%)	19 / 279 (6.81%)	
occurrences (all)	3	25	
Pruritus			
subjects affected / exposed	7 / 136 (5.15%)	42 / 279 (15.05%)	
occurrences (all)	9	55	
Dry skin			
subjects affected / exposed	6 / 136 (4.41%)	54 / 279 (19.35%)	
occurrences (all)	6	66	
Dermatitis acneiform			
subjects affected / exposed	3 / 136 (2.21%)	41 / 279 (14.70%)	
occurrences (all)	3	70	
Skin fissures			
subjects affected / exposed	1 / 136 (0.74%)	16 / 279 (5.73%)	
occurrences (all)	1	18	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 136 (5.15%)	25 / 279 (8.96%)	
occurrences (all)	8	30	
Back pain			
subjects affected / exposed	14 / 136 (10.29%)	42 / 279 (15.05%)	
occurrences (all)	20	52	
Musculoskeletal chest pain			
subjects affected / exposed	8 / 136 (5.88%)	21 / 279 (7.53%)	
occurrences (all)	8	25	
Pain in extremity			
subjects affected / exposed	6 / 136 (4.41%)	25 / 279 (8.96%)	
occurrences (all)	11	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 anlysis data collection schedule reduced. Patient management post final OS analysis outlined.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported