



Clinical trial results:

Open Label, Multinational, Multicenter, Real-World Treatment Study of Single Agent AZD9291 for Patients with Advanced/Metastatic Epidermal Growth Factor Receptor (EGFR) T790M Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) Who Have Received Prior Therapy with an EGFR Tyrosine Kinase Inhibitor (EGFR-TKI)

Summary

EudraCT number	2015-001407-31
Trial protocol	SE BE IT AT DK ES IE
Global end of trial date	18 April 2019

Results information

Result version number	v1 (current)
This version publication date	28 August 2021
First version publication date	28 August 2021

Trial information

Trial identification

Sponsor protocol code	D5160C00022
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02474355
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Södertälje, Södertälje, Sweden, 151 85
Public contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, 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	Final
Date of interim/final analysis	10 February 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of single agent AZD9291 in a real world setting in adult patients with advanced or metastatic, epidermal growth factor receptor (EGFR) T790M mutation-positive Non-Small Cell Lung Cancer (NSCLC), who have received prior EGFR-tyrosine kinase inhibitor (TKI) therapy.

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 2015
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	Argentina: 30
Country: Number of subjects enrolled	Australia: 31
Country: Number of subjects enrolled	Austria: 46
Country: Number of subjects enrolled	Belgium: 31
Country: Number of subjects enrolled	Brazil: 88
Country: Number of subjects enrolled	Canada: 99
Country: Number of subjects enrolled	China: 1350
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Ireland: 10
Country: Number of subjects enrolled	Italy: 510
Country: Number of subjects enrolled	Saudi Arabia: 3
Country: Number of subjects enrolled	Korea, Republic of: 466
Country: Number of subjects enrolled	Spain: 131
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Taiwan: 188
Country: Number of subjects enrolled	United Kingdom: 18
Worldwide total number of subjects	3014
EEA total number of subjects	741

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)	1798
From 65 to 84 years	1185
85 years and over	31

Subject disposition

Recruitment

Recruitment details:

Participants who met all the inclusion and none of the exclusion criteria received treatment in a total of 209 centres in 16 countries. The study started on 18 September 2015 and primary completion date was 18 April 2019.

Pre-assignment

Screening details:

During the screening period (28 days), eligible participants signed the informed consent. All the study assessments were performed as per the schedule of assessment.

Period 1

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

Arms

Arm title	Osimertinib
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Arm description:

All participants received oral 80 mg tablet once a day (the dose could be reduced to 40 mg for management of osimertinib-related toxicities)

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:

All participants received oral 80 mg tablet once a day (the dose could be reduced to 40 mg for management of osimertinib-related toxicities).

Number of subjects in period 1	Osimertinib
Started	3014
Completed	1386
Not completed	1628
Consent withdrawn by subject	124
Eligibility Criteria not Fulfilled	2
Other	43
Death	1361
Lost to follow-up	98

Baseline characteristics

Reporting groups

Reporting group title	Osimertinib
Reporting group description:	
All participants received oral 80 mg tablet once a day (the dose could be reduced to 40 mg for management of osimertinib-related toxicities)	

Reporting group values	Osimertinib	Total	
Number of subjects	3014	3014	
Age Categorical			
Units: Participants			
<=18 years	0	0	
Between 18 and 65 years	1798	1798	
>=65 years	1216	1216	
Age Continuous			
Units: Years			
arithmetic mean	61.7		
standard deviation	± 10.91	-	
Sex: Female, Male			
Units: Participants			
Female	1927	1927	
Male	1087	1087	
Country			
Units: Subjects			
Argentina	30	30	
Australia	31	31	
Austria	46	46	
Belgium	31	31	
Brazil	88	88	
Canada	99	99	
China	1350	1350	
Denmark	6	6	
Ireland	10	10	
Italy	510	510	
Saudi Arabia	3	3	
South Korea	466	466	
Spain	131	131	
Sweden	7	7	
Taiwan	188	188	
United Kingdom	18	18	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	2085	2085	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	21	21	
White	897	897	

More than one race	0	0	
Unknown or Not Reported	11	11	

End points

End points reporting groups

Reporting group title	Osimertinib
Reporting group description: All participants received oral 80 mg tablet once a day (the dose could be reduced to 40 mg for management of osimertinib-related toxicities)	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS) ^[1]
End point description: OS was defined as the time, in months from the date of first dose of Osimertinib until death due to any cause, or at last documented contact with participant status "alive" (in this study any participants alive at study discontinuation, or lost to follow-up was considered being censored at study discontinuation date or at the last known date participant was alive). OS was summarized using a Kaplan-Meier (KM) estimate of the median time to death or censoring together with their 95% confidence intervals.	
End point type	Primary
End point timeframe: From the date of first dose of Osimertinib until the date of death (due to any cause) or last participant contact [up to 43 months]	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical tests were performed, the statistical analyses were descriptive.	

End point values	Osimertinib			
Subject group type	Reporting group			
Number of subjects analysed	3014			
Units: Months				
median (confidence interval 95%)	22.8 (21.6 to 23.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with serious adverse events (SAEs), AEs leading to dose modification, AEs leading to discontinuation, AEs of special interest (AESIs)

End point title	Number of participants with serious adverse events (SAEs), AEs leading to dose modification, AEs leading to discontinuation, AEs of special interest (AESIs) ^[2]
End point description: Safety assessment of Osimertinib was analyzed by evaluating SAEs, AEs leading to dose modification, AEs leading to discontinuation, AESIs.	
End point type	Primary
End point timeframe: From screening to progression follow-up [every 6 weeks ($\pm$ 1 week) relative to the date of enrolment until end of study]	

Notes:

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

Justification: No statistical tests were performed, the statistical analyses were descriptive.

End point values	Osimertinib			
Subject group type	Reporting group			
Number of subjects analysed	3014			
Units: Participants				
AE of special interest (AESI) or SAE	923			
AESI or SAE a causally related to Osimertinib	338			
AE leading to dose modification	414			
AE leading to discontinuation	191			
AESI	113			
AESI causally related to Osimertinib	89			
SAE	657			
SAE causally related to Osimertinib	95			
AE leading to death	152			
AE leading to death related to Osimertinib	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival
End point description:	
PFS was defined as the time, in months from first dose of Osimertinib until the date of disease progression or death in the absence of progression. Participants who had not progressed or died at study discontinuation were censored at the time of the latest date of disease assessment. PFS was summarized using KM estimates of the median time to progression or death with their 95% confidence intervals.	
End point type	Secondary
End point timeframe:	
From the date of first dose of Osimertinib until disease progression or death in the absence of progression [up to 43 months]	

End point values	Osimertinib			
Subject group type	Reporting group			
Number of subjects analysed	3014			
Units: Months				
median (confidence interval 95%)	11.1 (11.0 to 12.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Discontinuation (TTD)

End point title	Time to Treatment Discontinuation (TTD)
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End point description:

TTD or death was assessed as a supportive summary to PFS and defined as the time from the date of the first dose of osimertinib in the study until the date of osimertinib discontinuation or death, regardless of the reason for discontinuation. TTD was summarized using KM estimates of the median times to progression or death or treatment discontinuation.

End point type	Secondary
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End point timeframe:

From the date of first dose of Osimertinib until disease progression or death in the absence of progression [up to 43 months]

End point values	Osimertinib			
Subject group type	Reporting group			
Number of subjects analysed	3014			
Units: Months				
median (confidence interval 95%)	13.5 (12.6 to 13.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate (RR)

End point title	Response rate (RR)
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End point description:

RR was defined as the number (%) of participants with a best response (by Investigator assessment) of 'responding', regardless of the method of evaluation, and was based on a subset of the full analysis set consisting of subjects with at least one documented response assessment. RR was summarised together with the 95% CI.

End point type	Secondary
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End point timeframe:

From the date of first dose of Osimertinib until disease progression or death in the absence of progression [up to 43 months]

End point values	Osimertinib			
Subject group type	Reporting group			
Number of subjects analysed	3014			
Units: Percentage				
number (confidence interval 95%)	57.3 (55.5 to 59.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening to progression follow-up [every 6 weeks ($\pm$ 1 week) relative to the date of enrolment until end of study]

Adverse event reporting additional description:

Safety of AZD9291 by assessment of SAEs, AEs of special interest (AESI) [Interstitial Lung Disease/pneumonitis-like events, and QTc prolongation events].

This study did not collect all AEs; only SAEs, adverse events leading to dose modification, adverse events leading to treatment discontinuation and AESI were collected.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	Osimertinib
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Reporting group description:

All participants received oral 80 mg tablet once a day (the dose could be reduced to 40 mg for management of osimertinib-related toxicities).

Serious adverse events	Osimertinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	657 / 3014 (21.80%)		
number of deaths (all causes)	1361		
number of deaths resulting from adverse events	19		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute myeloid leukaemia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Malignant pleural effusion			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Acute promyelocytic leukaemia subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Benign breast neoplasm subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bladder cancer recurrent subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bladder neoplasm subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bladder transitional cell carcinoma subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Breast cancer female subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Glioblastoma subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to bone subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to central nervous system				

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngeal cancer			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to meninges			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal carcinoma			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transitional cell carcinoma			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Uterine leiomyoma			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cancer metastatic			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	17 / 3014 (0.56%)		
occurrences causally related to treatment / all	2 / 18		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis limb			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior vena cava occlusion			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Superior vena cava syndrome			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vena cava thrombosis			

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Unintended pregnancy			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	34 / 3014 (1.13%)		
occurrences causally related to treatment / all	1 / 34		
deaths causally related to treatment / all	1 / 34		
Asthenia			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	12 / 3014 (0.40%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 0		
Gait disturbance			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Sudden death			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Chest discomfort			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Condition aggravated			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cyst			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Granuloma			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden cardiac death			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Reproductive system and breast disorders			

Benign prostatic hyperplasia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endometrial hyperplasia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic pain			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostatic obstruction			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vaginal haemorrhage			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	49 / 3014 (1.63%)		
occurrences causally related to treatment / all	5 / 49		
deaths causally related to treatment / all	3 / 13		
Pleural effusion			
subjects affected / exposed	20 / 3014 (0.66%)		
occurrences causally related to treatment / all	1 / 25		
deaths causally related to treatment / all	0 / 0		

Dyspnoea				
subjects affected / exposed	15 / 3014 (0.50%)			
occurrences causally related to treatment / all	2 / 15			
deaths causally related to treatment / all	0 / 1			
Respiratory failure				
subjects affected / exposed	11 / 3014 (0.36%)			
occurrences causally related to treatment / all	2 / 11			
deaths causally related to treatment / all	2 / 9			
Interstitial lung disease				
subjects affected / exposed	9 / 3014 (0.30%)			
occurrences causally related to treatment / all	7 / 9			
deaths causally related to treatment / all	3 / 4			
Pneumonitis				
subjects affected / exposed	9 / 3014 (0.30%)			
occurrences causally related to treatment / all	6 / 9			
deaths causally related to treatment / all	0 / 1			
Asphyxia				
subjects affected / exposed	4 / 3014 (0.13%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 3			
Pneumothorax				
subjects affected / exposed	5 / 3014 (0.17%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	4 / 3014 (0.13%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	4 / 3014 (0.13%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Bronchitis chronic				

subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchial haemorrhage				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Acute interstitial pneumonitis				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Asthma				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchiectasis				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Emphysema				

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laryngeal oedema			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleuritic pain			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary toxicity			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory arrest			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Delirium			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Depression			

subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Breath holding			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device dislocation			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Amylase increased			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase			

increased			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza A virus test			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lipase increased			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Troponin increased			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	8 / 3014 (0.27%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Lumbar vertebral fracture				
subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Traumatic fracture				
subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Multiple injuries				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				

subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ankle fracture				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brain herniation				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Compression fracture				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Foreign body in respiratory tract				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiation pneumonitis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haemorrhage			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulnar nerve injury			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	9 / 3014 (0.30%)		
occurrences causally related to treatment / all	1 / 10		
deaths causally related to treatment / all	1 / 3		
Cardiac arrest			
subjects affected / exposed	6 / 3014 (0.20%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 5		
Myocardial infarction			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 1		
Cardiac failure congestive			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			

subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Cardiomyopathy				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Arrhythmia				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorder				

subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac dysfunction				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failure				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiotoxicity				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Congestive cardiomyopathy				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hypertensive heart disease				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular fibrillation			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	22 / 3014 (0.73%)		
occurrences causally related to treatment / all	5 / 22		
deaths causally related to treatment / all	2 / 11		
Headache			
subjects affected / exposed	6 / 3014 (0.20%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 2		
Epilepsy			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Lacunar infarction			

subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cognitive disorder				
subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Generalised tonic-clonic seizure				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic stroke				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Apraxia				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Basal ganglia infarction				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brain oedema				

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebellar infarction			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebellar ischaemia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coma			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial paralysis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorder			

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polyneuropathy			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychomotor hyperactivity			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychomotor skills impaired			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombotic stroke			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tremor			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular headache			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Myelosuppression			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Thrombocytopenia			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Anaemia of chronic disease			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood disorder			

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone marrow disorder			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Middle ear inflammation			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertigo			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Vertigo positional			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Dacryostenosis acquired			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Glaucoma			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Vomiting				
subjects affected / exposed	13 / 3014 (0.43%)			
occurrences causally related to treatment / all	0 / 16			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	12 / 3014 (0.40%)			
occurrences causally related to treatment / all	6 / 12			
deaths causally related to treatment / all	1 / 1			
Nausea				
subjects affected / exposed	6 / 3014 (0.20%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	7 / 3014 (0.23%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	4 / 3014 (0.13%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	4 / 3014 (0.13%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Chronic gastritis				
subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Dysphagia				

subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Pancreatitis acute				
subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer haemorrhage				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal haemorrhagic				

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorder			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastric perforation			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal perforation			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gingival ulceration			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematochezia			

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ischaemic enteritis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestinal obstruction			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine perforation			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Obstructive pancreatitis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peptic ulcer			

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peptic ulcer haemorrhage			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Hepatic function abnormal			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Drug-induced liver injury			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Biliary colic			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Jaundice cholestatic			

subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatotoxicity			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hypertransaminasaemia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Liver injury			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Cutaneous lupus erythematosus			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dermatitis allergic			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic foot			

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erythema multiforme			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash papular			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 1		
Renal failure			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Haematuria			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Calculus urinary			

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrotic syndrome			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal injury			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 3014 (0.23%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	6 / 3014 (0.20%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		

Arthralgia				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Osteoporotic fracture				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bone pain				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fracture pain				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant psoas syndrome				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myopathy				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myositis				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoporosis				

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rotator cuff syndrome			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Synovitis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spondylolisthesis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertebral lesion			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	74 / 3014 (2.46%)		
occurrences causally related to treatment / all	7 / 79		
deaths causally related to treatment / all	4 / 20		
Upper respiratory tract infection			
subjects affected / exposed	10 / 3014 (0.33%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			

subjects affected / exposed	10 / 3014 (0.33%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	6 / 3014 (0.20%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	7 / 3014 (0.23%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	6 / 3014 (0.20%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Device related infection			

subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Emphyema				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal abscess				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Complicated appendicitis				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea infectious				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				

subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic fever				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterobacter pneumonia				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Infection				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infectious pleural effusion				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infective spondylitis				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Labyrinthitis				

subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Laryngitis				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Localised infection				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection bacterial				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphangitis				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis aseptic				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mucosal infection				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nasal abscess				

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis media acute			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral nerve infection			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia fungal			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scrub typhus			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection bacterial			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 2		
Metabolism and nutrition disorders			
Hyponatraemia			

subjects affected / exposed	8 / 3014 (0.27%)		
occurrences causally related to treatment / all	2 / 11		
deaths causally related to treatment / all	0 / 1		
Decreased appetite			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Hyperuricaemia			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 2		
Cachexia			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Hyperglycaemia			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Osimertinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	380 / 3014 (12.61%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Haematoma			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 3014 (0.23%)		
occurrences (all)	7		
Asthenia			

subjects affected / exposed	8 / 3014 (0.27%)		
occurrences (all)	8		
Fatigue			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences (all)	5		
General physical health deterioration			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences (all)	4		
Inflammation			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Testicular cyst			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	13 / 3014 (0.43%)		
occurrences (all)	14		
Cough			

subjects affected / exposed	4 / 3014 (0.13%)		
occurrences (all)	4		
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Interstitial lung disease			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	3		
Haemoptysis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Organising pneumonia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Pulmonary toxicity			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 3014 (0.33%)		
occurrences (all)	11		
Platelet count decreased			

subjects affected / exposed	17 / 3014 (0.56%)		
occurrences (all)	25		
Electrocardiogram QT prolonged			
subjects affected / exposed	88 / 3014 (2.92%)		
occurrences (all)	122		
Blood creatinine increased			
subjects affected / exposed	10 / 3014 (0.33%)		
occurrences (all)	14		
Alanine aminotransferase increased			
subjects affected / exposed	9 / 3014 (0.30%)		
occurrences (all)	10		
Neutrophil count decreased			
subjects affected / exposed	9 / 3014 (0.30%)		
occurrences (all)	12		
White blood cell count decreased			
subjects affected / exposed	8 / 3014 (0.27%)		
occurrences (all)	8		
Amylase increased			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	4		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Blood bilirubin increased			

subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Blood pressure systolic increased subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Blood uric acid increased subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Hepatic enzyme increased subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Lipase increased subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 3		
Transaminases increased subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Injury, poisoning and procedural complications Radiation pneumonitis subjects affected / exposed occurrences (all)	2 / 3014 (0.07%) 2		
Chemical burns of eye subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Corneal abrasion subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Cardiac disorders Sinus bradycardia subjects affected / exposed occurrences (all)	2 / 3014 (0.07%) 2		
Atrioventricular block first degree subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Atrial fibrillation			

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Ventricular extrasystoles			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Extrasystoles			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Cardiac failure			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Bundle branch block left			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Nodal rhythm			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Supraventricular extrasystoles			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Ventricular arrhythmia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences (all)	3		
Presyncope			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Balance disorder			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Brain oedema			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		

Cognitive disorder			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Demyelination			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Facial nerve disorder			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Nervous system disorder			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Psychomotor skills impaired			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Seizure			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	20 / 3014 (0.66%)		
occurrences (all)	22		
Neutropenia			
subjects affected / exposed	16 / 3014 (0.53%)		
occurrences (all)	24		
Myelosuppression			

subjects affected / exposed	6 / 3014 (0.20%)		
occurrences (all)	8		
Anaemia			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences (all)	6		
Leukopenia			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences (all)	4		
Pancytopenia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Eye disorders			
Cataract			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Blepharitis			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Ulcerative keratitis			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Conjunctival haemorrhage			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Swelling of eyelid			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Visual acuity reduced			

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Vitreoretinal traction syndrome			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	11 / 3014 (0.36%)		
occurrences (all)	12		
Diarrhoea			
subjects affected / exposed	30 / 3014 (1.00%)		
occurrences (all)	37		
Vomiting			
subjects affected / exposed	10 / 3014 (0.33%)		
occurrences (all)	14		
Stomatitis			
subjects affected / exposed	9 / 3014 (0.30%)		
occurrences (all)	10		
Abdominal pain upper			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Dysphagia			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Anal inflammation			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Gastrointestinal disorder			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		

Mouth ulceration subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Lip swelling subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Rectal haemorrhage subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all)	3 / 3014 (0.10%) 3		
Drug-induced liver injury subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Hepatotoxicity subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Hypertransaminaemia subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Hyperbilirubinaemia subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 2		
Liver injury subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	10 / 3014 (0.33%) 11		
Dermatitis acneiform subjects affected / exposed occurrences (all)	6 / 3014 (0.20%) 6		
Skin toxicity			

subjects affected / exposed	6 / 3014 (0.20%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences (all)	7		
Pruritus			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences (all)	4		
Nail disorder			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Drug eruption			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Eczema asteatotic			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Onycholysis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Rash papular			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Skin fissures			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Skin reaction			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		

Skin ulcer			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Renal impairment			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Acute kidney injury			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Hydronephrosis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	2		
Nephropathy toxic			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Renal disorder			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Urinary incontinence			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Hypercreatinaemia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Arthralgia			

subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Spinal pain			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Pathological fracture			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Infections and infestations			
Influenza			
subjects affected / exposed	7 / 3014 (0.23%)		
occurrences (all)	9		
Paronychia			
subjects affected / exposed	11 / 3014 (0.36%)		
occurrences (all)	11		
Herpes zoster			
subjects affected / exposed	6 / 3014 (0.20%)		
occurrences (all)	6		
Pneumonia			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences (all)	5		
Atypical pneumonia			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Cystitis			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		

Gastroenteritis viral subjects affected / exposed occurrences (all)	2 / 3014 (0.07%) 2		
Herpes ophthalmic subjects affected / exposed occurrences (all)	2 / 3014 (0.07%) 2		
Pneumonia viral subjects affected / exposed occurrences (all)	2 / 3014 (0.07%) 2		
Bronchitis subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Cellulitis subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Gingivitis subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Oral herpes subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	5 / 3014 (0.17%) 5		
Hyponatraemia			

subjects affected / exposed	3 / 3014 (0.10%)		
occurrences (all)	3		
Dehydration			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Abnormal loss of weight			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2015	- Patient recruitment was expanded to other regions (America and Asia), a clause about study termination in each country was added and procedures for discontinuation of a subject from study treatment were added, details about what will happen in case of study withdrawal and follow up of overall survival were added, the study plan (Table 4) was amended to provide more details in line with the CRF and more details about the enrolment process, clarification about T790M testing and what will happen to the samples if a central laboratory is used. - Male patient contraception was clarified. - Details regarding QTc prolongation and identity and dose of investigational product were aligned to the core data sheet. - The statistical methods and analysis included a more robust description of statistical evaluations and sample size determination.
23 June 2016	- The number of patients enrolled was revised in Europe from 1500 to 600 due to lower enrolment than initially planned. The total enrolment was more defined as approximately 3500 with the participation of China. - The data collection is to stop at last patient last visit due to the removal of the patient registry after national reimbursement. - The primary efficacy outcome was clarified as overall survival, the secondary efficacy outcomes were clarified as investigator assessed response rate, investigator assessed progression free survival and time to treatment discontinuation. - Definition for response rate and time to treatment discontinuation was added. - The exclusion criteria relating to patients being excluded due to evidence of an active infection was clarified with a definition for active infection. - An interim analysis of the global data was added to take place annually for the first 3 years. - A steering committee was added for oversight and supervision of the study.
20 October 2016	- Details were added regarding an addendum to the informed consent form to be signed and dated to enable the collection of images (CT scans or MRI) from a selected subset of patients for independent central analysis by an AstraZeneca appointed CRO. - Table 4 (footnote c) was amended to clarify the 30 days post last follow up contact is by a visit or by telephone (for new/ongoing serious adverse events (SAEs) and adverse events of special interest. - Details regarding definition and management of overdose were added and it was clarified that all overdose data (not just those relating to an SAE) should be reported to AstraZeneca with details of the process.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 August 2018	Delay to database lock due to needing a further approval to consent patients and collect scans in one of the participating countries.	-

Notes:

Limitations and caveats

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

Participants alive at the time of national reimbursement or site closure were no longer followed for survival and therefore prematurely censored for the OS, PFS, and TTD analysis, leading to less mature data.

Notes: