



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
Death	1361
Other	43
Eligibility Criteria not Fulfilled	2
Consent withdrawn by subject	124
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		
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		
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		

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 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			
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			
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 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			
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			
Glioblastoma subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
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			
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			
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			
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			
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			
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		
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		
Pyrexia subjects affected / exposed	12 / 3014 (0.40%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 0		
Asthenia subjects affected / exposed	4 / 3014 (0.13%)		
occurrences causally related to treatment / all	2 / 4		
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		
Malaise subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
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		
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		
Cyst 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		
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		
Psychiatric disorders Delirium subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to	0 / 2		

treatment / all			
deaths causally related to treatment / all	0 / 0		
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		
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		
Depression			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
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		
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		
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		
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		
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		
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		
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		
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 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		
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		
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		
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		
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			
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			
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			
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			
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			
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			
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			
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			
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			
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			

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		
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		
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		
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		
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		
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		
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		
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			
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			
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			
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			
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			
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			
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		
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		
Cardiomyopathy			
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			
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			
Palpitations				
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			
Arrhythmia				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
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			
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			
Cardiotoxicity				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	1 / 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		
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		
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		
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		
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		
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		
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			

Cough				
subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
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			
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			
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			
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		
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		
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		
Emphysema			
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		
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		
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		
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		
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		
Thrombocytopenia			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences causally related to treatment / all	3 / 4		
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		
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		
Transient ischaemic attack			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences causally related to	0 / 5		

treatment / all				
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			
Epilepsy				
subjects affected / exposed	4 / 3014 (0.13%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
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			
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			
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			
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		
Eye disorders			
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		
Cataract			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Glaucoma			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to	0 / 2		

treatment / all			
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 positional			
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		
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			
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			
Enteritis				
subjects affected / exposed	4 / 3014 (0.13%)			
occurrences causally related to treatment / all	1 / 4			
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			
Dysphagia				
subjects affected / exposed	3 / 3014 (0.10%)			
occurrences causally related to treatment / all	0 / 3			
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			
Colitis				
subjects affected / exposed	2 / 3014 (0.07%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
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			
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			
Pancreatitis 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			
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			
Enterocolitis subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
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			

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			
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			
Haemorrhoids 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			
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			
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		
Stomatitis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences causally related to treatment / all	1 / 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		
Renal and urinary disorders			
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		
Acute kidney injury			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences causally related to	1 / 5		

treatment / all			
deaths causally related to treatment / all	0 / 1		
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		
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		
Nephrolithiasis			
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		
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			
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			
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			
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			

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

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		
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		
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		
Myopathy			
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			
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			
Spondylolisthesis				
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			
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			
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		
Metabolism and nutrition disorders			
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		
Hyponatraemia			
subjects affected / exposed	8 / 3014 (0.27%)		
occurrences causally related to treatment / all	2 / 11		
deaths causally related to treatment / all	0 / 1		
Hyperkalaemia			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
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		
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		
Hypoglycaemia			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Hyperglycaemia			
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		
Infections and infestations			
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		
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		
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		
Bronchitis			
subjects affected / exposed	6 / 3014 (0.20%)		
occurrences causally related to treatment / all	0 / 6		
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		
Urosepsis			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Osteomyelitis			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Empyema			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
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		
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			
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			
Infection				
subjects affected / exposed	1 / 3014 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
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			
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			
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			
Influenza				
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			
Laryngitis				
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			
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			
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			
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			
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		
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		
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		
Sepsis			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 2		

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%)		
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		
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 occurrences (all)	1 / 3014 (0.03%) 1		
General disorders and administration site conditions			
Pyrexia subjects affected / exposed occurrences (all)	7 / 3014 (0.23%) 7		
Fatigue subjects affected / exposed occurrences (all)	4 / 3014 (0.13%) 5		
Asthenia subjects affected / exposed occurrences (all)	8 / 3014 (0.27%) 8		
Inflammation subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
General physical health deterioration subjects affected / exposed occurrences (all)	4 / 3014 (0.13%) 4		
Malaise subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Influenza like illness subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Mucosal inflammation subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Non-cardiac chest pain subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Peripheral swelling subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Reproductive system and breast disorders			

Testicular cyst subjects affected / exposed occurrences (all)	1 / 3014 (0.03%) 1		
Injury, poisoning and procedural complications Radiation pneumonitis subjects affected / exposed occurrences (all) Chemical burns of eye subjects affected / exposed occurrences (all) Corneal abrasion subjects affected / exposed occurrences (all)	2 / 3014 (0.07%) 2 1 / 3014 (0.03%) 1 1 / 3014 (0.03%) 1		
Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) Electrocardiogram QT prolonged subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all) Alanine aminotransferase increased subjects affected / exposed occurrences (all) Blood alkaline phosphatase increased	10 / 3014 (0.33%) 11 17 / 3014 (0.56%) 25 88 / 3014 (2.92%) 122 9 / 3014 (0.30%) 12 8 / 3014 (0.27%) 8 10 / 3014 (0.33%) 14 9 / 3014 (0.30%) 10		

subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Amylase increased			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	4		
Weight decreased			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Blood pressure systolic increased			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Transaminases increased			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Lipase increased			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	3		
Hepatic enzyme increased			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Blood uric acid increased			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Ventricular extrasystoles			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Atrioventricular block first degree			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Sinus bradycardia			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Nodal rhythm			
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		
Extrasystoles			
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		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	13 / 3014 (0.43%)		
occurrences (all)	14		
Chronic obstructive pulmonary disease			

subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	3		
Interstitial lung disease			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	4 / 3014 (0.13%)		
occurrences (all)	4		
Productive cough			
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		
Haemoptysis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Pulmonary toxicity			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Rhinorrhoea			
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		
Myelosuppression			
subjects affected / exposed	6 / 3014 (0.20%)		
occurrences (all)	8		

Neutropenia			
subjects affected / exposed	16 / 3014 (0.53%)		
occurrences (all)	24		
Pancytopenia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences (all)	4		
Anaemia			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences (all)	6		
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		
Eye disorders			
Ulcerative keratitis			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Cataract			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Blepharitis			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Conjunctival haemorrhage			
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		
Dry eye			
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		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	30 / 3014 (1.00%)		
occurrences (all)	37		
Stomatitis			
subjects affected / exposed	9 / 3014 (0.30%)		
occurrences (all)	10		
Vomiting			
subjects affected / exposed	10 / 3014 (0.33%)		
occurrences (all)	14		
Nausea			
subjects affected / exposed	11 / 3014 (0.36%)		
occurrences (all)	12		
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		
Lip swelling			
subjects affected / exposed	1 / 3014 (0.03%)		

occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Gastrointestinal disorder			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Rectal haemorrhage			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Azotaemia			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
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		
Acute kidney injury			
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 occurrences (all)	1 / 3014 (0.03%) 1		
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences (all)	3		
Drug-induced liver injury			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	2		
Hypertransaminaemia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Hepatotoxicity			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Liver injury			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	6 / 3014 (0.20%)		
occurrences (all)	6		
Rash			
subjects affected / exposed	10 / 3014 (0.33%)		
occurrences (all)	11		
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		
Eczema asteatotic			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Drug eruption			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Onycholysis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome			
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		
Rash papular			
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		
Musculoskeletal and connective tissue disorders			

Myalgia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Hypercreatinaemia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Pathological fracture			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Spinal pain			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
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		
Hyponatraemia			
subjects affected / exposed	3 / 3014 (0.10%)		
occurrences (all)	3		
Decreased appetite			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences (all)	5		
Hypokalaemia			
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		
Infections and infestations			
Influenza			
subjects affected / exposed	7 / 3014 (0.23%)		
occurrences (all)	9		
Herpes zoster			
subjects affected / exposed	6 / 3014 (0.20%)		
occurrences (all)	6		
Paronychia			
subjects affected / exposed	11 / 3014 (0.36%)		
occurrences (all)	11		
Cystitis			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Pneumonia			
subjects affected / exposed	5 / 3014 (0.17%)		
occurrences (all)	5		
Atypical pneumonia			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Herpes ophthalmic			
subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Pneumonia viral			

subjects affected / exposed	2 / 3014 (0.07%)		
occurrences (all)	2		
Cellulitis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 3014 (0.03%)		
occurrences (all)	1		
Oral herpes			
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	<ul style="list-style-type: none">- 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	<ul style="list-style-type: none">- 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	<ul style="list-style-type: none">- 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: