Clinical trial results:
A randomised phase II trial of osimertinib and bevacizumab versus osimertinib alone as second-line treatment in stage IIIb-IVb NSCLC with confirmed EGFRm and T790M

Summary

EudraCT number	2016-002029-12
Trial protocol	IE ES NL
Global end of trial date	22 February 2021

Results information

Result version number	v1 (current)
This version publication date	27 April 2023
First version publication date	27 April 2023
Summary attachment (see zip file)	Statistical analysis plan (BOOSTER_SAP_FINAL_ANALYSIS.pdf)

Trial information

Trial identification

Sponsor protocol code	ETOP10-16

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03133546
WHO universal trial number (UTN)	-
Other trial identifiers	Astra Zeneca: ESR-15-11666, Roche: MO39447

Notes:

Sponsors

Sponsor organisation name	ETOP IBCSG Partners Foundation
Sponsor organisation address	Effingerstrasse 33, Bern, Switzerland, 3008
Public contact	ETOP IBCSG Partners Foundation, ETOP IBCSG Partners Foundation, +41 31 511 94 00, etop-regulatory@etop.ibcsg.org
Scientific contact	ETOP IBCSG Partners Coordinating Center, ETOP IBCSG Partners Foundation, +41 31 511 94 00, etop-regulatory@etop.ibcsg.org

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	22 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2021
Global end of trial reached?	Yes
Global end of trial date	22 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of the combination of osimertinib and bevacizumab versus osimertinib alone in terms of progression-free survival (PFS) assessed by RECIST 1.1.

Protection of trial subjects:

The investigator will ensure that this trial is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The trial must fully adhere to the principles outlined in "Guideline for Good Clinical Practice (GCP)" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Spain: 78
Country: Number of subjects enrolled	Ireland: 10
Country: Number of subjects enrolled	Singapore: 31
Country: Number of subjects enrolled	Korea, Republic of: 28
Country: Number of subjects enrolled	Switzerland: 5
Worldwide total number of subjects	155
EEA total number of subjects	91

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)	67
From 65 to 84 years	87
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Between May 31, 2017 and February 21, 2019, 188 patients were captured in the iBiobank.

Pre-assignment

Screening details:

Out of the 188 patients, 155 coming from 22 centers (12 Spanish, 3 Swiss, 2 Irish, 2 in Singapore, 2 South Korean and 1 Dutch) were randomised. 33 patients were not randomized due to 'Screening failure' or 'Error' status.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Osimertinib Plus Bevacizumab

Arm description:

Patients will receive treatment with osimertinib and bevacizumab until disease progression, lack of tolerability or the patient declines further treatment. Treatment may also continue beyond progression for as long as the patient may still derive benefit.
Osimertinib: Osimertinib is administered orally at 80mg once daily. Doses should be taken approximately 24 hours apart at the same time point each day. The appropriate number of osimertinib tablets will be provided to patients to be self-administered at home. AstraZeneca will supply osimertinib as tablets for oral administration.
AstraZeneca will supply osimertinib as tablets for oral administration.
Bevacizumab: Bevacizumab is administered at 15mg/kg intravenously on day 1 of every 3-week cycle. Bevacizumab for intravenous administration will be supplied by Roche.

Arm type	Experimental
Investigational medicinal product name	Avastin and Tagrisso
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Osimertinib, 80 mg p.o., once daily plus bevacizumab 15 mg/kg i.v. on day 1 of every 3-week cycle.

Arm title	Osimertinib Alone

Arm description:

Patients will receive treatment with osimertinib until disease progression, lack of tolerability or the patient declines further treatment. Treatment may also continue beyond progression for as long as the patient may still derive benefit.
Osimertinib: Osimertinib is administered orally at 80mg once daily. Doses should be taken approximately 24 hours apart at the same time point each day. The appropriate number of osimertinib tablets will be provided to patients to be self-administered at home. AstraZeneca will supply osimertinib as tablets for oral administration.
AstraZeneca will supply osimertinib as tablets for oral administration.

Arm type	Control
Investigational medicinal product name	Tagrisso
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Osimertinib, 80 mg p.o., once daily

Number of subjects in period 1	Osimertinib Plus Bevacizumab	Osimertinib Alone
Started	78	77
Received Treatment	76	77
On Treatment	1 [1]	8 [2]
Treatment Failures	75	69
Never Started Treatment	2 [3]	0 [4]
Completed	27	27
Not completed	51	50
Death	46	43
Withdrawal/Lost to follow-up	5	7

Notes:

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

Justification: Osimertinib Plus Bevacizumab, among the 78 patients randomised, 76 received treatment (2 patients never started treatment). Out of the 76 who received treatment, 1 is still on treatment, while there are 75 patients with treatment failures (36 toxicities, 29 progressions, 4 other reasons, 3 patient decisions, 2 deaths, 1 investigator decision).
In total, 27 patients are still on follow-up at final database cut-off, while 51 are lost to follow-up/withdrawal.

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

Justification: Osimertinib, among the 77 patients randomised, all patients received treatment, 8 are still on treatment, while there are 69 patients with treatment failures (3 toxicities, 53 progressions, 1 other reason, 4 patient decisions, 7 deaths, 1 investigator decision).
In total, 27 patients are still on follow-up at final database cut-off, while 50 are lost to follow-up/withdrawal.

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

Justification: Osimertinib Plus Bevacizumab, among the 78 patients randomised, 76 received treatment (2 patients never started treatment). Out of the 76 who received treatment, 1 is still on treatment, while there are 75 patients with treatment failures (36 toxicities, 29 progressions, 4 other reasons, 3 patient decisions, 2 deaths, 1 investigator decision).
In total, 27 patients are still on follow-up at final database cut-off, while 51 are lost to follow-up/withdrawal.

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

Justification: Osimertinib, among the 77 patients randomised, all patients received treatment, 8 are still on treatment, while there are 69 patients with treatment failures (3 toxicities, 53 progressions, 1 other reason, 4 patient decisions, 7 deaths, 1 investigator decision).
In total, 27 patients are still on follow-up at final database cut-off, while 50 are lost to follow-up/withdrawal.

Baseline characteristics

Reporting groups

Reporting group title	Osimertinib Plus Bevacizumab

Reporting group description:

Patients will receive treatment with osimertinib and bevacizumab until disease progression, lack of tolerability or the patient declines further treatment. Treatment may also continue beyond progression for as long as the patient may still derive benefit.
Osimertinib: Osimertinib is administered orally at 80mg once daily. Doses should be taken approximately 24 hours apart at the same time point each day. The appropriate number of osimertinib tablets will be provided to patients to be self-administered at home. AstraZeneca will supply osimertinib as tablets for oral administration.
AstraZeneca will supply osimertinib as tablets for oral administration.
Bevacizumab: Bevacizumab is administered at 15mg/kg intravenously on day 1 of every 3-week cycle. Bevacizumab for intravenous administration will be supplied by Roche.

Reporting group title	Osimertinib Alone

Reporting group description:

Patients will receive treatment with osimertinib until disease progression, lack of tolerability or the patient declines further treatment. Treatment may also continue beyond progression for as long as the patient may still derive benefit.
Osimertinib: Osimertinib is administered orally at 80mg once daily. Doses should be taken approximately 24 hours apart at the same time point each day. The appropriate number of osimertinib tablets will be provided to patients to be self-administered at home. AstraZeneca will supply osimertinib as tablets for oral administration.
AstraZeneca will supply osimertinib as tablets for oral administration.

Reporting group values	Osimertinib Plus Bevacizumab	Osimertinib Alone	Total
Number of subjects	78	77	155
Age categorical Units: Subjects			
Age continuous Units: years			
median	68	66	
full range (min-max)	34 to 85	41 to 83	-
Gender categorical Units: Subjects			
Female	47	49	96
Male	31	28	59
Ethnicity Units: Subjects			
Asian	32	31	63
Non-Asian	46	46	92
ECOG Performance Status			
ECOG Performance status scaling: PS 0:Fully active, able to carry on all pre-disease performance without restriction. PS 1:Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. PS 2:Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. PS 3:Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours. PS 4:Completely disabled. Cannot carry on any self-care. Totally confined to bed or cha			
Units: Subjects			
PS 0	22	25	47
PS 1	51	48	99

PS 2	5	4	9
Smoking status			
Current smoker: Still smokes cigarettes, Former smoker: Smoked at least 100 cigarettes in the past during the whole life, Never smoker: Smoked 0-99 cigarettes during the whole life.			
Units: Subjects			
Current smoker	4	1	5
Former smoker	30	27	57
Never smoked	44	49	93
Stage			
According to the American Joint Committee on Cancer 8th TNM classification.			
Units: Subjects			
IIIB/C	2	0	2
IVA/B	76	76	152
Missing	0	1	1
Use of prior platinum-based chemotherapy Units: Subjects			
Yes	11	13	24
No	67	64	131
Prior EGFR TKI			
TKI: tyrosine kinase inhibitors			
Units: Subjects			
Erlotinib/gefitinib	57	57	114
Afatinib/dacomitinib	21	19	40
Other	0	1	1
EGFR mutation type Units: Subjects			
Exon 19 deletion	58	51	109
Exon 21 L858R	20	26	46
T790M testing material Units: Subjects			
ctDNA	38	37	75
Tumour	40	40	80
Brain metastasis Units: Subjects			
Yes	13	8	21
No	65	69	134
Liver metastasis Units: Subjects			
Yes	14	8	22
No	64	69	133
Pleural effusion and ascites Units: Subjects			
Yes	7	9	16
No	71	68	139

End points

End points reporting groups

Reporting group title	Osimertinib Plus Bevacizumab

Reporting group description:

Patients will receive treatment with osimertinib and bevacizumab until disease progression, lack of tolerability or the patient declines further treatment. Treatment may also continue beyond progression for as long as the patient may still derive benefit.
Osimertinib: Osimertinib is administered orally at 80mg once daily. Doses should be taken approximately 24 hours apart at the same time point each day. The appropriate number of osimertinib tablets will be provided to patients to be self-administered at home. AstraZeneca will supply osimertinib as tablets for oral administration.
AstraZeneca will supply osimertinib as tablets for oral administration.
Bevacizumab: Bevacizumab is administered at 15mg/kg intravenously on day 1 of every 3-week cycle. Bevacizumab for intravenous administration will be supplied by Roche.

Reporting group title	Osimertinib Alone

Reporting group description:

Patients will receive treatment with osimertinib until disease progression, lack of tolerability or the patient declines further treatment. Treatment may also continue beyond progression for as long as the patient may still derive benefit.
Osimertinib: Osimertinib is administered orally at 80mg once daily. Doses should be taken approximately 24 hours apart at the same time point each day. The appropriate number of osimertinib tablets will be provided to patients to be self-administered at home. AstraZeneca will supply osimertinib as tablets for oral administration.
AstraZeneca will supply osimertinib as tablets for oral administration.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS is defined as the time from the date of randomisation until documented progression (based on RECIST 1.1 criteria) or death, if progression is not documented. Censoring (for patients without progression/death) will occur at the last tumour assessment if patient is lost to follow-up or refuses further documentation of follow-up.

End point type	Primary

End point timeframe:

Evaluated up to 48 months from randomisation of the first patient (expected follow-up for the required events, assuming an accrual of 29 months).

End point values	Osimertinib Plus Bevacizumab	Osimertinib Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	77		
Units: months				
median (confidence interval 95%)	15.4 (9.2 to 18)	12.3 (6.2 to 17.2)		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Assumption: Median PFS with osimertinib 11 months Target: Detect a 36% improvement in PFS (HR=0.64, corresponding to an increase in median PFS to 17.2 months) under osimertinib and bevacizumab (80% power, at one-sided significant level of 5%)
126 events required

Comparison groups	Osimertinib Alone v Osimertinib Plus Bevacizumab
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.37

Notes:

[1] - significance level: 5%

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR is defined as the percentage of patients reaching a complete or partial response, across all assessment time-points according to RECIST criteria v1.1, during the period from randomisation to termination of trial treatment.

End point type	Secondary

End point timeframe:

Evaluated up to 48 months from randomisation of the first patient.

End point values	Osimertinib Plus Bevacizumab	Osimertinib Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	77		
Units: percentage of participants				
number (confidence interval 95%)	0.55 (0.43 to 0.66)	0.55 (0.43 to 0.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

DCR is defined as the percentage of patients reaching a complete or partial response, or disease stabilisation confirmed at subsequent radiological assessment, across all assessment time-points according to RECIST criteria v1.1, during the period from randomisation to termination of trial treatment.

End point type	Secondary

End point timeframe:

Evaluated up to 48 months from enrolment of the first patient.

End point values	Osimertinib Plus Bevacizumab	Osimertinib Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	77		
Units: percentage of participants				
number (confidence interval 95%)	0.90 (0.81 to 0.95)	0.82 (0.71 to 0.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events

End point title	Adverse Events

End point description:

Adverse events, graded by CTCAE version 4.0, will be recorded from date of signature of informed consent until 30 days after all trial treatment discontinuation.

End point type	Secondary

End point timeframe:

Evaluated up to 48 months from randomisation of the first patient.

End point values	Osimertinib Plus Bevacizumab	Osimertinib Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[2]	77		
Units: participants				
Experienced AE/SAE	76	76		
No AE/SAE	0	1		
Experienced SAE	33	27		

Notes:

[2] - Two patients never started treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as time from the date of randomisation until death from any cause. Censoring will occur at the last follow-up date.

End point type	Secondary

End point timeframe:

Evaluated up to 48 months from randomisation of the first patient.

End point values	Osimertinib Plus Bevacizumab	Osimertinib Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	77		
Units: months				
median (confidence interval 95%)	24.0 (17.8 to 32.1)	24.3 (16.9 to 37.0)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: T790M Evolution in Tissue and Plasma/Serum Between Baseline and Disease Progression (PD) on Trial Treatment.

End point title	T790M Evolution in Tissue and Plasma/Serum Between Baseline and Disease Progression (PD) on Trial Treatment.

End point description:

Tumour tissue blocks, plasma and serum samples will be collected at trial entry and at disease progression on trial treatment.

End point type	Other pre-specified

End point timeframe:

Available for translational research, following completion of the primary trial research objectives.

End point values	Osimertinib Plus Bevacizumab	Osimertinib Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[3]	73[4]		
Units: participants				
MD-MD	8	8		
MD-MND	18	13		
MND-MD	0	1		
MND-MND	6	8		
Missing	22	25		

Not applicable (No PD)	22	18		

Notes:

[3] - Patients with NGS plasma sample T790M base to PD
MD: Mutation Detected
MND: Mutation Not Detected

[4] - Patients with NGS plasma sample T790M base to PD
MD: Mutation Detected
MND: Mutation Not Detected

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Continuously from date of Informed Consent signature to 30 days after all treatments discontinuation.

Adverse event reporting additional description:

Adverse event (AE) is defined as any untoward medical occurrence that occurs from the date of signature of informed consent until 30 days after all trial treatment discontinuation, regardless of whether it is considered related to a medication. Adverse events are classified according to CTCAE version 4.0.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Osimertinib Plus Bevacizumab

Reporting group description:

Patients will receive treatment with osimertinib and bevacizumab until disease progression, lack of tolerability or the patient declines further treatment. Treatment may also continue beyond progression for as long as the patient may still derive benefit.
Osimertinib: Osimertinib is administered orally at 80mg once daily. Doses should be taken approximately 24 hours apart at the same time point each day. The appropriate number of osimertinib tablets will be provided to patients to be self-administered at home. AstraZeneca will supply osimertinib as tablets for oral administration.
AstraZeneca will supply osimertinib as tablets for oral administration.
Bevacizumab: Bevacizumab is administered at 15mg/kg intravenously on day 1 of every 3-week cycle. Bevacizumab for intravenous administration will be supplied by Roche.

Reporting group title	Osimertinib Alone

Reporting group description:

Patients will receive treatment with osimertinib until disease progression, lack of tolerability or the patient declines further treatment. Treatment may also continue beyond progression for as long as the patient may still derive benefit.
Osimertinib: Osimertinib is administered orally at 80mg once daily. Doses should be taken approximately 24 hours apart at the same time point each day. The appropriate number of osimertinib tablets will be provided to patients to be self-administered at home. AstraZeneca will supply osimertinib as tablets for oral administration.
AstraZeneca will supply osimertinib as tablets for oral administration.

Serious adverse events	Osimertinib Plus Bevacizumab	Osimertinib Alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 76 (43.42%)	27 / 77 (35.06%)	
number of deaths (all causes)	46	43	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric carcinoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	2 / 76 (2.63%)	3 / 77 (3.90%)	
occurrences causally related to treatment / all	2 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Pleurodesis of malignant pleural effusion			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 76 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug overdose			
subjects affected / exposed	3 / 76 (3.95%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Dyspnea			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 76 (1.32%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary hemorrhage			
subjects affected / exposed	1 / 76 (1.32%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal hemorrhage			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mania			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Lipase increased			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Heart failure			
subjects affected / exposed	2 / 76 (2.63%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 76 (3.95%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 76 (1.32%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			

subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischemia cerebrovascular			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis oral			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 76 (0.00%)	3 / 77 (3.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 76 (0.00%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			

subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Skin and subcutaneous tissue disorders			
Rash acneiform			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			

subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Upper respiratory infection			
subjects affected / exposed	1 / 76 (1.32%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 76 (2.63%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	4 / 76 (5.26%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pharyngitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			

subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis caused by COVID-19 infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			

subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalemia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycemia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Osimertinib Plus Bevacizumab	Osimertinib Alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 76 (100.00%)	76 / 77 (98.70%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	32 / 76 (42.11%)	7 / 77 (9.09%)	
occurrences (all)	32	7	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	33 / 76 (43.42%)	29 / 77 (37.66%)	
occurrences (all)	33	29	
Pain			
subjects affected / exposed	22 / 76 (28.95%)	12 / 77 (15.58%)	
occurrences (all)	22	12	
Fever			
subjects affected / exposed	6 / 76 (7.89%)	10 / 77 (12.99%)	
occurrences (all)	6	10	
Edema limbs			
subjects affected / exposed	10 / 76 (13.16%)	4 / 77 (5.19%)	
occurrences (all)	10	4	
Non-cardiac chest pain			

subjects affected / exposed	9 / 76 (11.84%)	1 / 77 (1.30%)	
occurrences (all)	9	1	
Flu like symptoms			
subjects affected / exposed	6 / 76 (7.89%)	3 / 77 (3.90%)	
occurrences (all)	6	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	31 / 76 (40.79%)	28 / 77 (36.36%)	
occurrences (all)	31	28	
Dyspnea			
subjects affected / exposed	13 / 76 (17.11%)	17 / 77 (22.08%)	
occurrences (all)	13	17	
Epistaxis			
subjects affected / exposed	16 / 76 (21.05%)	4 / 77 (5.19%)	
occurrences (all)	16	4	
Sore throat			
subjects affected / exposed	7 / 76 (9.21%)	3 / 77 (3.90%)	
occurrences (all)	7	3	
Pleural effusion			
subjects affected / exposed	3 / 76 (3.95%)	5 / 77 (6.49%)	
occurrences (all)	3	5	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 76 (1.32%)	7 / 77 (9.09%)	
occurrences (all)	1	7	
Investigations			
Lipase increased			
subjects affected / exposed	12 / 76 (15.79%)	13 / 77 (16.88%)	
occurrences (all)	12	13	
Serum amylase increased			
subjects affected / exposed	12 / 76 (15.79%)	13 / 77 (16.88%)	
occurrences (all)	12	13	
Platelet count decreased			
subjects affected / exposed	15 / 76 (19.74%)	9 / 77 (11.69%)	
occurrences (all)	15	9	
Neutrophil count decreased			

subjects affected / exposed	7 / 76 (9.21%)	10 / 77 (12.99%)	
occurrences (all)	7	10	
Alanine aminotransferase increased			
subjects affected / exposed	10 / 76 (13.16%)	6 / 77 (7.79%)	
occurrences (all)	10	6	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 76 (13.16%)	5 / 77 (6.49%)	
occurrences (all)	10	5	
Electrocardiogram QT corrected interval prolonged			
subjects affected / exposed	10 / 76 (13.16%)	5 / 77 (6.49%)	
occurrences (all)	10	5	
Ejection fraction decreased			
subjects affected / exposed	9 / 76 (11.84%)	1 / 77 (1.30%)	
occurrences (all)	9	1	
Alkaline phosphatase increased			
subjects affected / exposed	6 / 76 (7.89%)	3 / 77 (3.90%)	
occurrences (all)	6	3	
Creatinine increased			
subjects affected / exposed	7 / 76 (9.21%)	2 / 77 (2.60%)	
occurrences (all)	7	2	
White blood cell decreased			
subjects affected / exposed	5 / 76 (6.58%)	4 / 77 (5.19%)	
occurrences (all)	5	4	
GGT increased			
subjects affected / exposed	6 / 76 (7.89%)	2 / 77 (2.60%)	
occurrences (all)	6	2	
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 76 (23.68%)	9 / 77 (11.69%)	
occurrences (all)	18	9	
Dizziness			
subjects affected / exposed	9 / 76 (11.84%)	11 / 77 (14.29%)	
occurrences (all)	9	11	
Blood and lymphatic system disorders			

Anemia			
subjects affected / exposed	7 / 76 (9.21%)	12 / 77 (15.58%)	
occurrences (all)	7	12	
Eye disorders			
Dry eye			
subjects affected / exposed	4 / 76 (5.26%)	10 / 77 (12.99%)	
occurrences (all)	4	10	
Blurred vision			
subjects affected / exposed	4 / 76 (5.26%)	5 / 77 (6.49%)	
occurrences (all)	4	5	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	41 / 76 (53.95%)	38 / 77 (49.35%)	
occurrences (all)	41	38	
Constipation			
subjects affected / exposed	19 / 76 (25.00%)	16 / 77 (20.78%)	
occurrences (all)	19	16	
Mucositis oral			
subjects affected / exposed	19 / 76 (25.00%)	10 / 77 (12.99%)	
occurrences (all)	19	10	
Nausea			
subjects affected / exposed	17 / 76 (22.37%)	13 / 77 (16.88%)	
occurrences (all)	17	13	
Vomiting			
subjects affected / exposed	17 / 76 (22.37%)	7 / 77 (9.09%)	
occurrences (all)	17	7	
Abdominal pain			
subjects affected / exposed	7 / 76 (9.21%)	4 / 77 (5.19%)	
occurrences (all)	7	4	
Dry mouth			
subjects affected / exposed	2 / 76 (2.63%)	8 / 77 (10.39%)	
occurrences (all)	2	8	
Skin and subcutaneous tissue disorders			
Rash acneiform			
subjects affected / exposed	27 / 76 (35.53%)	19 / 77 (24.68%)	
occurrences (all)	27	19	
Dry skin			

subjects affected / exposed	16 / 76 (21.05%)	15 / 77 (19.48%)	
occurrences (all)	16	15	
Pruritus			
subjects affected / exposed	8 / 76 (10.53%)	15 / 77 (19.48%)	
occurrences (all)	8	15	
Rash maculo-papular			
subjects affected / exposed	6 / 76 (7.89%)	5 / 77 (6.49%)	
occurrences (all)	6	5	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	37 / 76 (48.68%)	2 / 77 (2.60%)	
occurrences (all)	37	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	10 / 76 (13.16%)	11 / 77 (14.29%)	
occurrences (all)	10	11	
Pain in extremity			
subjects affected / exposed	3 / 76 (3.95%)	9 / 77 (11.69%)	
occurrences (all)	3	9	
Myalgia			
subjects affected / exposed	4 / 76 (5.26%)	5 / 77 (6.49%)	
occurrences (all)	4	5	
Arthralgia			
subjects affected / exposed	5 / 76 (6.58%)	3 / 77 (3.90%)	
occurrences (all)	5	3	
Infections and infestations			
Upper respiratory infection			
subjects affected / exposed	16 / 76 (21.05%)	15 / 77 (19.48%)	
occurrences (all)	16	15	
Paronychia			
subjects affected / exposed	13 / 76 (17.11%)	13 / 77 (16.88%)	
occurrences (all)	13	13	
Urinary tract infection			
subjects affected / exposed	6 / 76 (7.89%)	6 / 77 (7.79%)	
occurrences (all)	6	6	
Metabolism and nutrition disorders			

Anorexia			
subjects affected / exposed	24 / 76 (31.58%)	17 / 77 (22.08%)	
occurrences (all)	24	17	
Hyponatremia			
subjects affected / exposed	6 / 76 (7.89%)	4 / 77 (5.19%)	
occurrences (all)	6	4	
Hypokalemia			
subjects affected / exposed	3 / 76 (3.95%)	6 / 77 (7.79%)	
occurrences (all)	3	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported