Clinical trial results:
A multicentre, open-label, single-arm, molecular profiling study of patients with epidermal growth factor receptor (EGFR) mutation-positive locally advanced or metastatic non-small-cell lung cancer (NSCLC) treated with osimertinib

Summary

EudraCT number	2017-002359-27
Trial protocol	ES IT
Global end of trial date	19 September 2023

Results information

Result version number	v2 (current)
This version publication date	30 October 2024
First version publication date	19 September 2024
Version creation reason	• Correction of full data set Correction of information

Trial information

Trial identification

Sponsor protocol code	D5161C00003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03239340
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 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To examine the tumour genetic and proteomic profile at the point of disease progression in patients receiving osimertinib as first-line epidermal growth factor receptor (EGFR) TKI therapy for EGFRm+ locally advanced or metastatic non-small-cell lung cancer (NSCLC) compared to the profile prior to initiation of treatment.

Protection of trial subjects:

The study was performed in accordance with ethical principles that had their origin in the Declaration of Helsinki and were consistent with International Council of Harmonisation Good Clinical Practice and the AstraZeneca policy on Bioethics and Human Biological Samples applicable laws and regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 May 2018
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	Italy: 11
Country: Number of subjects enrolled	Korea, Republic of: 65
Country: Number of subjects enrolled	Malaysia: 50
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	154
EEA total number of subjects	27

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)	83
From 65 to 84 years	70
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in this study from 30 May 2018 (First subject in) and analyses presented in this results form are based on a data cut-off of 18 July 2023.

Pre-assignment

Screening details:

Participants meeting eligibility criteria predefined in protocol were enrolled in the study. All the assessments were performed as per the schedule of the assessments.

Period 1

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

Arms

Arm title	Osimertinib 80mg

Arm description:

Participants received Osimertinib 80mg orally once daily.

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

Dosage and administration details:

Participants received 80 mg Osimertinib orally once daily

Number of subjects in period 1	Osimertinib 80mg
Started	154
Completed	33
Not completed	121
Physician decision	16
Lost to follow-up	2
Patients who are ongoing in the study at DCO	10
Death	40
Other	26
Withdrawal by Subject	27

Baseline characteristics

Reporting groups	
Reporting group title	Osimertinib 80mg
Reporting group description:	
Participants received Osimertinib 80mg orally once daily.	

Reporting group values	Osimertinib 80mg	Total	
Number of subjects	154	154	
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adults (<50)	18	18	
>=50 - <65	65	65	
>=65 - <75	50	50	
>=75	21	21	
Age Continuous Units: years			
arithmetic mean	62.7		
standard deviation	± 10.36	-	
Sex: Female, Male Units: Participants			
Female	92	92	
Male	62	62	
Race/Ethnicity, Customized Units: Subjects			
White	30	30	
Black or African American	5	5	
Asian	118	118	
Other	1	1	
Race/Ethnicity, Customized Units: Subjects			
Hispanic	6	6	
Not Hispanic or Latino	148	148	

Subject analysis sets	
Subject analysis set title	Exon19del- EGFR tumor mutation at baseline
Subject analysis set type	Full analysis
Subject analysis set description: Participants with Exon19del received Osimertinib 80mg orally once daily.	
Subject analysis set title	L858R- EGFR tumor mutation at baseline
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with L858R received Osimertinib 80mg orally once daily

Subject analysis set title	Exon19del- Detectable in plasma ctDNA at baseline
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with Exon19del received Osimertinib 80mg orally once daily

Subject analysis set title	L858R-Detectable in plasma ctDNA at baseline
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with L858R received Osimertinib 80mg orally once daily

Reporting group values	Exon19del- EGFR tumor mutation at baseline	L858R- EGFR tumor mutation at baseline	Exon19del- Detectable in plasma ctDNA at baseline
Number of subjects	85	58	62
Age categorical Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adults (<50)	11	5	
>=50 - <65	41	23	
>=65 - <75	21	22	
>=75	12	8	
Age Continuous Units: years			
arithmetic mean	61.6	63.8	
standard deviation	± 10.74	± 9.51	±
Sex: Female, Male Units: Participants			
Female	34	23	
Male	51	35	
Race/Ethnicity, Customized Units: Subjects			
White	11	17	
Black or African American	4	0	
Asian	69	41	
Other	1	0	
Race/Ethnicity, Customized Units: Subjects			
Hispanic	3	3	
Not Hispanic or Latino	82	55	

Reporting group values	L858R-Detectable in plasma ctDNA at baseline		
Number of subjects	46		
Age categorical Units: Subjects			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adults (<50) >=50 - <65 >=65 - <75 >=75			
Age Continuous Units: years arithmetic mean standard deviation	±		
Sex: Female, Male Units: Participants			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
White Black or African American Asian Other			
Race/Ethnicity, Customized Units: Subjects			
Hispanic Not Hispanic or Latino			

End points

End points reporting groups

Reporting group title	Osimertinib 80mg
Reporting group description: Participants received Osimertinib 80mg orally once daily.	
Subject analysis set title	Exon19del- EGFR tumor mutation at baseline
Subject analysis set type	Full analysis
Subject analysis set description: Participants with Exon19del received Osimertinib 80mg orally once daily.	
Subject analysis set title	L858R- EGFR tumor mutation at baseline
Subject analysis set type	Full analysis
Subject analysis set description: Participants with L858R received Osimertinib 80mg orally once daily	
Subject analysis set title	Exon19del- Detectable in plasma ctDNA at baseline
Subject analysis set type	Full analysis
Subject analysis set description: Participants with Exon19del received Osimertinib 80mg orally once daily	
Subject analysis set title	L858R-Detectable in plasma ctDNA at baseline
Subject analysis set type	Full analysis
Subject analysis set description: Participants with L858R received Osimertinib 80mg orally once daily	

Primary: Proportion of patients with a given tumour genetic and proteomic marker at the point of disease progression

End point title	Proportion of patients with a given tumour genetic and proteomic marker at the point of disease progression[1]

End point description:

The frequency of genetic and proteomic markers at disease progression regardless of their prevalence was evaluated. The primary analysis set included all patients with evaluable paired biopsies, which were defined as follows: the first biopsy was taken prior to osimertinib treatment, and the second biopsy was taken at any time between Investigator-assessed RECIST 1.1-defined progression and before the start of any new anticancer treatment. The primary analysis set was included for the analysis for the endpoint.

End point type	Primary

End point timeframe:

Genetic and proteomic markers were assessed at baseline and progression (up to 5 years after baseline)

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 analysis was calculated for the Outcome measure

End point values	Osimertinib 80mg			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: Percentage of participants				
number (confidence interval 95%)				
AKT2; Copy Number Alteration: Type; amplification	2.0 (0.05 to 10.45)			
ALK; Rearrangement	3.9 (0.48 to 13.46)			
APC; Copy Number Alteration; Type: loss	2.0 (0.05 to 10.45)			

ARAF; Copy Number Alteration; Type: amplification	3.9 (0.48 to 13.46)			
ASXL1; Short Variant; Type: Q588*	2.0 (0.05 to 10.45)			
ATRX; Short Variant; Type: P599fs*22	2.0 (0.05 to 10.45)			
AXL; Copy Number Alteration; Type: amplification	2.0 (0.05 to 10.45)			
BCL2L2; Copy Number Alteration; Type:amplification	3.9 (0.48 to 13.46)			
BRAF; Rearrangement	2.0 (0.05 to 10.45)			
BRAF; Short variant; Type: G469A	2.0 (0.05 to 10.45)			
BRAF; Short variant Type: V600E	3.9 (0.48 to 13.46)			
CBL; Short Variant; Type: R149Q	2.0 (0.05 to 10.45)			
CCND1 Copy Number Alteration Type: amplification	3.9 (0.48 to 13.46)			
CCNE1 Copy Number Alteration Type: amplification	5.9 (1.23 to 16.24)			
CDK4 Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
CDK6 Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
CDKN1B Short Variant Type: S2*	2.0 (0.05 to 10.45)			
CDKN2A Copy Number Alteration Type: loss	15.7 (7.02 to 28.59)			
CDKN2A; Short Variant Type: P38L	2.0 (0.05 to 10.45)			
CDKN2B Copy Number Alteration Type: loss	15.7 (7.02 to 28.59)			
CRKL Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
CUL4A Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
DIS3 Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
EGFR Copy Number Alteration Type: amplification	11.8 (4.44 to 23.87)			
EGFR Rearrangement	2.0 (0.05 to 10.45)			
EGFR Short Variant Type: C797S	13.7 (5.70 to 26.26)			
EGFR Short Variant Type: L858R	2.0 (0.05 to 10.45)			
EMSY Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
ERBB2 Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
FANCG Rearrangement	2.0 (0.05 to 10.45)			
FGF10 Copy Number Alteration Type: amplification	3.9 (0.48 to 13.46)			
FGF14; Copy Number Alteration; Type: amplification	2.0 (0.05 to 10.45)			
FGF19 Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
FGFR1 Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			

FGFR3 Rearrangement	2.0 (0.05 to 10.45)			
FGFR4 Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
HGF Copy Number Alteration Type: amplification	3.9 (0.48 to 13.46)			
HRAS Short Variant Type: Q61R	2.0 (0.05 to 10.45)			
IDH1 Short Variant Type: R132L	2.0 (0.05 to 10.45)			
IGF1R Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
IRS2 Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
KRAS Copy Number Alteration Type: amplification	3.9 (0.48 to 13.46)			
LYN Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
MAP2K1 Short Variant Type: E102_I103del	2.0 (0.05 to 10.45)			
MCL1 Copy Number Alteration Type: amplification	5.9 (1.23 to 16.24)			
MDM2 Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
MET Copy Number Alteration Type: amplification	17.6 (8.40 to 30.87)			
MTAP Copy Number Alteration Type: loss	13.7 (5.70 to 26.26)			
MYC Copy Number Alteration Type: amplification	3.9 (0.48 to 13.46)			
MYCN Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
NF1 Short Variant Type: M1I	2.0 (0.05 to 10.45)			
NFE2L2 Short Variant Type: D29N	2.0 (0.05 to 10.45)			
NFKBIA Copy Number Alteration Type: amplification	9.8 (3.26 to 21.41)			
NKX2-1 Copy Number Alteration Type: amplification	9.8 (3.26 to 21.41)			
NOTCH3 Rearrangement	2.0 (0.05 to 10.45)			
NTRK1 Copy Number Alteration Type: amplification	3.9 (0.48 to 13.46)			
PARP1 Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
PDGFRB Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
PIK3CA Short Variant Type: E542K	2.0 (0.05 to 10.45)			
PIM1 Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
RAD21 Copy Number Alteration Type: amplification	3.9 (0.48 to 13.46)			
RB1 Copy Number Alteration Type: loss	3.9 (0.48 to 13.46)			
RB1 Short Variant Type: Q846*	2.0 (0.05 to 10.45)			
RICTOR Copy Number Alteration Type: amplification	7.8 (2.18 to 18.88)			
SMAD4 Rearrangement	2.0 (0.05 to 10.45)			

SMAD4 Short Variant Type: W524L	2.0 (0.05 to 10.45)			
SPEN Short Variant Type: D2047fs*17	2.0 (0.05 to 10.45)			
STK11 Copy Number Alteration Type: loss	2.0 (0.05 to 10.45)			
STK11 Short Variant Type: K269fs*18	2.0 (0.05 to 10.45)			
TERC Copy Number Alteration Type: amplification	2.0 (0.05 to 10.45)			
TERT Short Variant Type: promoter -146C>T	2.0 (0.05 to 10.45)			
TET2 Short Variant Type: Q916*	2.0 (0.05 to 10.45)			
TET2 Short Variant Type: V1862fs*13	2.0 (0.05 to 10.45)			
TP53 Short Variant Type: R213*	2.0 (0.05 to 10.45)			
WHSC1L1 Copy Number Alteration Type: amplification	3.9 (0.48 to 13.46)			
ZNF703 Copy Number Alteration Type: amplification	3.9 (0.48 to 13.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

PFS is defined as the time from first dose of osimertinib until the date of Investigator assessed Response Evaluation Criteria in Solid Tumours (RECIST) 1.1-defined progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression. The full analysis set included all patients who received at least one dose of Osimertinib.

End point type	Secondary

End point timeframe:

From date of first dose until date of progression or death (by any cause in the absence of recurrence), up to 5 years

End point values	Osimertinib 80mg			
Subject group type	Reporting group			
Number of subjects analysed	154			
Units: Months				
median (confidence interval 95%)	16.4 (12.7 to 20.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR is defined as the number (%) of patients with at least one visit response of complete response (CR) or partial response (PR) that is confirmed at least 4 weeks later. The full analysis set included all patients who received at least one dose of Osimertinib.

End point type	Secondary

End point timeframe:

From date of first dose until progression, or last evaluable assessment in the absence of progression, up to 5 years

End point values	Osimertinib 80mg			
Subject group type	Reporting group			
Number of subjects analysed	154			
Units: Percentage of participants				
number (confidence interval 95%)	73.4 (65.66 to 80.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

Duration of response is defined as the time from the date of first documented response, (that is subsequently confirmed) until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was CR or PR that was subsequently confirmed. The full analysis set included all patients who received at least one dose of Osimertinib. The Duration of response is calculated for only participants with a confirmed response. Participants must have had measurable disease at baseline to be included in the study.

End point type	Secondary

End point timeframe:

From date of first documentation of complete/partial response until the date of progression, or last evaluable RECIST assessment for participants that did not progress within 2 missed visits of last assessment, up to 5 years

End point values	Osimertinib 80mg			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: Months				
median (confidence interval 95%)	18.8 (14.2 to 22.3)			

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 percentage of patients with confirmed complete response, confirmed partial response or with stable disease. The full analysis set included all patients who received at least one dose of Osimertinib.

End point type	Secondary

End point timeframe:

8 weeks

End point values	Osimertinib 80mg			
Subject group type	Reporting group			
Number of subjects analysed	154			
Units: Percentage of participants				
number (confidence interval 95%)	94.8 (90.02 to 97.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Discontinuation or Death (TTD)

End point title	Time to Treatment Discontinuation or Death (TTD)

End point description:

TTD is defined as the time from the date of first dose of osimertinib to the earliest of treatment discontinuation or death. The full analysis set included all patients who received at least one dose of osimertinib.

End point type	Secondary

End point timeframe:

From date of first dose to treatment discontinuation or death (by any cause in the absence of recurrence), up to 5 years

End point values	Osimertinib 80mg			
Subject group type	Reporting group			
Number of subjects analysed	154			
Units: Months				
median (confidence interval 95%)	20.0 (16.3 to 23.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first subsequent therapy or Death (TFST)

End point title	Time to first subsequent therapy or Death (TFST)

End point description:

TFST is defined as the time from the date of first dose of Osimertinib to the earlier of the date of anticancer therapy start date following study treatment discontinuation, or death. The full analysis set included all patients who received at least one dose of Osimertinib.

End point type	Secondary

End point timeframe:

From date of first dose to start of subsequent anticancer therapy or death (by any cause in the absence of recurrence), up to 5 years

End point values	Osimertinib 80mg			
Subject group type	Reporting group			
Number of subjects analysed	154			
Units: Months				
median (confidence interval 95%)	32.1 (24.0 to 47.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in patient subgroups defined by molecular profile: Epidermal growth factor receptor (EGFR) tumor mutation at baseline

End point title	PFS in patient subgroups defined by molecular profile: Epidermal growth factor receptor (EGFR) tumor mutation at baseline

End point description:

PFS is defined as the time from first dose of osimertinib until the date of Investigator assessed Response Evaluation Criteria in Solid Tumours (RECIST) 1.1-defined progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another

anticancer therapy prior to progression. PFS was analysed in patient subgroups defined by molecular profile, including but not limited to: EGFR tumor mutation at baseline-Exon19del or L858R. The full analysis set included all patients who received at least one dose of Osimertinib.

End point type	Secondary

End point timeframe:

From date of first dose until date of progression or death (by any cause in the absence of recurrence), up to 5 years

End point values	Exon19del-EGFR tumor mutation at baseline	L858R- EGFR tumor mutation at baseline		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	58		
Units: Months				
median (confidence interval 95%)	22.0 (16.0 to 27.6)	12.9 (10.8 to 18.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in patient subgroups defined by molecular profile: Detectable in plasma derived ctDNA at baseline

End point title	PFS in patient subgroups defined by molecular profile: Detectable in plasma derived ctDNA at baseline

End point description:

PFS is defined as the time from first dose of osimertinib until the date of Investigator assessed Response Evaluation Criteria in Solid Tumours (RECIST) 1.1-defined progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression. PFS was analysed in patient subgroups defined by molecular profile, including but not limited to: Exon19del or L858R detectable in plasma derived circulating tumour deoxyribonucleic acid (ctDNA) at baseline. The full analysis set included all patients who received at least 1 dose of Osimertinib.

End point type	Secondary

End point timeframe:

From date of first dose until date of progression or death (by any cause in the absence of recurrence), up to 5 years

End point values	Exon19del-Detectable in plasma ctDNA at baseline	L858R-Detectable in plasma ctDNA at baseline		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	46		
Units: Months				
median (confidence interval 95%)	19.6 (12.7 to 24.0)	13.7 (9.0 to 18.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR in patient subgroups defined by molecular profile: EGFR tumor mutation at baseline

End point title	ORR in patient subgroups defined by molecular profile: EGFR tumor mutation at baseline

End point description:

ORR is defined as the number (%) of patients with at least one visit response of complete response or partial response that is confirmed at least 4 weeks later. ORR was analysed in patient subgroups defined by molecular profile: EGFR tumor mutation at baseline-Exon19del or L858R. The full analysis set included all patients who received at least 1 dose of Osimertinib.

End point type	Secondary

End point timeframe:

From date of first dose until progression, or last evaluable assessment in the absence of progression, up to 5 years

End point values	Exon19del-EGFR tumor mutation at baseline	L858R- EGFR tumor mutation at baseline		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	58		
Units: Percentage of participants				
number (confidence interval 95%)	82.4 (72.57 to 89.77)	69.0 (55.46 to 80.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR in patient subgroups defined by molecular profile: Detectable in plasma derived ctDNA at baseline

End point title	ORR in patient subgroups defined by molecular profile: Detectable in plasma derived ctDNA at baseline

End point description:

ORR is defined as the number (%) of patients with at least one visit response of complete response or partial response that is confirmed at least 4 weeks later. ORR was analysed in patient subgroups defined by molecular profile: Exon19del or L858R detectable in plasma derived ctDNA at baseline. The full analysis set included all patients who received at least 1 dose of Osimertinib.

End point type	Secondary

End point timeframe:

From date of first dose until progression, or last evaluable assessment in the absence of progression, up

End point values	Exon19del-Detectable in plasma ctDNA at baseline	L858R-Detectable in plasma ctDNA at baseline		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	46		
Units: Percentage of participants				
number (confidence interval 95%)	85.5 (74.22 to 93.14)	71.7 (56.54 to 84.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: TTD in patient subgroups defined by molecular profile: EGFR tumor mutation at baseline

End point title	TTD in patient subgroups defined by molecular profile: EGFR tumor mutation at baseline

End point description:

TTD is defined as the time from the date of first dose of Osimertinib to the earliest of treatment discontinuation or death. TTD was analysed in patient subgroups defined by molecular profile: EGFR tumor mutation at baseline-Exon19del or L858R. The full analysis set included all patients who received at least 1 dose of Osimertinib.

End point type	Secondary

End point timeframe:

From date of first dose to treatment discontinuation or death (by any cause in the absence of recurrence), up to 5 years

End point values	Exon19del-EGFR tumor mutation at baseline	L858R- EGFR tumor mutation at baseline		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	58		
Units: Months				
median (confidence interval 95%)	25.5 (19.6 to 32.1)	16.5 (12.1 to 21.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: TTD in patient subgroups defined by molecular profile: Detectable in

plasma derived ctDNA at baseline

End point title	TTD in patient subgroups defined by molecular profile: Detectable in plasma derived ctDNA at baseline

End point description:

TTD is defined as the time from the date of first dose of osimertinib to the earliest of treatment discontinuation or death. TTD was analysed in patient subgroups defined by molecular profile: Exon19del or L858R detectable in plasma derived ctDNA at baseline. The full analysis set included all patients who received at least one dose of Osimertinib.

End point type	Secondary

End point timeframe:

From date of first dose to treatment discontinuation or death (by any cause in the absence of recurrence), up to 5 years

End point values	Exon19del-Detectable in plasma ctDNA at baseline	L858R-Detectable in plasma ctDNA at baseline		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	62	46		
Units: Months				
median (confidence interval 95%)	24.5 (17.8 to 29.6)	16.5 (12.1 to 21.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tumour shrinkage/depth of response in patient subgroups defined by molecular profile: EGFR tumor mutation at baseline

End point title	Tumour shrinkage/depth of response in patient subgroups defined by molecular profile: EGFR tumor mutation at baseline

End point description:

Tumor shrinkage is defined as the best change from baseline in the sum of diameters of target lesions, in patient subgroups defined by molecular profile: EGFR tumor mutation at baseline-Exon19del or L858R. A negative change denotes a reduction in target lesion size. The full analysis set included all patients who received at least 1 dose of Osimertinib.

End point type	Secondary

End point timeframe:

From date of first dose until last recorded post baseline RECIST target lesion assessment scan, up to 5 years

End point values	Exon19del-EGFR tumor mutation at baseline	L858R- EGFR tumor mutation at baseline		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83	55		
Units: Percentage change				

median (full range (min-max))	-59.68 (-100.0 to 6.5)	-54.29 (-100.0 to 7.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tumour shrinkage/depth of response in patient subgroups defined by molecular profile: Detectable in plasma derived ctDNA at baseline

End point title	Tumour shrinkage/depth of response in patient subgroups defined by molecular profile: Detectable in plasma derived ctDNA at baseline

End point description:

Tumour shrinkage is defined as the best change from baseline in the sum of diameters of target lesions, in patient subgroups defined by molecular profile: Exon19del or L858R detectable in plasma derived ctDNA at baseline. A negative change denotes a reduction in target lesion size. The full analysis set included all patients who received at least 1 dose of Osimertinib.

End point type	Secondary

End point timeframe:

From date of first dose until last recorded post baseline RECIST target lesion assessment scan, up to 5 years

End point values	Exon19del-Detectable in plasma ctDNA at baseline	L858R-Detectable in plasma ctDNA at baseline		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	44		
Units: Percentage change				
median (full range (min-max))	-60.80 (-100.0 to 6.5)	-58.33 (-100.0 to 7.6)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Day 1 to Follow-up (28 days post last dose) up to 5 years	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups	
Reporting group title	Osimertinib 80 mg
Reporting group description:	
Participants received Osimertinib 80mg orally once daily.	

Serious adverse events	Osimertinib 80 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 154 (34.42%)		
number of deaths (all causes)	40		
number of deaths resulting from adverse events	12		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Vaginal haemorrhage				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Haemoptysis				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	2 / 154 (1.30%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Dyspnoea				
subjects affected / exposed	2 / 154 (1.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Asthma				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pneumothorax				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	2 / 154 (1.30%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	4 / 154 (2.60%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Mania				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Platelet count decreased				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foreign body aspiration			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fibula fracture			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure			
subjects affected / exposed	2 / 154 (1.30%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Atrial fibrillation			
subjects affected / exposed	3 / 154 (1.95%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Acute coronary syndrome			
subjects affected / exposed	2 / 154 (1.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Immune thrombocytopenia			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood loss anaemia			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastritis			
subjects affected / exposed	3 / 154 (1.95%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Duodenitis			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 154 (1.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal impairment			

subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 154 (0.65%)		
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	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	3 / 154 (1.95%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Tuberculosis			
subjects affected / exposed	1 / 154 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	4 / 154 (2.60%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		

Respiratory tract infection				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia				
subjects affected / exposed	12 / 154 (7.79%)			
occurrences causally related to treatment / all	0 / 12			
deaths causally related to treatment / all	0 / 3			
Lower respiratory tract infection				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	2 / 154 (1.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyperglycaemic hyperosmolar nonketotic syndrome				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	2 / 154 (1.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	1 / 154 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Osimertinib 80 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	148 / 154 (96.10%)		
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 154 (5.84%)		
occurrences (all)	16		
Platelet count decreased			
subjects affected / exposed	11 / 154 (7.14%)		
occurrences (all)	16		
Weight decreased			
subjects affected / exposed	11 / 154 (7.14%)		
occurrences (all)	14		
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 154 (9.09%)		
occurrences (all)	14		
Alanine aminotransferase increased			
subjects affected / exposed	16 / 154 (10.39%)		
occurrences (all)	16		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 154 (7.14%)		
occurrences (all)	11		
Dizziness			
subjects affected / exposed	11 / 154 (7.14%)		
occurrences (all)	12		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	26 / 154 (16.88%)		
occurrences (all)	34		

Thrombocytopenia subjects affected / exposed occurrences (all)	9 / 154 (5.84%) 10		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all)	 11 / 154 (7.14%) 17 13 / 154 (8.44%) 14		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) Mouth ulceration subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 13 / 154 (8.44%) 16 8 / 154 (5.19%) 9 63 / 154 (40.91%) 94 14 / 154 (9.09%) 16 22 / 154 (14.29%) 30 15 / 154 (9.74%) 20 17 / 154 (11.04%) 21		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 8 / 154 (5.19%) 10		

Cough subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all)	32 / 154 (20.78%) 36 9 / 154 (5.84%) 9		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Dermatitis acneiform subjects affected / exposed occurrences (all)	 26 / 154 (16.88%) 30 23 / 154 (14.94%) 27 30 / 154 (19.48%) 37 21 / 154 (13.64%) 32		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 10 / 154 (6.49%) 11		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	 10 / 154 (6.49%) 12 18 / 154 (11.69%) 21 16 / 154 (10.39%) 20		
Infections and infestations Upper respiratory tract infection			

subjects affected / exposed	24 / 154 (15.58%)		
occurrences (all)	39		
Urinary tract infection			
subjects affected / exposed	16 / 154 (10.39%)		
occurrences (all)	21		
COVID-19			
subjects affected / exposed	14 / 154 (9.09%)		
occurrences (all)	14		
Paronychia			
subjects affected / exposed	36 / 154 (23.38%)		
occurrences (all)	72		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	27 / 154 (17.53%)		
occurrences (all)	32		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2023	There had been substantial amendment of the Protocol Version 2.0 on 05Sep17, version 3.0 on 24 January 2018, Version 4.0 on 25 September 2018, Version 5.0, 28 April 2022, Version 6.0, 02 November 2022 and Version 7.0 14 April 2023

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported