



Clinical trial results:

APPLE trial: Feasibility and activity of AZD9291 (osimertinib) treatment on Positive PLasma T790M in EGFR mutant NSCLC patients

Summary

EudraCT number	2016-001834-82
Trial protocol	SI ES PL
Global end of trial date	06 May 2022

Results information

Result version number	v1
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	1613-LCG
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02856893
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	EORTC
Sponsor organisation address	Avenue Emmanuel Mounier 83/11, Brussels, Belgium, 1200
Public contact	Regulatory Affairs Department, European Organisation for Research and Treatment of Cancer (EORTC), +32 2774 13 53, regulatory@eortc.org
Scientific contact	Regulatory Affairs Department, European Organisation for Research and Treatment of Cancer (EORTC), +32 2774 13 53, regulatory@eortc.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	06 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 May 2022
Global end of trial reached?	Yes
Global end of trial date	06 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the best strategy for delivering osimertinib (AZD9291) in NSCLC patients with EGFR mutation. The objective is assessed by Progression Free Survival rate at 18 months (PFSR-18).

Protection of trial subjects:

Safety data were reviewed within the EORTC Headquarters on a regular basis as part of the Medical Review process. Safety information was included in trial status reports which served as a basis of discussion during EORTC Group meetings.

Background therapy:

In treatment arm B, patients received Gefitinib until RECIST-based progressive disease, before switching to Osimertinib. In treatment arm C, patients received Gefitinib until RECIST-based progressive disease, before switching to Osimertinib.

Evidence for comparator:

No

Prior studies have indicated that Gefitinib improves the response rate (RR), progression-free survival (PFS) and quality of life over standard first-line platinum-doublet chemotherapy in several randomized phase III trials in EGFR mutant advanced NSCLC patients

Actual start date of recruitment	01 September 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	Spain: 74
Country: Number of subjects enrolled	France: 63
Country: Number of subjects enrolled	Jordan: 15
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Poland: 1
Worldwide total number of subjects	156
EEA total number of subjects	141

Notes:

Subjects enrolled per age group

In utero	0
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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)	72
From 65 to 84 years	78
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

The study intended to randomize 156 patients (52 patients per arm). It was expected that 156 patients would be randomized within 2 years and 2 months from the first patient randomized into the study.

In total, 156 patients have been randomized.

ECOG performance status of 0 or 1

Pre-assignment

Screening details:

Main eligibility criteria:

Stage IV NSCLC

common EGFR activating mutations associated with EGFR-TKI sensitivity (Del19 or L858R)

EGFR TKI treatment-naïve eligible to receive first-line treatment with

EGFR TKI

If brain metastases, only stable allowed

Adequate hepatic, renal and bone marrow function

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: first-line treatment with Osimertinib until RECIST pro

Arm description:

Osimertinib until PD according to RECIST 1.1

Arm type	Experimental
Investigational medicinal product name	Osimertinib
Investigational medicinal product code	DM09330
Other name	AZD9291 (Tagrisso)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

orally taken, beige, filmcoated tablet containing 40 mg or 80 mg of Osimertinib expressed as free base (equivalent of 47.7 mg or 95.4 mg of Osimertinib mesalate).

Osimertinib (TAGRISSO[™]1, laboratory code AZD9291) is an oral, irreversible inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor activating mutation (EGFRm) and the resistance mutation (T790M) specifically

Arm title	Arm B: Gefitinib until (cfDNA) PD followed by Osimertinib
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Arm description:

If patients have RECIST 1.1 progression without cfDNA T790M positive test, they will be switched to osimertinib. Note that that after protocol amendment 4, the T790M tests no longer needed to be performed for patients still on gefitinib. These patients should continue on gefitinib until progression by RECIST 1.1 (as in Arm C) .

Arm type	Active comparator
Investigational medicinal product name	Gefinitib
Investigational medicinal product code	DM00317
Other name	ZD1839 (IRESSA [™] , laboratory code)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

orally taken, brown, round, biconvex tablets containing 250 mg of gefitinib
Gefitinib (IRESSA™, laboratory code) is an oral, reversible inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor activating mutation (EGFRm).

Dose: Once a day (QD)

Investigational medicinal product name	Osimertinib
Investigational medicinal product code	DM09330
Other name	AZD9291 (Tagrisso)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

orally taken, beige, filmcoated tablet containing 40 mg or 80 mg of Osimertinib expressed as free base (equivalent of 47.7 mg or 95.4 mg of Osimertinib mesalate).

Osimertinib (TAGRISSO™1, laboratory code AZD9291) is an oral, irreversible inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor activating mutation (EGFRm) and the resistance mutation (T790M) specifically

Arm title	Arm C: Gefitinib until PD followed by Osimertinib
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Arm description:

Gefitinib until PD according to RECIST 1.1 followed by Osimertinib until PD according to RECIST 1.1 .

Arm type	Active comparator
Investigational medicinal product name	Gefitinib
Investigational medicinal product code	DM00317
Other name	ZD1839 (IRESSA™, laboratory code)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

orally taken, brown, round, biconvex tablets containing 250 mg of gefitinib

Gefitinib (IRESSA™, laboratory code) is an oral, reversible inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor activating mutation (EGFRm).

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Other name	AZD9291 (Tagrisso)
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Dosage and administration details:

orally taken, beige, filmcoated tablet containing 40 mg or 80 mg of Osimertinib expressed as free base (equivalent of 47.7 mg or 95.4 mg of Osimertinib mesalate).

Osimertinib (TAGRISSO™1, laboratory code AZD9291) is an oral, irreversible inhibitor of the tyrosine kinase activity of the epidermal growth factor receptor activating mutation (EGFRm) and the resistance mutation (T790M) specifically

Number of subjects in period 1	Arm A: first-line treatment with Osimertinib until RECIST pro	Arm B: Gefitinib until (cfDNA) PD followed by Osimertinib	Arm C: Gefitinib until PD followed by Osimertinib
Started	53	52	51
Completed	47	34	37
Not completed	6	18	14

death not due to malignant disease or tox	1	1	1
Investigator's decision	-	2	5
Adverse event, non-fatal	2	5	5
Other malignancy	2	-	-
Patient's decision	1	2	1
other	-	4	2
Missing	-	4	-

Baseline characteristics

Reporting groups

Reporting group title	Arm A: first-line treatment with Osimertinib until RECIST pro
Reporting group description:	
Osimertinib until PD according to RECIST 1.1	
Reporting group title	Arm B: Gefitinib until (cfDNA) PD followed by Osimertinib
Reporting group description:	
If patients have RECIST 1.1 progression without cfDNA T790M positive test, they will be switched to osimertinib. Note that that after protocol amendment 4, the T790M tests no longer needed to be performed for patients still on gefitinib. These patients should continue on gefitinib until progression by RECIST 1.1 (as in Arm C) .	
Reporting group title	Arm C: Gefitinib until PD followed by Osimertinib
Reporting group description:	
Gefitinib until PD according to RECIST 1.1 followed by Osimertinib until PD according to RECIST 1.1 .	

Reporting group values	Arm A: first-line treatment with Osimertinib until RECIST pro	Arm B: Gefitinib until (cfDNA) PD followed by Osimertinib	Arm C: Gefitinib until PD followed by Osimertinib
Number of subjects	53	52	51
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	21	20	31
From 65-84 years	29	32	17
85 years and over	3	0	3
Age continuous			
Units: years			
median	68	69	61
inter-quartile range (Q1-Q3)	60 to 76	61.5 to 75.5	54 to 68
Gender categorical			
Units: Subjects			
Female	30	39	33
Male	23	13	18
Prior neo-adjuvant therapy			
Was Prior neo-adjuvant therapy given?			
Units: Subjects			
yes	0	2	1
no	53	50	50
Prior adjuvant therapy			
Was prior adjuvant therapy given?			
Units: Subjects			
yes	2	0	1

no	51	52	50
T790M			
Stratification factor used for randomization			
Units: Subjects			
Mutation	0	0	0
No mutation	53	52	51
EGFR mutation			
Stratification factor used for randomization			
Units: Subjects			
Del19	35	33	33
L858R	18	19	18
Presence of brain metastases			
Stratification factor used for randomisation			
Units: Subjects			
yes	10	16	14
no	43	36	37
Smoking history			
Smoking history			
Units: Subjects			
Never smoked	35	37	30
Ex-smoker	17	12	17
Current smoker	1	3	3
missing	0	0	1

Reporting group values	Total		
Number of subjects	156		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	72		
From 65-84 years	78		
85 years and over	6		
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	102		
Male	54		
Prior neo-adjuvant therapy			
Was Prior neo-adjuvant therapy given?			
Units: Subjects			
yes	3		
no	153		

Prior adjuvant therapy			
Was prior adjuvant therapy given?			
Units: Subjects			
yes	3		
no	153		
T790M			
Stratification factor used for randomization			
Units: Subjects			
Mutation	0		
No mutation	156		
EGFR mutation			
Stratification factor used for randomization			
Units: Subjects			
Del19	101		
L858R	55		
Presence of brain metastases			
Stratification factor used for randomisation			
Units: Subjects			
yes	40		
no	116		
Smoking history			
Smoking history			
Units: Subjects			
Never smoked	102		
Ex-smoker	46		
Current smoker	7		
missing	1		

End points

End points reporting groups

Reporting group title	Arm A: first-line treatment with Osimertinib until RECIST pro
Reporting group description: Osimertinib until PD according to RECIST 1.1	
Reporting group title	Arm B: Gefitinib until (cfDNA) PD followed by Osimertinib
Reporting group description: If patients have RECIST 1.1 progression without cfDNA T790M positive test, they will be switched to osimertinib. Note that that after protocol amendment 4, the T790M tests no longer needed to be performed for patients still on gefitinib. These patients should continue on gefitinib until progression by RECIST 1.1 (as in Arm C) .	
Reporting group title	Arm C: Gefitinib until PD followed by Osimertinib
Reporting group description: Gefitinib until PD according to RECIST 1.1 followed by Osimertinib until PD according to RECIST 1.1 .	

Primary: Progression Free Survival at 18 months (PFSR-OSI-18)

End point title	Progression Free Survival at 18 months (PFSR-OSI-18)
End point description: The primary endpoint in this study is Progression Free Survival rate according to RECIST 1.1 "while receiving Osimertinib" at 18 months (PFSR-OSI-18). This endpoint is evaluated in arm B and C. In arm A (osimertinib alone), the endpoint is assessed to simply provide a point estimate for PFSR-OSI-18 and the corresponding confidence interval. The primary endpoint is defined as the proportion of patients at 18 months who are alive and did not experience an event for PFS-OSI according to the definition below. Practically, the time point of disease evaluation corresponding to the primary endpoint is 18 months after randomization. Therefore, disease evaluation at 18 months (+/- 14 days) is required for all patients who are still alive and without an event for PFS-OSI at the 18th month. Disease evaluation done within a window of +/- 2 weeks will be taken into account for the 18-month assessment.	
End point type	Primary
End point timeframe: 18 months after randomization	

End point values	Arm A: first-line treatment with Osimertinib until RECIST pro	Arm B: Gefitinib until (cfDNA) PD followed by Osimertinib	Arm C: Gefitinib until PD followed by Osimertinib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45 ^[1]	47 ^[2]	44 ^[3]	
Units: events per 1.5 years				
number (confidence interval 95%)	51.1 (35.8 to 64.5)	67.2 (51.5 to 78.8)	53.5 (37.7 to 67.0)	

Notes:

[1] - per-protocol patient population

[2] - per-protocol patient population

[3] - per-protocol patient population

Statistical analyses

Statistical analysis title	Progression-free survival rate at 18 months Arm B
Statistical analysis description: analysis of progression free survival rate at 18 months while on osimertinib. The decision rule is based on the lower bound of the 84% confidence interval: If it above 40% (null hypothesis), the arm will be declared worthwhile of further investigation, if below the arm should be rejected from further exploration	
Comparison groups	Arm A: first-line treatment with Osimertinib until RECIST pro v Arm B: Gefitinib until (cfDNA) PD followed by Osimertinib v Arm C: Gefitinib until PD followed by Osimertinib
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other ^[4]
Parameter estimate	PFSR-OSI-18 rate
Point estimate	67.2
Confidence interval	
level	Other: 84 %
sides	2-sided
lower limit	56.4
upper limit	75.9

Notes:

[4] - derivation of 84% confidence intervals was done using the Kaplan-Meier technique.

Statistical analysis title	Progression free survival rate at 18 months Arm C
Statistical analysis description: analysis of progression free survival rate at 18 months while on osimertinib. The decision rule is based on the lower bound of the 84% confidence interval: If it above 40% (null hypothesis), the arm will be declared worthwhile of further investigation, if below the arm should be rejected from further exploration	
Comparison groups	Arm C: Gefitinib until PD followed by Osimertinib v Arm B: Gefitinib until (cfDNA) PD followed by Osimertinib v Arm A: first-line treatment with Osimertinib until RECIST pro
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other ^[5]
Parameter estimate	PFSR-OSI-18 rate
Point estimate	53.5
Confidence interval	
level	Other: 84 %
sides	2-sided
lower limit	42.3
upper limit	63.5

Notes:

[5] - derivation of 84% confidence intervals was done using the Kaplan-Meier technique.

Secondary: Overall Survival

End point title	Overall Survival
End point description:	
End point type	Secondary
End point timeframe:	
Overall survival time is computed from date of registration until date of death from any cause. If no death has been observed, then the patient is censored at the last date known to be alive.	

End point values	Arm A: first-line treatment with Osimertinib until RECIST pro	Arm B: Gefitinib until (cfDNA) PD followed by Osimertinib	Arm C: Gefitinib until PD followed by Osimertinib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45 ^[6]	47 ^[7]	44 ^[8]	
Units: Months				
median (confidence interval 95%)	84.4 (70.1 to 92.3)	87.0 (73.3 to 93.9)	77.3 (61.9 to 87.1)	

Notes:

[6] - Per protocol set

[7] - Per protocol set

[8] - Per protocol set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The number of patients who had specific adverse events in the period between the randomization and time of treatment discontinuation was reported

Adverse event reporting additional description:

Adverse events are evaluated using CTC grading. Serious adverse events were defined following the Good Clinical Practice Guideline.

Adverse events are reported as belonging to the treatment period if the adverse event start date falls on the first day of treatment and up till the date of last treatment administration + 30 days.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Arm A
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Reporting group description: -

Reporting group title	Arm B
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Reporting group description:

for the Serious adverse events and deaths, no distinction is made between between the GEFITINIB and OSIMERITINIB period.

Reporting group title	Arm C
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Reporting group description: -

Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 53 (26.42%)	10 / 52 (19.23%)	22 / 51 (43.14%)
number of deaths (all causes)	20	20	20
number of deaths resulting from adverse events	2	1	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Carcinoma in situ			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to meninges			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			

subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Ventricular dyskinesia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood and lymphatic system disorders			
Splenic infarction			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	3 / 51 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Dyspnoea			
subjects affected / exposed	2 / 53 (3.77%)	0 / 52 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung disorder			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal infarct			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			

subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Diverticulitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Septic shock			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypophagia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 53 (98.11%)	51 / 52 (98.08%)	50 / 51 (98.04%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 53 (0.00%)	2 / 52 (3.85%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Neoplasms Other			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	1	1	1
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Hot Flashes			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Hypertension			
subjects affected / exposed	7 / 53 (13.21%)	8 / 52 (15.38%)	5 / 51 (9.80%)
occurrences (all)	7	8	5

Hypotension			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Thromboembolic Event			
subjects affected / exposed	7 / 53 (13.21%)	2 / 52 (3.85%)	2 / 51 (3.92%)
occurrences (all)	7	2	2
Vascular Other			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	1	1	1
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 53 (1.89%)	4 / 52 (7.69%)	0 / 51 (0.00%)
occurrences (all)	1	4	0
oedema limbs			
subjects affected / exposed	2 / 53 (3.77%)	2 / 52 (3.85%)	4 / 51 (7.84%)
occurrences (all)	2	2	4
Facial pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Fatigue			
subjects affected / exposed	18 / 53 (33.96%)	17 / 52 (32.69%)	15 / 51 (29.41%)
occurrences (all)	18	17	15
Fever			
subjects affected / exposed	3 / 53 (5.66%)	2 / 52 (3.85%)	3 / 51 (5.88%)
occurrences (all)	3	2	3
Flu Like Symptoms			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	3 / 51 (5.88%)
occurrences (all)	1	1	3
Gait disturbance			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Localised oedema			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Malaise			

subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 52 (1.92%) 1	1 / 51 (1.96%) 1
Multi-Organ Failure subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	0 / 52 (0.00%) 0	0 / 51 (0.00%) 0
Non-cardiac chest pain subjects affected / exposed occurrences (all)	6 / 53 (11.32%) 6	2 / 52 (3.85%) 2	7 / 51 (13.73%) 7
Pain subjects affected / exposed occurrences (all)	5 / 53 (9.43%) 5	4 / 52 (7.69%) 4	7 / 51 (13.73%) 7
GENERAL Other subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	0 / 52 (0.00%) 0	1 / 51 (1.96%) 1
Immune system disorders Allergic Reaction subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 52 (1.92%) 1	1 / 51 (1.96%) 1
Reproductive system and breast disorders Irregular menstruation subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 52 (1.92%) 1	0 / 51 (0.00%) 0
Menorrhagia subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	1 / 52 (1.92%) 1	0 / 51 (0.00%) 0
Vaginal inflammation subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 52 (0.00%) 0	2 / 51 (3.92%) 2
Respiratory, thoracic and mediastinal disorders Adult Respiratory Distress Syndrome subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 52 (0.00%) 0	1 / 51 (1.96%) 1
Allergic Rhinitis subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	3 / 52 (5.77%) 3	0 / 51 (0.00%) 0
Bronchospasm			

subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	10 / 53 (18.87%)	9 / 52 (17.31%)	10 / 51 (19.61%)
occurrences (all)	10	9	10
Dyspnoea			
subjects affected / exposed	10 / 53 (18.87%)	3 / 52 (5.77%)	6 / 51 (11.76%)
occurrences (all)	10	3	6
Epistaxis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	4 / 51 (7.84%)
occurrences (all)	1	0	4
Hoarseness			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Laryngeal mucositis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	2 / 51 (3.92%)
occurrences (all)	1	1	2
Pharyngeal haemorrhage			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
pharyngeal mucositis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Pharyngolaryngeal Pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			
subjects affected / exposed	0 / 53 (0.00%)	2 / 52 (3.85%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Pleuratic pain			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	1	1	0
Pneumonitis			

subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Pneumothorax			
subjects affected / exposed	2 / 53 (3.77%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	2	0	0
Postnasal Drip			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	2 / 53 (3.77%)	2 / 52 (3.85%)	2 / 51 (3.92%)
occurrences (all)	2	2	2
Sore Throat			
subjects affected / exposed	1 / 53 (1.89%)	2 / 52 (3.85%)	2 / 51 (3.92%)
occurrences (all)	1	2	2
Voice Alteration			
subjects affected / exposed	2 / 53 (3.77%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	2	0	0
Respiratory Other			
subjects affected / exposed	2 / 53 (3.77%)	3 / 52 (5.77%)	2 / 51 (3.92%)
occurrences (all)	2	3	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	6 / 51 (11.76%)
occurrences (all)	0	1	6
Confusion			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	2 / 51 (3.92%)
occurrences (all)	0	1	2
Depression			
subjects affected / exposed	2 / 53 (3.77%)	3 / 52 (5.77%)	0 / 51 (0.00%)
occurrences (all)	2	3	0
Insomnia			
subjects affected / exposed	4 / 53 (7.55%)	1 / 52 (1.92%)	3 / 51 (5.88%)
occurrences (all)	4	1	3
Psychosis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 53 (13.21%)	14 / 52 (26.92%)	15 / 51 (29.41%)
occurrences (all)	7	14	15
Alkaline Phosphatase Increased			
subjects affected / exposed	4 / 53 (7.55%)	3 / 52 (5.77%)	5 / 51 (9.80%)
occurrences (all)	4	3	5
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 53 (9.43%)	12 / 52 (23.08%)	13 / 51 (25.49%)
occurrences (all)	5	12	13
Blood bilirubin increased			
subjects affected / exposed	0 / 53 (0.00%)	2 / 52 (3.85%)	4 / 51 (7.84%)
occurrences (all)	0	2	4
Cholesterol High			
subjects affected / exposed	2 / 53 (3.77%)	3 / 52 (5.77%)	2 / 51 (3.92%)
occurrences (all)	2	3	2
Cpk Increased			
subjects affected / exposed	2 / 53 (3.77%)	1 / 52 (1.92%)	3 / 51 (5.88%)
occurrences (all)	2	1	3
Creatinine Increased			
subjects affected / exposed	3 / 53 (5.66%)	5 / 52 (9.62%)	3 / 51 (5.88%)
occurrences (all)	3	5	3
Electrocardiogram Qt Corrected Interval			
subjects affected / exposed	4 / 53 (7.55%)	3 / 52 (5.77%)	2 / 51 (3.92%)
occurrences (all)	4	3	2
Ggt Increased			
subjects affected / exposed	6 / 53 (11.32%)	3 / 52 (5.77%)	4 / 51 (7.84%)
occurrences (all)	6	3	4
Haemoglobin increased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 53 (0.00%)	2 / 52 (3.85%)	1 / 51 (1.96%)
occurrences (all)	0	2	1
Neutrophil count decreased			

subjects affected / exposed	5 / 53 (9.43%)	9 / 52 (17.31%)	4 / 51 (7.84%)
occurrences (all)	5	9	4
Platelet count decreased			
subjects affected / exposed	12 / 53 (22.64%)	7 / 52 (13.46%)	2 / 51 (3.92%)
occurrences (all)	12	7	2
Weight gain			
subjects affected / exposed	5 / 53 (9.43%)	4 / 52 (7.69%)	10 / 51 (19.61%)
occurrences (all)	5	4	10
Weight loss			
subjects affected / exposed	19 / 53 (35.85%)	15 / 52 (28.85%)	19 / 51 (37.25%)
occurrences (all)	19	15	19
White blood cell decreased			
subjects affected / exposed	3 / 53 (5.66%)	3 / 52 (5.77%)	0 / 51 (0.00%)
occurrences (all)	3	3	0
INV other			
subjects affected / exposed	2 / 53 (3.77%)	3 / 52 (5.77%)	6 / 51 (11.76%)
occurrences (all)	2	3	6
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Hip fracture			
subjects affected / exposed	2 / 53 (3.77%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	2	0	0
Injury to carotid artery			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Spinal fracture			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	1	1	0
Injury Other			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	3 / 51 (5.88%)
occurrences (all)	1	0	3
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Acute coronary syndrome			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
heart failure			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Pericardial effusion			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Sinus tachycardia			
subjects affected / exposed	1 / 53 (1.89%)	3 / 52 (5.77%)	1 / 51 (1.96%)
occurrences (all)	1	3	1
Supraventricular tachycardia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Atrial flutter			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Mitral valve disease			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Pericardial Tamponade			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Sinus bradycardia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1

Cardiac OTHER			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	2 / 51 (3.92%)
occurrences (all)	0	0	2
Concentration impairment			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Depressed level of consciousness			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	2 / 51 (3.92%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	2 / 53 (3.77%)	8 / 52 (15.38%)	4 / 51 (7.84%)
occurrences (all)	2	8	4
Dysaesthesia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	7 / 53 (13.21%)	2 / 52 (3.85%)	4 / 51 (7.84%)
occurrences (all)	7	2	4
Dysphagia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Oedema cerebral			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Facial nerve disorder			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	1 / 53 (1.89%)	10 / 52 (19.23%)	11 / 51 (21.57%)
occurrences (all)	1	10	11
Memory impairment			

subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	1	1	1
Neuralgia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Oculomotor nerve disorder			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Paresthesia			
subjects affected / exposed	4 / 53 (7.55%)	3 / 52 (5.77%)	3 / 51 (5.88%)
occurrences (all)	4	3	3
Peripheral motor neuropathy			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 53 (3.77%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	2	1	0
Presyncope			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Radiculitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Recurrent Laryngeal Nerve Palsy			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Seizure			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Spasticity			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Stroke			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	2 / 51 (3.92%)
occurrences (all)	0	0	2
Transient ischaemic attack			

subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Nervous Other			
subjects affected / exposed	0 / 53 (0.00%)	3 / 52 (5.77%)	2 / 51 (3.92%)
occurrences (all)	0	3	2
Blood and lymphatic system disorders			
anemia			
subjects affected / exposed	10 / 53 (18.87%)	10 / 52 (19.23%)	5 / 51 (9.80%)
occurrences (all)	10	10	5
Leukocytosis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Bood OTHER			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 53 (3.77%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	2	0	1
Vertigo			
subjects affected / exposed	2 / 53 (3.77%)	1 / 52 (1.92%)	2 / 51 (3.92%)
occurrences (all)	2	1	2
EAR OTHER			
subjects affected / exposed	0 / 53 (0.00%)	2 / 52 (3.85%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
External ear inflammation			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Hearing disability			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Tinnitus			

subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 52 (0.00%) 0	1 / 51 (1.96%) 1
Eye disorders			
Blurred vision			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	2 / 51 (3.92%)
occurrences (all)	1	1	2
Cataract			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	1	1	1
Conjunctivitis			
subjects affected / exposed	2 / 53 (3.77%)	3 / 52 (5.77%)	3 / 51 (5.88%)
occurrences (all)	2	3	3
Dry eye			
subjects affected / exposed	1 / 53 (1.89%)	6 / 52 (11.54%)	7 / 51 (13.73%)
occurrences (all)	1	6	7
Papilloedema			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Vitreous haemorrhage			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Watering Eyes			
subjects affected / exposed	2 / 53 (3.77%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	2	0	1
EYES OTHER			
subjects affected / exposed	1 / 53 (1.89%)	4 / 52 (7.69%)	3 / 51 (5.88%)
occurrences (all)	1	4	3
Eye pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Keratitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	2 / 51 (3.92%)
occurrences (all)	0	1	2
Glaucoma			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 53 (7.55%)	6 / 52 (11.54%)	6 / 51 (11.76%)
occurrences (all)	4	6	6
Anal ulcer			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	7 / 53 (13.21%)	6 / 52 (11.54%)	5 / 51 (9.80%)
occurrences (all)	7	6	5
Dental caries			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	27 / 53 (50.94%)	30 / 52 (57.69%)	28 / 51 (54.90%)
occurrences (all)	27	30	28
Dry mouth			
subjects affected / exposed	3 / 53 (5.66%)	3 / 52 (5.77%)	3 / 51 (5.88%)
occurrences (all)	3	3	3
Gastritis			
subjects affected / exposed	1 / 53 (1.89%)	2 / 52 (3.85%)	0 / 51 (0.00%)
occurrences (all)	1	2	0
Gastroesophageal Reflux Disease			
subjects affected / exposed	2 / 53 (3.77%)	5 / 52 (9.62%)	6 / 51 (11.76%)
occurrences (all)	2	5	6
Abdominal distension			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Anal haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	2 / 52 (3.85%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Colitis			
subjects affected / exposed	0 / 53 (0.00%)	2 / 52 (3.85%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Dyspepsia			

subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	2 / 51 (3.92%)
occurrences (all)	0	1	2
Dysphagia			
subjects affected / exposed	0 / 53 (0.00%)	3 / 52 (5.77%)	1 / 51 (1.96%)
occurrences (all)	0	3	1
Enterocolitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Esophagitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	2 / 51 (3.92%)
occurrences (all)	0	0	2
Gastrointestinal pain			
subjects affected / exposed	2 / 53 (3.77%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	2	1	0
Gingival pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	4 / 53 (7.55%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	4	0	1
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Mucositis Oral			
subjects affected / exposed	7 / 53 (13.21%)	9 / 52 (17.31%)	6 / 51 (11.76%)
occurrences (all)	7	9	6
Nausea			
subjects affected / exposed	4 / 53 (7.55%)	8 / 52 (15.38%)	8 / 51 (15.69%)
occurrences (all)	4	8	8
Oral dysaesthesia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Oral Hemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Oral pain			

subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Periodontal disease			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Rectal haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Salivary duct inflammation			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
stomach pain			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Toothache			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	1	1	1
Vomiting			
subjects affected / exposed	2 / 53 (3.77%)	4 / 52 (7.69%)	4 / 51 (7.84%)
occurrences (all)	2	4	4
GASTRO Other			
subjects affected / exposed	4 / 53 (7.55%)	2 / 52 (3.85%)	1 / 51 (1.96%)
occurrences (all)	4	2	1
Hepatobiliary disorders			
HEPATO Other			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	5 / 51 (9.80%)
occurrences (all)	0	0	5
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 53 (5.66%)	5 / 52 (9.62%)	1 / 51 (1.96%)
occurrences (all)	3	5	1
Bullous Dermatitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Dry skin			

subjects affected / exposed	22 / 53 (41.51%)	18 / 52 (34.62%)	17 / 51 (33.33%)
occurrences (all)	22	18	17
Erythema multiforme			
subjects affected / exposed	3 / 53 (5.66%)	1 / 52 (1.92%)	3 / 51 (5.88%)
occurrences (all)	3	1	3
Hirsutism			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	1	1	0
Hypertrichosis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	3 / 51 (5.88%)
occurrences (all)	0	0	3
Nail discolouration			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Nail Loss			
subjects affected / exposed	3 / 53 (5.66%)	1 / 52 (1.92%)	2 / 51 (3.92%)
occurrences (all)	3	1	2
Nail ridging			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Pain of skin			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	1	1	1
Periorbital oedema			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Photosensitivity			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	7 / 53 (13.21%)	10 / 52 (19.23%)	10 / 51 (19.61%)
occurrences (all)	7	10	10

Rash acneiform subjects affected / exposed occurrences (all)	11 / 53 (20.75%) 11	24 / 52 (46.15%) 24	19 / 51 (37.25%) 19
Rash maculo-papular subjects affected / exposed occurrences (all)	4 / 53 (7.55%) 4	7 / 52 (13.46%) 7	5 / 51 (9.80%) 5
Skin hyperpigmentation subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	0 / 52 (0.00%) 0	0 / 51 (0.00%) 0
Skin ulceration subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	2 / 52 (3.85%) 2	2 / 51 (3.92%) 2
Skin Other subjects affected / exposed occurrences (all)	9 / 53 (16.98%) 9	11 / 52 (21.15%) 11	6 / 51 (11.76%) 6
Renal and urinary disorders			
Acute kidney injury subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 2	3 / 52 (5.77%) 3	0 / 51 (0.00%) 0
Chronic kidney disease subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	0 / 52 (0.00%) 0	0 / 51 (0.00%) 0
Cystitis noninfective subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	1 / 52 (1.92%) 1	5 / 51 (9.80%) 5
Haematuria subjects affected / exposed occurrences (all)	2 / 53 (3.77%) 2	0 / 52 (0.00%) 0	2 / 51 (3.92%) 2
Renal colic subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	2 / 52 (3.85%) 2	1 / 51 (1.96%) 1
Urinary frequency subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	2 / 52 (3.85%) 2	1 / 51 (1.96%) 1
Urinary incontinence			

subjects affected / exposed	1 / 53 (1.89%)	2 / 52 (3.85%)	0 / 51 (0.00%)
occurrences (all)	1	2	0
Urinary tract pain			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	3 / 51 (5.88%)
occurrences (all)	0	1	3
Urinary urgency			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Urine discoloration			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Renal Other			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	2 / 51 (3.92%)
occurrences (all)	1	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 53 (9.43%)	1 / 52 (1.92%)	3 / 51 (5.88%)
occurrences (all)	5	1	3
Arthritis			
subjects affected / exposed	2 / 53 (3.77%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	2	1	0
Back pain			
subjects affected / exposed	9 / 53 (16.98%)	8 / 52 (15.38%)	10 / 51 (19.61%)
occurrences (all)	9	8	10
Bone pain			
subjects affected / exposed	4 / 53 (7.55%)	3 / 52 (5.77%)	6 / 51 (11.76%)
occurrences (all)	4	3	6
Chest wall pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Flank pain			
subjects affected / exposed	0 / 53 (0.00%)	5 / 52 (9.62%)	1 / 51 (1.96%)
occurrences (all)	0	5	1
Generalized Muscle Weakness			

subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	0	0	0
Muscle Weakness Upper Limb			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	4 / 53 (7.55%)	2 / 52 (3.85%)	6 / 51 (11.76%)
occurrences (all)	4	2	6
Myositis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	5 / 53 (9.43%)	2 / 52 (3.85%)	5 / 51 (9.80%)
occurrences (all)	5	2	5
Osteoporosis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	2 / 53 (3.77%)	3 / 52 (5.77%)	5 / 51 (9.80%)
occurrences (all)	2	3	5
Musculoskeletal Other			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	2 / 51 (3.92%)
occurrences (all)	1	0	2
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Bronchial Infection			
subjects affected / exposed	2 / 53 (3.77%)	2 / 52 (3.85%)	2 / 51 (3.92%)
occurrences (all)	2	2	2
Gum Infection			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Hepatitis viral			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0

Lip infection			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Lung Infection			
subjects affected / exposed	1 / 53 (1.89%)	3 / 52 (5.77%)	3 / 51 (5.88%)
occurrences (all)	1	3	3
Meningitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Mucosal infection			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Nail infection			
subjects affected / exposed	4 / 53 (7.55%)	4 / 52 (7.69%)	3 / 51 (5.88%)
occurrences (all)	4	4	3
Otitis media			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Papulopustular Rash			
subjects affected / exposed	0 / 53 (0.00%)	3 / 52 (5.77%)	2 / 51 (3.92%)
occurrences (all)	0	3	2
Paronychia			
subjects affected / exposed	7 / 53 (13.21%)	7 / 52 (13.46%)	8 / 51 (15.69%)
occurrences (all)	7	7	8
Pharyngitis			
subjects affected / exposed	3 / 53 (5.66%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	3	0	0
Rash pustular			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	2 / 51 (3.92%)
occurrences (all)	0	1	2
Rhinitis Infective			
subjects affected / exposed	3 / 53 (5.66%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	3	0	0
Sepsis			
subjects affected / exposed	1 / 53 (1.89%)	2 / 52 (3.85%)	2 / 51 (3.92%)
occurrences (all)	1	2	2

Skin infection			
subjects affected / exposed	2 / 53 (3.77%)	5 / 52 (9.62%)	2 / 51 (3.92%)
occurrences (all)	2	5	2
Tooth infection			
subjects affected / exposed	0 / 53 (0.00%)	0 / 52 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Upper respiratory infection			
subjects affected / exposed	2 / 53 (3.77%)	6 / 52 (11.54%)	5 / 51 (9.80%)
occurrences (all)	2	6	5
Urinary tract infection			
subjects affected / exposed	3 / 53 (5.66%)	7 / 52 (13.46%)	5 / 51 (9.80%)
occurrences (all)	3	7	5
Infections Other			
subjects affected / exposed	8 / 53 (15.09%)	5 / 52 (9.62%)	4 / 51 (7.84%)
occurrences (all)	8	5	4
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Anorexia			
subjects affected / exposed	12 / 53 (22.64%)	11 / 52 (21.15%)	9 / 51 (17.65%)
occurrences (all)	12	11	9
Hypercalcaemia			
subjects affected / exposed	0 / 53 (0.00%)	2 / 52 (3.85%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Hyperglycaemia			
subjects affected / exposed	3 / 53 (5.66%)	3 / 52 (5.77%)	0 / 51 (0.00%)
occurrences (all)	3	3	0
Hyperkalaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Hypernatraemia			
subjects affected / exposed	0 / 53 (0.00%)	2 / 52 (3.85%)	1 / 51 (1.96%)
occurrences (all)	0	2	1
Hypertriglyceridaemia			

subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	1	1	0
Hyperuricaemia			
subjects affected / exposed	1 / 53 (1.89%)	4 / 52 (7.69%)	0 / 51 (0.00%)
occurrences (all)	1	4	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 53 (1.89%)	2 / 52 (3.85%)	1 / 51 (1.96%)
occurrences (all)	1	2	1
Hypocalcaemia			
subjects affected / exposed	2 / 53 (3.77%)	2 / 52 (3.85%)	1 / 51 (1.96%)
occurrences (all)	2	2	1
Hypoglycaemia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 53 (0.00%)	3 / 52 (5.77%)	2 / 51 (3.92%)
occurrences (all)	0	3	2
Hypomagnesaemia			
subjects affected / exposed	0 / 53 (0.00%)	5 / 52 (9.62%)	1 / 51 (1.96%)
occurrences (all)	0	5	1
Hyponatraemia			
subjects affected / exposed	2 / 53 (3.77%)	2 / 52 (3.85%)	0 / 51 (0.00%)
occurrences (all)	2	2	0
Hypophosphataemia			
subjects affected / exposed	1 / 53 (1.89%)	3 / 52 (5.77%)	3 / 51 (5.88%)
occurrences (all)	1	3	3
Metabolism Other			
subjects affected / exposed	1 / 53 (1.89%)	2 / 52 (3.85%)	1 / 51 (1.96%)
occurrences (all)	1	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2022	Due to a funding gap in the study budget driven by the cost of the T790M testing in all arms as well as by some patients being long term responders to the both study treatments, the study team had prepared different scenarios for HBM collection of varying cost with the aim of mitigating the budget gap. The least costly of these scenarios involved only keeping the T790M testing for patients in arm B still under gefitinib, while also providing the study drugs to all patients still under treatment. These scenario were presented and discussed with Astra Zeneca during a TC on the 8th of December 2021, who agreed to keep providing study drugs to long term responders but declined to continue paying for the sample testing in all arms, arguing that only 2 patients were still under gefitinib treatment in arm B and interrupting the sample testing at the time would not influence the results since we were already past the clinical cut off date for the primary analysis. This required that the protocol be modified to indicate that blood samples for this T790M analysis will not be required any more in all arms. This implies that patients in arm B no longer switch from gefitinib to Osimertinib based on the result of the T790M mutation status, but switch based on RECIST progression as in arm C.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Regarding the reported of adverse events: for treatment arms B and C, the adverse events experienced during Gefitinib and Osimeritinib were grouped together.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36863484>