Clinical trial results:
An Open-Label, Multicentre, Single-Arm Study to Characterise the Efficacy, Safety, and Tolerability of Gefitinib 250 mg (IRESSA™1) as First-Line Treatment in Caucasian Patients Who Have Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Summary

EudraCT number	2010-018614-70
Trial protocol	PT ES GB FR IT NO HU GR BG
Global end of trial date	06 June 2016

Results information

Result version number	v1 (current)
This version publication date	10 June 2017
First version publication date	10 June 2017

Trial information

Trial identification

Sponsor protocol code	D791AC00014

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	One Medimmune Way, 101 ORD, 2233C, Gaithersburg, United States, MD 20878
Public contact	Yuri Rukazenkov, AstraZeneca, +44 01625 231825, yuri.rukazenkov@astrazeneca.com
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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	15 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 August 2012
Global end of trial reached?	Yes
Global end of trial date	06 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the ORR (confirmed complete response [CR] or partial response [PR]) of gefitinib using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, in Caucasian patients with Activating sensitising EGFR mutation-positive (EGFR M+) Non-small cell lung cancer (NSCLC).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator:

This was a single arm trial - there were no comparators

Actual start date of recruitment	08 September 2010
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	Bulgaria: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Romania: 19
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Poland: 12
Worldwide total number of subjects	107
EEA total number of subjects	99

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)	53
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

1060 Caucasian patients with locally advanced or metastatic NSCLC were screened, and 118 patients had activating sensitizing EGFR mutation eligible for the study (EGFR M+). 107 patients received at least 1 dose of gefitinib: 106 were EGFR M+ and one EGFR M+I (ineligible).

Pre-assignment

Screening details:

1060 Caucasian patients with locally advanced or metastatic NSCLC were screened, and 118 patients had activating sensitizing EGFR mutation eligible for the study (EGFR M+). 107 patients received at least 1 dose of gefitinib: 106 were EGFR M+ and one EGFR M+I (ineligible).

Period 1

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

Arms

Arm title	Gefitinib

Arm description:

Gefitinib 250 mg oral tablets once daily, administered continuously from Visit 2 until objective disease progression was documented or any other criterion for discontinuation was met. Gefitinib tablets were taken at approximately the same time each day.

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

Dosage and administration details:

250mg tablet once daily

Number of subjects in period 1	Gefitinib
Started	107
Completed	71
Not completed	36
Adverse event, serious fatal	29
Consent withdrawn by subject	3
Due to EGFR M+I patient	1
Due to objective disease progression	1
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Gefitinib
Reporting group description:	
Gefitinib 250 mg oral tablets once daily, administered continuously from Visit 2 until objective disease progression was documented or any other criterion for discontinuation was met. Gefitinib tablets were taken at approximately the same time each day.	

Reporting group values	Gefitinib	Total	
Number of subjects	107	107	
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	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	53	53	
From 65-84 years	54	54	
85 years and over	0	0	
Age Continuous | Units: Years			
arithmetic mean	63.8		
standard deviation	± 12	-	
Gender, Male/Female Units: Participants			
Female	76	76	
Male	31	31	
Race/Ethnicity, Customized Units: Subjects			
White	107	107	
Age, Customized Units: Subjects			
>=18 to <65 years	53	53	
>=65 to <75 years	28	28	
>=75 years	26	26	

End points

End points reporting groups

Reporting group title	Gefitinib

Reporting group description:

Gefitinib 250 mg oral tablets once daily, administered continuously from Visit 2 until objective disease progression was documented or any other criterion for discontinuation was met. Gefitinib tablets were taken at approximately the same time each day.

Primary: Objective response rate (ORR) (Investigator)

End point title	Objective response rate (ORR) (Investigator)[1]

End point description:

% of patients in the Full analysis set who have a complete response [CR] or partial response [PR] confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits (as defined by Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1)). CR: disappearance of all target lesions (TLs) & non-target lesions (NTLs). PR: >= 30% decrease in the sum of diameters compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions. Outcome is based on measurements made at site by investigator.

End point type	Primary

End point timeframe:

Scans taken at baseline and then follow up assessments taken every 6 weeks until progression, or last evaluable assessment in the absence of progression, assessed up to 23 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm study with no planned comparative analysis and so non is included in this form

End point values	Gefitinib			
Subject group type	Reporting group			
Number of subjects analysed	106[2]			
Units: Percentage of Participants				
number (confidence interval 95%)				
% Responders	69.8 (60.5 to 77.7)			

Notes:

[2] - One subject excluded from analysis as not eligible for study

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) (Investigator)

End point title	Disease Control Rate (DCR) (Investigator)

End point description:

DCR is calculated as the % of the FAS patient population with a best visit response of CR, PR (a visit response of CR or PR which is confirmed at least 4 weeks later) or stable disease (SD). SD is defined as no evidence of CR, PR or progression and must have occurred at a minimum of 6 weeks after first dose of study treatment. (progression is defined as ≥20% increase in the sum of the diameters of target lesions from minimum; clinically significant progression in non-target lesions; the presence of a new lesion or death). Outcome is based on measurements made at site by investigator.

End point type	Secondary

End point timeframe:

Scans taken at baseline and then follow up assessments taken every 6 weeks until progression, or last evaluable assessment in the absence of progression, assessed up to 23 months

End point values	Gefitinib			
Subject group type	Reporting group			
Number of subjects analysed	106[3]			
Units: Percentage of Participants				
number (confidence interval 95%)				
% Controlled	90.6 (83.5 to 94.8)			

Notes:

[3] - One subject excluded from analysis as not eligible for study.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression - Free Survival (PFS) (Investigator)

End point title	Progression - Free Survival (PFS) (Investigator)

End point description:

PFS was defined as the time from the first dose of gefitinib study treatment until objective disease progression as defined by RECIST 1.1 (≥20% increase in the sum of the diameters of target lesions from minimum, clinically significant progression in non-target lesions or the presence of a new lesion) or death (by any cause in the absence of progression). Progression is based on measurements made at site by investigator.

End point type	Secondary

End point timeframe:

Scans taken at baseline and then follow up assessments taken every 6 weeks until progression, or last evaluable assessment in the absence of progression, assessed up to 23 months

End point values	Gefitinib			
Subject group type	Reporting group			
Number of subjects analysed	106[4]			
Units: Months				
median (confidence interval 95%)	9.72 (8.48 to 11.04)			

Notes:

[4] - One subject excluded from analysis as not eligible for study.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from first dose of gefitinib study treatment until death by any cause. Patients who had not died at the time of analysis were censored at the last date the patient was known to be alive.

End point type	Secondary

End point timeframe:

Survival follow up from first dose of gefitinib till death of the patient or till end of study in absence of death.

End point values	Gefitinib			
Subject group type	Reporting group			
Number of subjects analysed	106[5]			
Units: Months				
median (confidence interval 95%)	19.22 (16.95 to 99999999999)			

Notes:

[5] - NB Upper limit of confidence interval for Median is Not Calculable due to insufficient data.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Disease Control Rate (DCR) (Independent central review)

End point title	Disease Control Rate (DCR) (Independent central review)

End point description:

DCR is calculated as the % of the FAS patient population with a best visit response of CR, PR (a visit response of CR or PR which is confirmed at least 4 weeks later) or stable disease (SD). SD is defined as no evidence of CR, PR or progression and must have occurred at a minimum of 6 weeks after first dose of study treatment. (progression is defined as ≥20% increase in the sum of the diameters of target lesions from minimum; clinically significant progression in non-target lesions; the presence of a new lesion or death). Outcome is based on measurements of scans by central review.

End point type	Other pre-specified

End point timeframe:

Scans taken at baseline and then follow up assessments taken every 6 weeks until progression, or last evaluable assessment in the absence of progression, assessed up to 23 months

End point values	Gefitinib			
Subject group type	Reporting group			
Number of subjects analysed	106[6]			
Units: Percentage of Participants				
number (confidence interval 95%)				
% Controlled	88.7 (81.2 to 93.4)			

Notes:

[6] - One subject excluded from analysis as not eligible for study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Objective response rate (ORR) (Independent central review))

End point title	Objective response rate (ORR) (Independent central review))

End point description:

% of patients in the Full analysis set who have a complete response [CR] or partial response [PR] confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits (as defined by Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1)). CR: disappearance of all target lesions (TLs) & non-target lesions (NTLs). PR: >= 30% decrease in the sum of diameters compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions. Outcome is based on measurements of scans by central review.

End point type	Other pre-specified

End point timeframe:

Scans taken at baseline and then follow up assessments taken every 6 weeks until progression, or last evaluable assessment in the absence of progression, assessed up to 23 months

End point values	Gefitinib			
Subject group type	Reporting group			
Number of subjects analysed	106[7]			
Units: Percentage of Participants				
number (confidence interval 95%)				
% Responders	50 (40.6 to 59.4)			

Notes:

[7] - One subject excluded from analysis as not eligible for study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Progression - Free Survival (PFS) (Independent central review)

End point title	Progression - Free Survival (PFS) (Independent central review)

End point description:

PFS was defined as the time from the first dose of gefitinib study treatment until objective disease progression as defined by RECIST 1.1 (≥20% increase in the sum of the diameters of target lesions from minimum, clinically significant progression in non-target lesions or the presence of a new lesion) or death (by any cause in the absence of progression). Progression is based on measurements of scans by central review.

End point type	Other pre-specified

End point timeframe:

Scans taken at baseline and then follow up assessments taken every 6 weeks until progression, or last evaluable assessment in the absence of progression, assessed up to 23 months

End point values	Gefitinib			
Subject group type	Reporting group			
Number of subjects analysed	106[8]			
Units: Months				
median (confidence interval 95%)	6.97 (6.41 to 9.86)			

Notes:

[8] - One subject excluded from analysis as not eligible for study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events and Serious Adverse Events were collected from the time of screening informed consent throughout the treatment period, until 30 days after discontinuation of gefitinib treatment. All ongoing AEs & SAEs were to be followed until resolution.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	Gefitinib 250 mg

Reporting group description: -

Serious adverse events	Gefitinib 250 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 107 (19.63%)		
number of deaths (all causes)	29		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
ANKLE FRACTURE			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
RADIUS FRACTURE			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
TIBIA FRACTURE			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
HYPERTENSION			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
CARDIAC FAILURE			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Nervous system disorders			
DEMENTIA ALZHEIMER'S TYPE			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
HYPOAESTHESIA			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SENILE DEMENTIA			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 107 (0.93%)		
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 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
VOMITING			
subjects affected / exposed	3 / 107 (2.80%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
HAEMOPTYSIS			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PLEURAL EFFUSION			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
SKIN NECROSIS			

subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
GASTROENTERITIS			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
subjects affected / exposed	3 / 107 (2.80%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VIRAL INFECTION			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 107 (0.93%)		
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	Gefitinib 250 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 107 (81.31%)		
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			

subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	10		
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	7 / 107 (6.54%)		
occurrences (all)	8		
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	12 / 107 (11.21%)		
occurrences (all)	12		
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	31 / 107 (28.97%)		
occurrences (all)	55		
NAUSEA			
subjects affected / exposed	11 / 107 (10.28%)		
occurrences (all)	14		
VOMITING			
subjects affected / exposed	12 / 107 (11.21%)		
occurrences (all)	13		
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	12 / 107 (11.21%)		
occurrences (all)	12		
DYSPNOEA			
subjects affected / exposed	7 / 107 (6.54%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			

DERMATITIS ACNEIFORM subjects affected / exposed occurrences (all) DRY SKIN subjects affected / exposed occurrences (all) RASH subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 7 12 / 107 (11.21%) 13 50 / 107 (46.73%) 65		
Infections and infestations URINARY TRACT INFECTION subjects affected / exposed occurrences (all)	7 / 107 (6.54%) 10		
Metabolism and nutrition disorders DECREASED APPETITE subjects affected / exposed occurrences (all)	10 / 107 (9.35%) 11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2011	The amendment included the following updates to the protocol: - Final IPASS OS analysis had been conducted and new data were added to the CSP. -New safety information regarding gastrointestinal perforation reported in patients taking IRESSA, in most cases this was associated with other known risk factors, including increasing age, concomitant medications such as steroids or NSAIDS, underlying history of GI ulceration, smoking or bowel metastases at sites of perforation. -Clarification of exclusion criteria no 3, that patients considered to require radiotherapy to the lung at the time of study entry or in the near future are excluded from the study. -Clarification that residual material (tumour) may be used for optional exploratory biomarker research if consent has been obtained for this research. -Clarification that Residual material (tumour, plasma, serum) will be stored for a maximum of 25 years. -Clarification that for each of the following objectives: ORR, DCR, PFS and OS, the mutation sub type of the positive mutations will be considered as subgroups.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported