Clinical trial results: *Randomized Proteomic Stratified Phase III Study of Second Line Erlotinib versus Chemotherapy in Patients with Inoperable Non−Small Cell Lung Cancer*

Summary

EudraCT number*	2007-006299-13
Trial protocol	IT
Global end of trial date*	May 2014

Trial information

Trial identification	
Sponsor protocol code*	HSRL-02-2007
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00989690
WHO universal trial number (UTN)	-

Notes:

Sponsors details*	
Sponsor organisation name	IRCCS Ospedale San Raffaele
Sponsor organisation address	Via Olgettina, 60, Milano, Italy, 20132
Public contact	Vanesa Gregorc
Scientific contact	Vanesa Gregorc

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

Results analysis stage	
Analysis stage*	Final
Date of interim/final analysis*	April 2012
Is this the analysis of the primary completion data?*	Yes
Global end of trial reached?*	Yes
Global end of trial date*	May 2014
Was the trial ended prematurely?	No

General information about the trial

Main objective of the trial*: Evaluate the predictive value of proteomic profile on the effect of erlotinib vs chemotherapy (pemetrexed or docetaxel) given as 2nd line therapy in patients with advanced NSCLC.

Actual start date of recruitment*	23rd January 2008
Long term follow-up planned*	Yes
If Yes, rationale:	Scientific research
Duration	Years
Independent data monitoring committee (IDMC) involvement?*	No
Protection of trial subjects*:	Yes
Background therapy:	Erlotinib vs Pemetrexed/Docetaxel
Evidence for comparator:	

Population of trial subjects

Subjects enrolled per country

Country:	Italy
Planned number of subjects	275
Actual Number of subjects enrolled*	285
Worldwide total number of subjects	0
EEA total number of subjects	285 (only in Italy)

Subjects enrolled per age group

In utero*	N/A
Preterm newborn - gestational age < 37wks*	N/A
Newborns (0-27 days)*	N/A
Infants and toddlers (28 days-23months)*	N/A
Children (2-11 years)*	N/A
Adolescents (12-17 years)*	N/A
Adults (18-64 years)*	Yes
From 65 to 84 years*	Yes
85 years and over*	Yes

Subject disposition

Recruitment details: Enrollment from 23/JAN/2008 to 11/APR/2011 in 14 Clinical Center

Pre-assignment - *Screening details*: The study population consists of adult Caucasian patients (≥ 18 years old), affected by NSCLC.

Inclusion criteria:

♦ Histologically or cytologicaly confirmed diagnosis of NSCLC

♦ Advanced NSCLC (stage IIIB or IV) patients previously treated with non TKIs as a first-line therapy

♦ Age ≥18 years

Version: Final 9 / 31

♦ ECOG Performance status 0 to 2

♦ Presence of measurable disease

♦ Absolute granulocyte count (AGC) >1.5 x 109/l

♦ Platelets ≥ 100 x 109/l

♦ Bilirubin <1.5-fold the upper limit of normal (ULN), may be elevated to 2.5-fold ULN in patients with known liver metastases

♦ Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) <3-fold ULN; ALT and AST <5-fold ULN in patients with known liver metastases

♦ Calculated (standard Cockcroft and Gault formula) creatinine clearance >50 ml/min

♦ Prior surgery or radiation therapy is permitted if completed at least 3 weeks prior to enrollment

♦ Informed written consent

Exclusion criteria:

♦ Patient who cannot comply with planned protocols procedures

♦ Patient with multiple severe diseases who can compromise safety (cardiac and renal failure, peripheral neuropathy)

♦ Clinical evidence of uncontrolled brain metastases

♦ Other malignancy (except basal skin carcinoma) or pre-neoplastic condition not requiring chemotherapeutic treatment

♦ Pregnancy or nursing

Period 1	
Period title*	Overall trial
Is this the baseline period?	No
Allocation method*	Randomised - controlled
Blinding used*	Not blinded

Arms	
Arm title*	Erlotinib vs Pemetrexed/Docetaxel
Arm description:	
Arm type*	Active comparator
Investigational medicinal product name*	Erlotinib, Docetaxel, Pemetrexed
Investigational medicinal product code	

Other name	
Pharmaceutical forms*	Tablets (Erlotinib), Infusional solution (Pemetrexed and Docetaxel)
Routes of administration*	Oral (Erlotinib); EV (Pemetrexed and Docetaxel)
Dosage and administration details*	150 mg (Erlotinib), 500 mg/m^2 (Pemetrexed), 75 mg/m^2 (Docetaxel)

Number of subjects in period	Arm Title (overall population)	Arm Title *(repeat for each arms if applicable)*
Started*	23/JAN/2008	
Completed*	11/APR/2012	
Subject non-completion reason (if applicable)	13 patient Chemotherapy arm 9 patient Erlotinib arm	
AE, non fatal	36 (28%) of 129 chemotherapy group 31 (23%) of 134 erlotinib group	
AE, fatal	0	
Consent withdrawn by subject		
Lack of efficacy		
Lost to follow up		
Physician decision		
Pregnancy		
Protocol Deviation		
Other	**13 excluded from Chemotherapy arm:** 10 did not start treatment 2 received non-protocol treatments 1 did not have advanced non-small-cell lung cancer **9 excluded from Erlotinib arm** 9 did not start treatment	

Baseline characteristics

Reporting groups* Overall cohort	
Reporting group title*	Chemotherapy arm vs Erlotinib arm
Number of subjects at the baseline*	142 patient vs 143 patients

Reporting group description: *You can report per arm in the baseline period or for the overall baseline period*

Subject analysis sets

Add a subject analysis set if you wish to report on groups different from the reporting group defined above (repeat if applicable)

Subject analysis set title*	*Chemotherapy group*
Subject analysis set type*	Per protocol
Subject analysis set description*	*Patients assigned to chemotherapy treatment who followed the study protocol without significant violations.*
Number of subjects in subjects analysis set*	*129*
Subject analysis set title*	*Erlotinib group*
Subject analysis set type*	Per protocol
Subject analysis set description*	*Patients assigned to erlotinib treatment who followed the study protocol without significant violations.*
Number of subjects in subjects analysis set*	*134*

Age characteristics*

Complete either the age categorical, age continuous or complete both these characteristics in order to collect values for the reporting groups and optionally the subject analysis sets.

	Characteristic title*	Units*	Age categories*
Age categorical	Age	years	<40 40-49 50-59 60-69 70-79 ≥80

	Characteristic title*	Units*	Central tendency*	Dispersion type*
Age continuous	Overall cohort	Years	Median 65 years	full range (min-max) 33-85 years

Gender characteristics*

	Characteristic title*	Units*	Gender categories*
Gender categorical	Gender	Count	Female: 38 (chemotherapy group), 35 (Erlotinib group) Male: 91 (chemotherapy group), 99 (Erlotinib group)

Study specific characteristics

	Characteristic title*	Units *	Categories*	Number of subject for each categories
Study specific categorical	ECOG Performance Status	Count	0, 1, 2	Chemotherapy group: 0 (65), 1 (56), 2 (8) Erlotinib group: 0 (73), 1 (53), 2 (8)
Study specific categorical	Smoking History	Count	Never Former Current	Chemotherapy group: Never (17), Former (75), Current (37) Erlotinib group: Never (21), Former (77), Current (36)
Study specific categorical	Histology	Count	Adenocarcinoma Squamous Other	Chemotherapy group: Adenocarcinoma (91), Squamous (16), Other (22) Erlotinib group: Adenocarcinoma (76), Squamous (31), Other (27)
Study specific categorical	EGFR Status	Count	Mutated Wild type Not available	Chemotherapy group: Mutated (6), Wild type (84), Not available (39) Erlotinib group: Mutated (8), Wild type (79), Not available (47)
Study specific categorical	Proteomic Test Classification	Count	Good Poor	Chemotherapy group: Good (88), Poor (41) Erlotinib group: Good (96), Poor (38

End points

Add subject analysis set if you wish to report on groups different form reporting groups defined above

Subject analysis set title*	Chemotherapy group
Subject analysis set type*	Per protocol
Subject analysis set description*	Patients assigned to chemotherapy treatment who followed the study protocol without significant violations.
Number of subject in subject analysis set *	129
Subject analysis set title*	Erlotinib group
Subject analysis set type*	Per protocol
Subject analysis set description*	Patients assigned to erlotinib treatment who followed the study protocol without significant violations.
Number of subject in subject analysis set *	134

End points definitions

End point title*	**Overall Survival**	
		Values
Countable or measurable?*	Measurable	Median overall survival
If countable, Countable units*:		
If measurable, Measurable units*	Months	
Measure type*:	Median	

Precision/dyspersion type*	95% Confidence Interval (CI)	

End point type*	Primary

End point timeframe*: From randomization to death from any cause or last contact

End point title*	**Progression-Free Survival (PFS)**	
		Values
Countable or measurable?*	Measurable	Median progression-free survival
If countable, Countable units*:		
If measurable, Measurable units*	Months	
Measure type*:	Median	
Precision/dyspersion type*	95% Confidence Interval (CI)	

End point type*	Secondary

End point timeframe*: From randomization to progression or death from any cause or last on-study tumor assessment

End point title*	**Objective Response Rate**	
		Values
Countable or measurable?*	Countable	Proportion of patients with partial response
If countable, Countable units*:	Percentage (%)	
If measurable, Measurable units*		
Measure type*:	Number	
Precision/dyspersion type*	None	

End point type*	Secondary

End point timeframe*: During the study treatment period

Use categories only if the data for the end point can be categorized

Category title

Specify the groups of subjects applicable to this end point

Reporting groups*	Chemotherapy group	Erlotinib group	
Period	Study treatment period	Study treatment period	
Arms	Chemotherapy	Erlotinib	
subject analysis sets	Per protocol analysis sets for chemotherapy and erlotinib groups	Per protocol analysis sets for chemotherapy and erlotinib groups	

Adverse events

Adverse events information

Timeframe for reporting adverse events*: *Enter the time point(s) or time period for AE assessment*

First patient first visit: February 26, 2008
Last recruitment date: April 11, 2012
Study closure: May 2014

Adverse event reporting additional description: *Adverse events (AEs) were collected systematically throughout the study. Patients were assessed for AEs at each study visit, and AEs were monitored continuously. The severity of AEs was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Serious adverse events (SAEs) were reported immediately to the study sponsor and ethics committees.*

Assessment type*	Systematic
Frequency threshold for reporting non-serious adverse events*	Typically, non-serious AEs are reported if they occur in more than 5% of subjects in any treatment group.

Dictionary used

Dictionary name*	CTCAE
Dictionary version*	Version 3.0

Adverse events reporting group definition

Use arms from baseline period as reporting groups
OR

Reporting group title*: *Overall cohort*

For this reporting group, provide the following totals:

Subject exposed*	263 (129 in chemotherapy group + 134 in erlotinib group)
Subjects affected by non -SAE*	256
Total number of deaths (all causes)*	226 (108 in chemotherapy group + 118 in erlotinib group)
Total number of deaths resulting from adverse event*	None

Serious adverse event details and values

System organ class*: Blood and lymphatic system disorders, Gastrointestinal disorders, Skin and subcutaneous tissue disorders)

Event term*: neutropenia, nausea, neurotoxicity, alopecia, and asthenia (for chemotherapy group); rash and diarrhoea (for erlotinib group)

Values for serious adverse event per reporting group *

Reporting groups	Subjects affected number	Subjects exposed number	Occurrences all number	Occurrences causally related to treatment number	Fatalities number	Fatalities causally related to treatment number
Chemotherapy group Erlotinib group	3 (2%) of 129 4 (3%) of 134	129 for chemotherapy 134 for Erlotinib	7 (3%) of 263	3 (2%) of 129 4 (3%) of 134	None	None

Non - Serious adverse event details and values

System organ class*: System organ class*: Blood and lymphatic system disorders, Gastrointestinal disorders, Skin and subcutaneous tissue disorders

Event term*: neutropenia, nausea, neurotoxicity, alopecia, and asthenia (for chemotherapy group) rash and diarrhoea (for erlotinib group)

Values for non-serious adverse event per reporting group*

Threshold for non-serious adverse event reporting is:

Reporting groups	Subjects affected number	Subjects exposed number	Occurrences all number
Chemotherapy group Erlotinib group	36 (28%) of 129 chemo group 31 (23%) of 134 Erlotinib group	129 for chemotherapy 134 for Erlotinib	Diarrhoea: 19 (15%) of chemo group and 30 (22%) of Erlotinib group. Alopecia: 22 (17%) of chemo group and 1 (<1%) of Erlotinib group. Asthenia: 38 (29%) of chemo group and 27 (20%) of Erlotinib group. Neurological events: 15 (12%) of chemo group and 4 (3%) of Erlotinib group. Nausea: 17 (13%) of chemo group and 2 (1%) of Erlotinib group. Dermatological events: 11 (9%) of chemo group and 69 (51%) of Erlotinib group. Neutropenia: 46 (36%) of chemo group and 4 (3%) of Erlotinib group.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol*? No

Date	Amendment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial*? No

If Yes, Interruption date

Interruption description

Limitations and caveats

None reported

Online references

Enter PubMed identifier (PMID)

- PMID: 24831979