AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: None
ACTIVE INGREDIENT: None

Study No: NIS-OES-DUM-2009/1 (NCT01081496)
REASON study: Epidemiological study to evaluate the prevalence of EGFR mutation status in patients with newly diagnosed locally advanced or metastatic **N**SCLC (stage IIIB/IV non-small cell lung cancer)

Developmental Phase: Epidemiological Study
Study Completion Date: 28 feb 2011
Date of Report: 19 Dec 2011

OBJECTIVES:

1. Primary objective
To estimate the prevalence of EGFR mutation in a representative sample of patients with newly diagnosed stage IIIB/IV NSCLC in Spain (predominantly Caucasian ethnicity).

2. Secondary objectives
Subgroups correlation
- To correlate EGFR mutation status with clinico-pathological characteristics (e.g. smoking status, sex, histology, etc). In particular, the study will aim to determine the prevalence of EGFR M+ lung cancers in patients with clinico-pathological characteristics that are not commonly associated with EGFR mutation positivity (i.e., smokers, men, and non-adenocarcinoma).

Diagnostic end points
- To describe different EGFR mutation methods used in Spain and testing turnaround time associated.
- To determine the % of confirmed stage IIIB/IV NSCLC patients who cannot be tested for EGFR mutation and the reasons for not testing (% of EGFR Mnt)
- To determine the % of patients who undergo mutation testing but whose test results are not evaluable and the reasons associated (e.g. for technical or methodological reasons) (% of EGFR Mx).

METHODS:

This was a national, multicentre, non-interventional, prospective cohort study to be carried out in a representative sample of patients with newly diagnosed stage IIIB/IV NSCLC in Spain (predominantly Caucasian ethnicity).

To ensure a valid prevalence of EGFR mutation figure all newly diagnosed stage IIIB/IV NSCLC patients attending Oncology Department for the first time at the participating sites during 6 months were included in the study. Each centre started the study at a different date depending on each hospital requirements but the whole inclusion period was 6 months.
Patients who had tumour tissue available were tested for EGFR mutation. In experienced hands and on a case by case basis EGFR mutation testing is technically feasible in cytological samples therefore these type of samples could also be tested.

DNA extracted from the tumour samples was analyzed for mutations of EGFR using different genetic analysis techniques, eg allele specific PCR (eg ARMS™) or direct sequencing. EGFR mutation status was defined as either EGFR M+ (i.e. mutation positive) or EGFR M- (i.e. mutation negative). Patients who underwent mutation testing but whose test results were not evaluable (e.g. for technical or methodological reasons) were considered Mx and patients who could not be were recorded as EGFR Mnt (Not tested). Only tissue that was already available could be used as no additional intervention to obtain tumour tissue could be performed under NIS requirements. For the purposes of EGFR mutation testing, the origin of the tissue sample could be either the primary tumour or a metastatic site including cytology. The methodology to be used for EGFR mutation testing was at the discretion of the pathologists.

There were two main laboratories that conducted EGFR mutation testing, Pangaea Biotech and Center for Applied Medical Research University of Navarra but other laboratories could conduct the mutation if they had the technology (7 laboratories).

Information regarding patient and disease characteristics were taken from the medical records.

Information about EGFR testing were taken from the medical record, test report forms and laboratory where EGFR testing was performed.

According to the main objective of estimating the prevalence of EGFR mutation in a representative sample of patients with newly diagnosed stage IIIB/IV NSCLC in Spain (predominantly Caucasian ethnicity), when the sample size was 1000, a two-sided 95.0% confidence interval for a single proportion using the large sample normal approximation would extend less than 2.0% from the observed proportion for an expected proportion of 10%.

For statistical analysis the software SAS® v.8.02 was used.
A descriptive analysis of baseline and demographic variables was performed. As continuous variables were presented: mean, median, number of observations, standard deviation, maximum and minimum, and in categories variables were presented absolute and relatives frequencies.

The prevalence of EGFR mutation in newly diagnosed stage IIIB/IV NSCLC was described by means of 95% confidence interval.
The correlation of EGFR mutation status with clinic-pathological characteristics was analyzed using a logistic regression model.
The secondary endpoints (diagnostics and treatments) were described by means of tables and if appropriate and interesting in graphs.

RESULTS:

From March 2010 to February 2011, 1113 patients from 40 Spanish centres were enrolled, of whom 1009 patients provided samples. 25 patients were excluded because unavailable information. Mutation analysis was not feasible in 146 patients due either to sample unavailability (7.3%) or inadequacy (6.3%) for mutation testing. 99.8% of patients were of Caucasian ethnicity. 74.5% patients were men, 39.3% were smokers, 45.5% ex-smokers, and 15.2% never-smokers. Median age was 66 years (range 25-90). 22.3% patients had squamous-cell carcinoma, 75.6% had non-squamous histology (57.8% adenocarcinoma, 1.8% bronchoalveolar, 11.1% large-cell carcinoma, 1.5% adenosquamous carcinoma, and 3.5% non-specified).

Next table summarize the main methodologies used for EGFR mutation testing:

EGFR Methodology			
Variable		**Total (N=1009)**	**IC 95%**
Fluorescent PCR frangment analysis	N(%)	478 (47.4%)	(44.2%,50.5%)
Qiagen's Therascreen EGFR PCR Kit TM	N(%)	450 (44.6%)	(41.5%,47.7%)
Allelic discrimination using fluorescence probes	N(%)	450 (44.6%)	(41.5%,47.7%)
Direct sequencing	N(%)	87 (8.6%)	(6.9%,10.5%)

Median Turnaround time (TAT) was 9.7 working days and did not vary by sample type (9.7 days tissue vs 9.5 days cytology). However, TAT was significantly shorter when a centralized diagnostic lab performed the testing (8.5 days for central laboratory vs 15.3 days for in-house testing).

Exon 19 deletion and exon 21 L858R point mutation were analyzed in 942 samples.

Mutation rate was 11.57% (82.6% exon 19 del and 17.4% exon 21 L858R).

Clinical factors with higher correlation with EGFR mutations were: never smoker (38.1%), female sex (25.4%), BAC (22.2%) and adenocarcinoma histology (15.4%)

Mutation rates according to clinical features are summarized in the following table:

		Patients with available tumor sample (N= 942)	Patients with EGFR Mut (Exon 19 del, L858R) (N= 109)	% of mutations and 95% CI
Gender	Men	702	48	6.8 (5.1-9.0)
	Women	240	61	25.4 (20.0-31.4)
Smoking Status	Current Smoker	354	16	4.5 (2.6-7.2)
	Ex-smoker	417	33	7.9 (5.5-10.9)
	Never-smoker	139	53	38.1 (30.0-46.7)
	Missing	32	7	
Tumor Type	Adenocarcinoma	550	85	15.4 (12.5-18.7)
	Bronchioloalveolar adenocarcinoma	18	4	22.2 (6.4-47.7)
	Large-cell carcinoma	101	6	5.9 (2.2-12.5)
	Adenosquamous Carcinoma	14	0	
	Squamous-Cell Carcinoma	210	9	4.3 (2.0-8.0)
	NOS	30	3	10 (2.1-26.5)
	Other	3	0	

	Missing	16	2	

Mutation rates in exons 18, 20 and 21 (excluding L858R) were 8.1%, 7.1%, and 1.4% respectively (505 samples were analyzed for the presence of these mutations).