Final Clinical Study Report - Synopsis	
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A diagnostic Study of European and Japanese advanced NSCLC patients to evaluate suitable sample types for EGFR testing: The ASSESS Study

Study dates: First patient enrolled: 11 Apr 2013
Last patient last visit: 17 Apr 2014

Phase of development: IV

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

STUDY REPORT SYNOPSIS

A diagnostic Study of European and Japanese advanced NSCLC patients to evaluate suitable sample types for EGFR testing: The ASSESS Study

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

Developmental Phase: IV

Study Completion Date: Last patient last visit (last visit date for data included in this report): 17 Apr 2014

Date of Report: 10 November 2014

OBJECTIVES:

Primary:

- The primary objective of the study was to determine the level of concordance between epidermal growth factor receptor (EGFR) mutation status obtained via tissue/cytology and blood (plasma) based testing.

Secondary:

- To determine the EGFR mutation frequency (including mutation subtypes) in patients with advanced non-small-cell lung carcinoma (aNSCLC) of adenocarcinoma and non-adenocarcinoma histologies
- To describe first-line therapy choice following EGFR mutation testing
- To describe second-line therapy choice following discontinuation of first-line treatment for patients confirmed as EGFR mutation positive via tissue/cytology
- To summarise EGFR mutation testing practices in terms of methods, sample types, success rate, mutation detection rate, testing turnaround time and reasons for not testing
- To describe the association between EGFR mutation status from tumour and demographic data and disease status
- To describe the association between EGFR mutation status derived from plasma (blood), demographic data, and disease status

Exploratory:

An exploratory objective of the study was the optional collection of 1 mL aliquot of plasma and tumour samples in order to investigate exploratory biomarkers, where informed consent was obtained. This was performed to help define molecular features of non-small-cell lung carcinoma (NSCLC). These samples may be used to investigate prevalence, co-occurrence, and association of exploratory biomarkers with demographic data. The exploratory results will not be reported in this study report.

METHODS:

This was an international, multicentre, cross-sectional, non-interventional diagnostic, and non-comparative study of EGFR mutation status in patients diagnosed with aNSCLC (locally advanced and/or metastatic disease) with adenocarcinoma and non-adenocarcinoma histologies. A non-interventional study (NIS) is a study in which no additional diagnostic, interventional, or monitoring procedures are applied to the patients. This study was conducted in Japan and 7 European countries to assess the concordance of EGFR mutation status derived from tumour samples and blood-based circulating tumour deoxyribonucleic acid (ctDNA). Patients were enrolled across 8 centres in Japan and 48 centres in Europe and. It was planned that every enrolled patient provided a diagnostic tumour sample (ie, biopsy, cytology, or other sample type containing tumour cells) and a diagnostic blood (plasma) sample upon inclusion to be tested for EGFR mutations. The tumour sample that was used to diagnose NSCLC underwent EGFR mutation testing according to local practices. The plasma samples were used for the extraction of ctDNA and for the determination of EGFR mutation status in designated central laboratories.

RESULTS:

Overall, data from 98.2% (1288 of 1311 initially enrolled) of patients were eligible for analysis, 98.6% (997/1011) of patients in Europe and 97.0% (291/300) of patients in Japan. The majority of patients were men (67.3%), Caucasian (75.8%) with mean age (standard deviation) of 66.5 years (9.78).

Primary Analysis:

The primary outcome, concordance between EGFR mutation results by local tumour and regional plasma testing showed concordance was 89.1%, with a sensitivity of 46.0% and a specificity of 97.4%. The positive predictive value was 77.7% and the negative predictive value was 90.3%. Demographic and sample information from patients with positive plasma EGFR mutations status/negative tumour EGFR mutation status suggested false negative results in tumour is likely to be a significant contributor to the low overall positive predictive value. Consistent with this, the positive predictive value was 93% in the subgroup of patients for which identical, highly sensitive, methods were used in both plasma and tumour.

Secondary Analyses:

Overall, patients with adenocarcinoma had a higher frequency of tumours with positive EGFR mutation status compared with patients with non-adenocarcinoma, which is consistent with published data. In Europe 13.9% of patients with adenocarcinoma and 3.3% of patients with non adenocarcinoma had tumours with positive EGFR mutation status. Major subtypes were L858R (28%) and Del19 (55%). In Japan, 40.0% of adenocarcinoma and 7.8% of non-adenocarcinoma had tumours with positive EGFR mutation status. Major subtypes were L858R (47%) and Del19 (51%)Multivariate logistic regression of EGFR mutation status from tumour and plasma samples and demographic characteristics and disease status implied that female sex, adenocarcinoma histological type, never smoked status, and the Japan region were more likely to be related to positive tumour EGFR mutation status. In plasma, in addition to the factors above, an association was seen between the number of organs with metastases and positive EGFR mutation status (p=0.054). In patients with positive EGFR mutation status, 55.7% of drug-treated patients were treated with gefitinib and 22.4% were treated with erlotinib, as first-line treatment. In patients with positive EGFR mutation status, the main reason for treatment choice was positive EGFR mutation status in Japan (81.4%) and cited more often than in Europe (73.3%). For the majority of patients (66.5% overall), first-line treatment was still ongoing. The majority of samples were obtained at current diagnosis (74.2%) and from primary tumour (80.0%). Tumour samples were mainly from lung (74.2% of patients). Bronchoscopy was the most common sample collection method (45.6%). Variability was present in where and how biopsies were taken among the European countries. The tumour test failure rate was low. No obvious differences were found in sampling between the evaluable versus (vs) non-evaluable samples. The median turnaround time for testing tumour samples was 11 days in Europe, 8 days in Japan; and for plasma samples: 9 days in Europe and 14 days in Japan. The main reason for not testing the tumour sample was insufficient material.