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Efficacy according to blind independent central review: Post-hoc analyses from the phase III, randomized, multicenter, IPASS study of first-line gefitinib versus carboplatin/paclitaxel in Asian patients with *EGFR* mutation-positive advanced NSCLC

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ABSTRACT

Objective: The Phase III, randomized, open-label IPASS study (NCT00322452) of first-line epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) gefitinib versus carboplatin/paclitaxel for Asian patients with advanced non-small-cell lung cancer (NSCLC) showed that investigator-assessed progression-free survival (PFS) and objective response rate (ORR) were significantly prolonged in patients with *EGFR* mutation-positive NSCLC who received gefitinib versus patients with *EGFR* mutation-negative NSCLC. We report post-hoc analyses of IPASS data by blind independent central review (BICR), performed at the request of the US FDA, in a subset of patients with *EGFR* mutation-positive NSCLC.
Patients and methods: Eligible patients (aged ≥18 years; histologically/cytologically confirmed Stage IIB/IV adenocarcinoma NSCLC; non- or former light-smokers; treatment-naïve) were randomly assigned 1:1 to gefitinib (250 mg/day) or carboplatin. (dose calculated to produce an area under the curve of 5 or 6 mg/mL/minute)/paclitaxel (200 mg/m^2). Primary endpoint: PFS. BICR analyses included PFS, ORR, and duration of response (DoR)

Abbreviations: ADC, adenocarcinoma; ALK, anaplastic lymphoma kinase; ASR, age-standardized rate; BICR, blind independent central review; CI, confidence interval; CNS, central nervous system; CONSORT, Consolidated Standards of Reporting Trials; CT, computed tomography; DoR, duration of response; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HR, hazard ratio; IPASS, Iressa Pan-ASia Study; ITT, intent-to-treat; NA, not available; NPV, negative predictive value; NSCLC, non-small-cell lung cancer; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PPV, positive predictive value; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; US, United States; WHO, World Health Organization.

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Results: Scans from 186 IPASS patients (gefitinib n = 88, carboplatin/paclitaxel n = 98) with *EGFR* mutation-positive NSCLC were available for BICR. Consistent with investigator-assessed results, in patients with *EGFR* mutation-positive NSCLC: PFS (hazard ratio 0.54; 95% confidence interval [CI] 0.38, 0.79; p = 0.0012) and ORR (odds ratio 3.00; 95% CI 1.63, 5.54; p = 0.0004) were significantly longer with gefitinib versus carboplatin/paclitaxel. The median DoR by BICR was 9.6 months with gefitinib and 5.5 months with carboplatin/paclitaxel.

Conclusion: BICR analysis of IPASS data support the original, investigator-assessed results. *EGFR* mutation-positive status remains a significant predictor of response to first-line TKI therapy.

1. Introduction

Statistics indicate that, in Asia, lung cancer represents a significant clinical burden: it is the most common cancer in men (age-standardized rate [ASR; per 100,000] 35.2) and the third most common cancer in women (ASR 12.7) [1]. As recommended by clinical guidelines, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are now widely accepted as a standard-of-care therapy for patients with non-small-cell lung cancer (NSCLC) whose tumors harbor activating *EGFR* mutations [2,3]. Although *EGFR* mutations may be detected in the tumor of any patient with NSCLC, certain clinical characteristics are associated with a high frequency of activating *EGFR* mutations and response to EGFR TKI therapy (Asian ethnicity, female gender, never-smokers, and adenocarcinoma [ADC] histology) [4,5]. The Phase III, multicenter, randomized, open-label, parallel-group IPASS (Iressa Pan-ASia Study) study (NCT00322452), which compared EGFR TKI gefitinib (IRESSA^{TM}) with carboplatin plus paclitaxel (carboplatin/paclitaxel) doublet chemotherapy as first-line treatment for Asian patients with advanced NSCLC, was the landmark study which established that the *EGFR* mutation status of a patient's tumor was a strong predictor of response to EGFR TKI therapy [6,7].

In support of this conclusion, in IPASS biomarker analyses, a significant interaction between *EGFR* mutation status and investigator-assessed progression-free survival (PFS; primary endpoint) was observed: in the subgroup of patients with *EGFR* mutation-positive NSCLC (gefitinib n = 132, carboplatin/paclitaxel n = 129) PFS was significantly longer in patients receiving gefitinib versus patients receiving carboplatin/paclitaxel (hazard ratio [HR] 0.48; 95% confidence interval [CI] 0.36, 0.64; p < 0.001). Conversely, in the subgroup of patients with *EGFR* mutation-negative NSCLC (gefitinib n = 91, carboplatin/paclitaxel n = 85), PFS was significantly longer in patients receiving carboplatin/paclitaxel versus patients receiving gefitinib (HR 2.85; 95% CI 2.05, 3.98; p < 0.001). Investigator-assessed objective response rate (ORR) was also significantly higher with gefitinib versus carboplatin/paclitaxel in the subgroup of patients with *EGFR* mutation-positive NSCLC (71.2% vs. 47.3%, respectively; odds ratio [OR] 2.75; 95% CI 1.65, 4.60; p < 0.001), and significantly higher with carboplatin/paclitaxel versus gefitinib in patients with *EGFR* mutation-negative NSCLC (23.5% vs. 1.1% [one patient], respectively; OR 0.04; 95% CI 0.01, 0.27; p = 0.001) [6]. Additionally, post-hoc analyses of IPASS found that the median duration of response (DoR) with gefitinib for patients with *EGFR* mutation-positive NSCLC was 8.7 months [8]. No differential treatment effect for overall survival (OS) was observed in the subsets of patients with *EGFR* mutation-positive (HR 1.00; 95% CI 0.76, 1.33; p = 0.990) or *EGFR* mutation-negative (HR 1.18; 95% CI 0.86, 1.63; p = 0.309) NSCLC [7].

As per protocol, the outcomes from the overall IPASS study were assessed by the local investigators from institutions that participated in the study. In 2015, to support the application of IRESSA with the US Food and Drug Administration (FDA), the FDA requested the re-analysis of PFS and other efficacy endpoints in a subgroup of patients from IPASS with *EGFR* mutation-positive NSCLC, using blind independent central review (BICR). BICR may be retrospectively implemented in clinical trials as an auditing step that aims to offset the potential measurement variation that may have resulted from local evaluation of tumor scans, and validate the results of investigator-assessed outcomes [9]. BICR is of particular value in non-blinded studies where potential bias cannot be excluded when assessments are conducted by investigators. FDA guidelines therefore recommend verification of study endpoints based on tumor measurements by central, independent reviewers blinded to the study treatment [10], and this has been utilized in previous first-line trials of EGFR TKIs in which investigators are not blinded to study treatment [11,12]. The post-hoc analyses requested by the FDA of efficacy endpoints according to BICR in a subgroup of IPASS patients with *EGFR* mutation-positive NSCLC are reported here.

2. Patients and methods

2.1. Study design, patients, and treatment

Full details of IPASS have been published previously [6]. Eligible patients were aged ≥18 years; had histologically/cytologically confirmed Stage IIB/IV NSCLC of ADC histology; were non-smokers (had smoked <100 cigarettes in their lifetime) or former light smokers (had stopped smoking ≤15 years previously and had ≤10 pack-years of smoking); had no prior chemotherapy, biologic, or immunologic therapy (adjuvant chemotherapy permitted if not platinum-based and completed >6 months previously); had a World Health Organization (WHO) performance status of 0, 1, or 2; had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) [13]; and had absolute neutrophil count >2.0 × 10^9/L with adequate hepatic function. Patients were randomly assigned 1:1 to gefitinib (250 mg/day) or carboplatin/paclitaxel (paclitaxel was administered intravenously over 3 h on Day 1, followed by carboplatin area under the serum concentration-time curve 5.0 or 6.0 intravenously over 15–60 min in once-every-3-weeks cycles for ≤6 cycles).

The primary endpoint of IPASS was PFS by investigator assessment, to indicate non-inferiority of gefitinib relative to carboplatin/paclitaxel. Secondary endpoints included ORR, OS, quality of life, reduction in symptoms, safety, and adverse-event profile. The post-hoc analyses presented here report PFS, ORR, and DoR data in a subgroup of IPASS patients with *EGFR* mutation-positive NSCLC according to BICR.

All patients provided written, informed consent, and an independent ethics committee at each participating institution approved the study protocol. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements, and AstraZeneca's policy on bioethics.