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Tumor response and health-related quality of life in clinically selected patients from Asia with advanced non-small-cell lung cancer treated with first-line gefitinib: Post hoc analyses from the IPASS study☆

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ABSTRACT

Background: In IPASS (NCT00322452), progression-free survival (PFS, primary endpoint) was significantly longer with first-line gefitinib versus carboplatin/paclitaxel in never/light ex-smokers with advanced pulmonary adenocarcinoma in Asia, both in the overall intent-to-treat (ITT) population and in the *EGFR* mutation-positive subgroup. To further characterize the clinical relevance of these data, we investigated objective response rate (ORR) and health-related quality of life (HRQoL) in patients treated with gefitinib.
Methods: Objective response was assessed (RECIST) 6-weekly (previously reported). Post hoc assessments included median time to response, median duration of response and change in tumor size. The analysis of response population included those patients treated with gefitinib who responded ($n = 262$ from ITT; $n = 94$ from *EGFR* mutation-positive subgroup). The percentage of patients with deterioration in HRQoL (Functional Assessment of Cancer Therapy-Lung [FACT-L], Trial Outcome Index [TOI]) and symptoms (Lung Cancer Subscale [LCS]) at 4 months post-randomization was analyzed according to progression status (EFQ population grouped by progressors/non-progressors in both treatment arms). The ORR (ITT) and incidence of skin rash/acne (evaluable-for-safety) were summarized.
Results: In patients whose tumors responded to gefitinib, median time to response was 6.1 weeks in the ITT population ($n = 262$) and 6.0 weeks in the *EGFR* mutation-positive subgroup ($n = 94$); median duration of response was 9.7 and 8.7 months in these groups, respectively. There was significant tumor shrinkage with gefitinib. A greater percentage of patients in the EFQ population whose tumors progressed experienced deterioration in HRQoL and symptoms at 4 months versus patients whose tumors did not progress (FACT-L 33.7% vs 16.3%; TOI 33.7% vs 13.2%; LCS 31.7% vs 15.5%). In the gefitinib arm of the EFS population, incidence of rash was 75.8% and 68.1% in *EGFR* mutation-positive and -negative subgroups, respectively (with ORR for the gefitinib arm of the ITT 71.2% vs 1.1%, respectively).
Conclusions: Patients whose tumors responded to first-line gefitinib experienced significant tumor shrinkage and a rapid, durable response. Deterioration in HRQoL and lung cancer symptoms at 4 months post-randomization was found to be associated with tumor progression, highlighting the role of patient-reported outcomes in the evaluation of advanced NSCLC disease. Rash was not supported as a predictive marker of response to gefitinib.

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1. Introduction

One of the consequences of the relatively asymptomatic nature of the early stages of non-small-cell lung cancer (NSCLC) is that approximately 55–60% of newly diagnosed cases are already at a

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locally advanced or metastatic stage [1]. Patients in the advanced stages of the disease experience great symptomatic burden [2–4], and whilst the instigation of molecular biomarker testing has helped to ensure that individual patients receive the most appropriate treatment regimen for their cancer [5], a rapid tumor response and symptom improvement are key to the management of the disease.

One licensed therapy for the treatment of advanced NSCLC is the oral epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) gefitinib. To date, four phase III studies have reported prolonged progression-free survival (PFS) with first-line gefitinib compared with chemotherapy in patients with advanced NSCLC with activating mutations of the *EGFR* gene [6–9].

The largest of these studies, the phase III Iressa Pan-ASia Study (IPASS; NCT00322452), compared gefitinib with carboplatin/paclitaxel in an overall population of 1217 patients who were previously untreated, never/light ex-smokers from East Asia with advanced pulmonary adenocarcinoma (261 of these patients had *EGFR* mutation-positive tumors). IPASS exceeded its primary objective and demonstrated superiority of gefitinib ($n = 609$) versus carboplatin/paclitaxel ($n = 608$) for PFS in this overall intent-to-treat (ITT) population (hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.65, 0.85; $P < 0.001$) [8]. The treatment effect was not constant over time, driven by a variation in outcomes according to *EGFR* mutation status. Pre-planned subgroup analyses showed that PFS was significantly longer with gefitinib vs carboplatin/paclitaxel in patients with *EGFR* mutation-positive tumors ($n = 261$; PFS HR 0.48; 95% CI 0.36, 0.64; $P < 0.0001$) [10] and significantly longer with carboplatin/paclitaxel versus gefitinib in patients with *EGFR* mutation-negative tumors ($n = 176$; HR 2.85; 95% CI 2.05, 3.98; $P < 0.0001$). Health-related quality of life (HRQoL) and lung cancer symptom assessments also favored gefitinib and carboplatin/paclitaxel in the *EGFR* mutation-positive and -negative subgroups, respectively [11].

Patients with solid tumors treated with EGFR-TKIs frequently experience skin rash/acne [12] and the hypothesis as to whether skin rash can be used as a predictive marker for response to EGFR-TKIs is debated [13]. Several phase II and III studies of the EGFR-TKI erlotinib have reported an association between improved survival and occurrence/severity of skin rash [14,15]. However, data supporting the use of rash as a surrogate marker for response to gefitinib are less conclusive; some studies reported a link [16–18] and others negated a possible correlation [19,20], which suggests further exploration of this hypothesis is required.

To further characterize the clinical relevance of the PFS improvement observed in IPASS, we performed post hoc summaries of time to objective response and duration of response in a subgroup of patients from the overall study population whose tumors responded to gefitinib. A separate post hoc analysis looked at HRQoL according to tumor progression status at a landmark time in patients treated with gefitinib (overall and by *EGFR* mutation status). Maximum percentage decrease in tumor size was reported for both study treatment groups in the overall population and by *EGFR* mutation status. The relationship between skin rash and response was also explored.

2. Methods

2.1. Patients and study design

Full details of the IPASS study design have been published previously [8]. Briefly, eligible patients had stage IIIB/IV pulmonary adenocarcinoma (including bronchoalveolar carcinoma), were either never-smokers or light ex-smokers, and had received no prior chemotherapy or biological/immunological therapy. Patients were randomized 1:1 to gefitinib (250 mg/day) or carboplatin/paclitaxel (200 mg/m^2 intravenously over 3 h on day 1, immediately followed by carboplatin area under the curve 5.0 or 6.0 intravenously over 15–60 min, in 3-weekly cycles for $\leq$6 cycles). Treatment continued until disease progression, intolerable toxicity, request to discontinue by patient/physician, serious non-compliance with the study protocol, or six chemotherapy cycles had been reached.

2.2. Assessment of tumor response

Objective tumor response (complete response [CR] or partial response [PR]) was determined by the Response Evaluation Criteria In Solid Tumors (RECIST) [21] 1.0 and assessed 6-weekly until disease progression. Objective response rates (ORRs) were calculated as the percentage of the total number of patients analyzed whose tumors had a confirmed overall response of CR or PR; these data have been reported previously for the overall ITT population [8,10].

In the present post hoc analysis, time to response to gefitinib was derived as the time from randomization until the first assessment when a tumor response was detected, for a subgroup of patients from the ITT population whose tumors had a confirmed response only to gefitinib ($n = 262$ from ITT; $n = 94$ from the *EGFR* mutation-positive subgroup). To determine the duration of response, patients from these subgroups without an end date for their tumor response were censored at their last evaluable assessment.

The post hoc analysis of maximum percentage decrease in tumor size was assessed in both treatment arms of the study. Data were analyzed for patients treated with gefitinib and carboplatin/paclitaxel in the overall ITT population ($n = 568$ and $n = 553$, respectively) and for *EGFR* mutation subgroups (*EGFR* mutation-positive: $n = 131$ and $n = 126$, respectively; *EGFR* mutation-negative: $n = 84$ and $n = 81$, respectively). Maximum percentage decrease in tumor size was also analyzed post hoc by *EGFR* mutation subtype for the gefitinib arm of the study (exon 19 deletions $n = 66$, exon 21 L858R point mutation $n = 63$). Change in tumor size (sum of the unidimensional diameters of the target lesion according to RECIST) was calculated at each 6-weekly visit from the initial baseline assessment, with the first assessment occurring at week 6.

A separate landmark analysis at 4 months was performed for patients in both treatment arms of the ITT population. Patients were classified as having progressed if they experienced tumor progression between 2.5 and 5.5 months post-randomization (ITT; gefitinib $n = 102$; carboplatin/paclitaxel $n = 124$). Patients were classified as having not progressed if they experienced tumor progression or were censored after 5.5 months (ITT; gefitinib $n = 298$; carboplatin/paclitaxel $n = 288$).

2.3. Assessment of EGFR mutation

Tumor *EGFR* mutation status was determined by extracting DNA from paraffin-embedded archival tumor tissue and analyzing for 29 *EGFR* mutations (including exon 19 deletions and L858R mutation) using an amplification refractory mutation system (ARMS)-based *EGFR* mutation detection kit (Qiagen, previously DxS, Manchester, UK) [22,23]. Tumors were considered *EGFR* mutation-positive if at least one of 29 *EGFR* mutations was detected [8,10].

2.4. Assessment of HRQoL

HRQoL methodology and analyses (pre-planned and some post hoc) have been previously published [11]. Briefly, HRQoL was assessed in the evaluable-for-quality of life (EFQ) population using the total score of the Functional Assessment of Cancer Therapy – Lung (FACT-L) questionnaire [24] and the Trial Outcome Index