European Journal of Cancer (2014) **50**, 2219–2230

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journal homepage: www.ejcancer.com

Clinical Trial

First-line pemetrexed plus cisplatin followed by gefitinib maintenance therapy versus gefitinib monotherapy in East Asian patients with locally advanced or metastatic non-squamous non-small cell lung cancer: A randomised, phase 3 trial ☆

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Received 6 March 2014; received in revised form 5 May 2014; accepted 9 May 2014
Available online 18 June 2014

KEYWORDS
Non-squamous non-small cell lung cancer
Pemetrexed
Gefitinib
Cisplatin
East Asian patients

Abstract ***Background:*** In the Iressa Pan-ASia Study (IPASS), gefitinib claimed improved progression-free survival (PFS) versus carboplatin-paclitaxel in clinically selected lung cancer patients. The primary objective of this study was to assess the PFS of pemetrexed-cisplatin (PC) followed by gefitinib maintenance versus gefitinib monotherapy in an IPASS-like population.

Methods: In this open-label, randomised, phase 3 trial, eligible patients were ⩾18 years, chemonaïve, East Asian, light ex-smokers/never-smokers with advanced non-squamous non-small cell lung cancer, an Eastern Cooperative Oncology Group (ECOG) performance

☆ Presented in part at the 15th World Conference on Lung Cancer, Sydney, Australia, 28th October 2013 (abstract #MO06.04).

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http://dx.doi.org/10.1016/j.ejca.2014.05.011

status 0–1 and unknown epidermal growth factor receptor (EGFR) mutation status who enrolled at 12 sites in Asia. Patients randomly received (1:1) pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) for six 21-day cycles, followed by gefitinib maintenance or gefitinib monotherapy (250 mg/day). Patient tissue was retrospectively analysed for EGFR mutations. This study is registered with ClinicalTrials.gov, NCT01017874.

Findings: Between 23rd November 2009 and 27th April 2012, 253 patients entered, and 236 patients were randomly assigned to and treated with PC therapy ($N = 114$) and gefitinib monotherapy ($N = 118$). Between-arm baseline characteristics were balanced. PFS was not significantly different between treatment arms ($p = 0.217$). The unadjusted hazard ratio (HR) was 0.85 (95% confidence interval (CI) 0.63–1.13). The HR should be cautiously interpreted as it was not constant. EGFR mutation status was determined for 74 tissue samples; 50 (67.6%) had mutations. In a pre-specified subgroup analysis, only the treatment-by-EGFR mutation interaction was significant ($p = 0.008$) for PFS. For the entire treatment period, a higher proportion of patients in the PC/gefitinib arm versus gefitinib experienced possibly drug-related grade 3–4 treatment-emergent adverse events (39 of 114 [34%] versus 19 of 118 [16%]; $p = 0.002$).

Interpretation: In the intention-to-treat (ITT) population, PFS was not significantly different. In the biomarker-assessable population, front-line EGFR tyrosine kinase inhibitor monotherapy was not efficacious in patients with wild-type EGFR. Identification of EGFR mutation status is key in the management of advanced non-squamous non-small cell lung cancer.

Funding: Eli Lilly and Company.

1. Introduction

Lung cancer is a main cause of cancer-related deaths in East Asia [1]. Most cases are diagnosed in advanced stages, and the current standard of care for chemonaïve patients with advanced non-small cell lung cancer (NSCLC) and a good performance status is 4–6 cycles of platinum-based induction therapy [2–4]. The only two options that have demonstrated improved outcomes for patients with non-squamous NSCLC are a platinum combination with pemetrexed [5] or bevacizumab combined with carboplatin plus paclitaxel [6].

Initial trials of second- and third-line treatments showed that epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) were most effective in Asians, never-smokers, females and patients with adenocarcinomas [7–9]. Interestingly, relatively high incidences of mutations in the kinase domain of the EGFR were subsequently found in these populations [10,11], and tumours with such mutations are responsive to EGFR-TKIs [12–14]. Therefore, many Asian physicians have selected gefitinib treatment based on clinical criteria.

The previously published phase 3 Iressa Pan-ASia Study (IPASS) was designed to compare gefitinib versus combination chemotherapy in chemonaïve East Asian patients with advanced pulmonary adenocarcinoma who were former light-/never-smokers [15]. Patients were randomised to receive gefitinib or carboplatin-paclitaxel. Although the intention-to-treat (ITT) results favoured gefitinib, in the preplanned biomarker analysis, progression-free survival (PFS) improved in the gefitinib versus carboplatin-paclitaxel arm (hazard ratio (HR) 0.48 [95% confidence interval (CI) 0.36–0.64]; $p < 0.001$) only in the EGFR-mutation subgroup ($n = 261$), whereas PFS was longer in the carboplatin-paclitaxel arm in the EGFR wild-type (WT) subgroup ($n = 176$) (HR 2.85 [95% CI 2.05–3.98]; $p < 0.001$).

Pemetrexed-cisplatin (PC) with vitamin supplementation is approved for the initial treatment of advanced or metastatic non-squamous NSCLC and pemetrexed alone as maintenance treatment for patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy [16–21]. In a retrospective analysis of the first-line pemetrexed registration trial, East Asian ethnicity was a favourable prognostic indicator [18,22].

In study S110, which was subsequent to the first-line pemetrexed registration trial, East Asian never-smokers of unknown EGFR mutation status were randomly assigned to receive PC followed by maintenance with gefitinib (PC/gefitinib) or pemetrexed [23]. Results from this phase 2 trial showed that patients treated with first-line PC and sequential gefitinib experienced a median PFS of 9.95 months.

On the basis of results from both the S110 and IPASS trials [15,23], which employed different study designs and chemotherapy regimens, the current phase 3 trial was designed to compare PFS with initial PC followed by maintenance gefitinib or initial gefitinib in an IPASS-like population of chemonaïve East Asian patients with advanced pulmonary adenocarcinoma who were light ex-smokers or never-smokers.