ORIGINAL ARTICLE

First-Line Pemetrexed plus Cisplatin followed by Gefitinib Maintenance Therapy versus Gefitinib Monotherapy in East Asian Never-Smoker Patients with Locally Advanced or Metastatic Nonsquamous Non–Small Cell Lung Cancer: Final Overall Survival Results from a Randomized Phase 3 Study

James Chih-Hsin Yang, MD, PhD,[a,*] Vichien Srimuninnimit, MD,[b] Myung-Ju Ahn, MD, PhD,[c] Chia-Chi Lin, MD, PhD,[a] Sang-We Kim, MD, PhD,[d] Chun-Ming Tsai, MD,[e] Tony Mok, MD,[f] Mauro Orlando, MD,[g] Tarun Puri, MD,[h] Xin Wang, PhD,[i] Keunchil Park, MD, PhD[c]

[a]*National Taiwan University Hospital, Taipei, Taiwan*
[b]*Siriraj Hospital, Mahidol University, Bangkok, Thailand*
[c]*Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[d]*Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea*
[e]*Taipei Veterans General Hospital and National Yang-Ming University, Shi-Pai, Taipei, Taiwan*
[f]*Prince of Wales Hospital, Sha Tin, Hong Kong*
[g]*Eli Lilly Interamerica Inc., Buenos Aires, Argentina*
[h]*Eli Lilly and Company, Gurgaon, Haryana, India*
[i]*Eli Lilly and Company, Shanghai, China*

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ABSTRACT

Introduction: The primary analysis of this open-label, randomized, multicenter phase 3 study revealed no significant difference in progression-free survival between pemetrexed plus cisplatin followed by maintenance gefitinib (PC/G) and gefitinib monotherapy (G) in patients with advanced nonsquamous non–small cell lung cancer (NSCLC) and unknown epidermal growth factor receptor gene (*EGFR*) mutation status; however, the hazard ratio favored PC/G. This report describes the final overall survival (OS) results.

Methods: Chemonaive, East Asian light ex-smokers/never-smokers with advanced nonsquamous NSCLC and unknown *EGFR* mutation status were randomized (1:1) to PC/G (n = 118) or G (n = 118). *EGFR* mutation status was retrospectively determined for 76 patients, 52 (68.4%) of whom had *EGFR*-mutated tumors (exon 19 deletions in 26 and L858R point mutation in 24). OS was analyzed by the Kaplan-Meier method. The study was registered at ClinicalTrials.gov (NCT01017874).

Results: Median OS was similar in the PC/G (26.9 months) and G (27.9 months) groups (hazard ratio = 0.94, 95% confidence interval: 0.68–1.31, $p = 0.717$). Median OS was longer with PC/G than with G in patients with *EGFR* wild-type tumors (28.4 versus 8.9 months) and longer with G than with PC/G in patients with *EGFR*-mutated tumors

***Corresponding author.**

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Address for correspondence: James Chih-Hsin Yang, MD, PhD, Department of Oncology, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan. E-mail: chihyang@ntu.edu.tw

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(45.7 versus 32.4 months), especially those with exon 19 deletions. Second-line postdiscontinuation therapy was common and included chemotherapy (PC/G, 41 of 118 [34.7%]; G, 73 of 118 [61.9%]) and rechallenge with an EGFR tyrosine kinase inhibitor (PC/G, 27 of 118 [22.9%]; G, 9 of 118 [7.6%]).

Conclusions: The progression-free survival and OS results from this study further demonstrate the importance of determining *EGFR* mutation status to select the most appropriate first-line treatment for patients with advanced NSCLC.

Keywords: Non–small cell lung cancer; East Asia; Gefitinib; Pemetrexed; Overall survival

Introduction

Lung cancer is a major cause of cancer mortality in East Asia, accounting for approximately one-quarter of cancer deaths.[1] As there are currently no pan-Asian guidelines for the treatment of non–small cell lung cancer (NSCLC), practitioners in Asia rely on guidelines issued by organizations such as the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the American College of Chest Physicians.[2] According to these guidelines, the current standard of care for chemonaive patients with advanced NSCLC and a good performance status is platinum-based, two-drug chemotherapy regimens.[3–5] For patients whose tumors have activating epidermal growth factor receptor gene (*EGFR*) mutations, EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib are the preferred first-line treatment option.[3,5] Activating *EGFR* mutations are common in patients with the following clinical characteristics: female sex, East Asian ethnicity, history of nonsmoking, and histologic diagnosis of adenocarcinoma.[6–8] The two most common activating *EGFR* mutations are deletions in exon 19 and the L858R point mutation in exon 21, which together account for approximately 85% to 90% of *EGFR* somatic mutations in patients with NSCLC.[8–10]

A previously conducted randomized phase 3 study compared pemetrexed plus cisplatin followed by maintenance gefitinib (PC/G) with gefitinib monotherapy (G) in chemonaive patients with locally advanced or metastatic nonsquamous NSCLC and unknown *EGFR* mutation status at study entry.[11] The patients in this study were clinically selected for response to gefitinib treatment (i.e., East Asian ethnicity, never-smokers or light ex-smokers, and tumors with a histologic diagnosis of adenocarcinoma). The primary analysis revealed no significant difference in progression-free survival (PFS) between the PC/G and G groups in the intention-to-treat (ITT) population, although the hazard ratio (HR) favored PC/G (HR = 0.85, 95% confidence interval [CI]: 0.63–1.13, $p = 0.261$).[11] In addition, a prespecified subgroup analysis showed that PFS was not significantly different between the PC/G and G groups in patients with *EGFR*-mutated tumors; however, PFS was significantly longer in the PC/G group than in the G group in patients with *EGFR* wild-type tumors.[11] The Iressa Pan-Asia Study (IPASS) also assessed chemotherapy versus gefitinib in chemonaive patients who had been clinically selected for response to gefitinib.[12] In this study, PFS was significantly longer with gefitinib than with carboplatin-paclitaxel in the subgroup of patients with *EGFR*-mutated tumors and significantly longer with carboplatin-paclitaxel than with gefitinib in the subgroup of patients with *EGFR* wild-type tumors. The results of these two studies support the current recommendation that only patients with *EGFR*-mutated tumors should receive an EGFR TKI as first-line treatment.[3,5]

This phase 3 study has now been completed, and here we report the overall survival (OS) data for the PC/G and G groups in the ITT population and by *EGFR* mutation status, along with the updated safety data. Also reported here are post hoc analyses assessing the individual effect of exon 19 deletions and the L858R point mutation and the effect of systemic postdiscontinuation therapy (PDT) on OS in the PC/G and G groups.

Materials and Methods

Study Design

Full details of the study design have been published elsewhere.[11] This was a multicenter, open-label, randomized phase 3 study comparing PC/G with G in East Asian patients with locally advanced or metastatic nonsquamous NSCLC. The study was conducted at 12 sites in Hong Kong, the Republic of Korea, Singapore, Taiwan, and Thailand. The study protocol was approved by the ethics review board at each site and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent before undergoing any study procedure. Separate consent was obtained for the optional provision of tissue samples for biomarker analysis. The study was registered at www.ClinicalTrials.gov (NCT01017874).

Study Population

Chemonaive patients of East Asian ethnicity and unknown tumor *EGFR* mutation status with stage IIIB (T4 malignant pleural effusion) or stage IV nonsquamous NSCLC[13,14] were eligible for inclusion in this study. Other eligibility criteria included the following: age 18 years or