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

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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

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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

older, a never-smoker (<100 cigarettes in one's lifetime) or light ex-smoker (had ceased smoking for at least 5 years and had not exceeded 10 pack-years), disease measurable by Response Evaluation Criteria in Solid Tumors version 1.0, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

Randomization

Patients were randomly assigned (1:1) to receive PC/G or G. Randomization was carried out using a computer-generated random sequence and an interactive voice response system. Randomization was stratified by baseline ECOG PS (0 or 1), sex (male or female), smoking history (never-smoker or light ex-smoker), and histologic diagnosis (adenocarcinoma or nonadenocarcinoma).

Treatment Protocol

Full details of the treatment protocol have been published elsewhere.[11] Patients assigned to PC/G received up to six cycles of pemetrexed (500 mg/m^2 intravenously) followed approximately 30 minutes later by cisplatin (75 mg/m^2 intravenously), both of which were administered on day 1 of 21-day cycles. After a maximum of six cycles of PC (the induction period), patients who had not progressed received oral G (250 mg/day) as maintenance therapy until progression, discontinuation, or death (the maintenance period). Patients assigned to PC/G received dexamethasone, folic acid, and vitamin B_{12} supplementation per the pemetrexed label. Patients assigned to G received gefitinib 250 mg/day until progression, discontinuation, or death. All patients were to be followed until death or study completion.

EGFR *Mutation Status*

Where available, tumor tissue was analyzed for *EGFR* mutations by means of a standardized Scorpions ARMS *EGFR* mutation assay using an *EGFR* polymerase chain reaction test kit (Qiagen, Valencia, CA). Tumors were classified as *EGFR* wild type (*EGFR* wild-type subgroup), *EGFR* mutation positive (*EGFR*-mutated subgroup), or *EGFR* mutation status unknown. Tumor tissue was assessed for exon 19 deletions (the Ex19del subgroup) and the L858R point mutation in exon 21 (the L858R subgroup).

Outcome Measures

Comparisons of OS between the PC/G and G groups in the ITT population and by *EGFR* mutation status (which were secondary objectives of the study) were performed. In addition, post hoc analyses of OS in patients determined to have exon 19 deletions or the L858R point mutation, and of OS by PDT, were conducted. OS was defined as the time from randomization to the date of death from any cause. Treatment-emergent adverse events (TEAEs) were reported according to the Medical Dictionary for Regulatory Activities (version 15.1) and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Statistical Analysis

The ITT population comprised all patients who were randomized to treatment. The safety population comprised all patients who were randomized to treatment and received at least one dose of pemetrexed, cisplatin, or gefitinib. Median follow-up was calculated using the reverse Kaplan-Meier method.[15] OS was analyzed using the Kaplan-Meier method and survival curves were plotted. HRs were estimated using unadjusted Cox regression analysis with assigned treatment as the only covariate and analyzed using Wald's test. PDT was summarized as the number and percentage of patients using therapy and analyzed using Fisher's exact test. TEAEs were summarized as the number and percentage of patients reporting each event. The level of significance was set at $p < 0.05$. Analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC).

Results

Patient Disposition

Of the 253 patients entered in the study, 236 were randomized to treatment (PC/G, 118 patients; G, 118 patients) and constituted the ITT population (Fig. 1). Of the randomized patients, 232 received at least one dose of pemetrexed, cisplatin, or gefitinib (PC/G, 114 patients; G, 118 patients) and constituted the safety population (see Fig. 1). Of the 236 patients in the ITT population, 149 (63.1%) consented to biomarker analyses and 142 (60.2%) provided tissue samples for *EGFR* mutation analysis. *EGFR* mutation status could be determined for 76 (53.5%) of 142 tissue samples. Overall, 24 patients had tumors that were classified as *EGFR* wild type and 52 patients had tumors that were classified as *EGFR* mutated (mutation rate, 52 of 76 patients [68.4%]; Table 1). Of the 52 patients with *EGFR*-mutated tumors, 26 had exon 19 deletions and 24 had the L858R point mutation (Table 1).

Demographic and Baseline Clinical Characteristics

Demographic and baseline clinical characteristics were similar between the PC/G and G groups (see Table 1). Most patients (>90%) were never-smokers and had stage IV disease. More than half of the patients had an ECOG PS of 1.

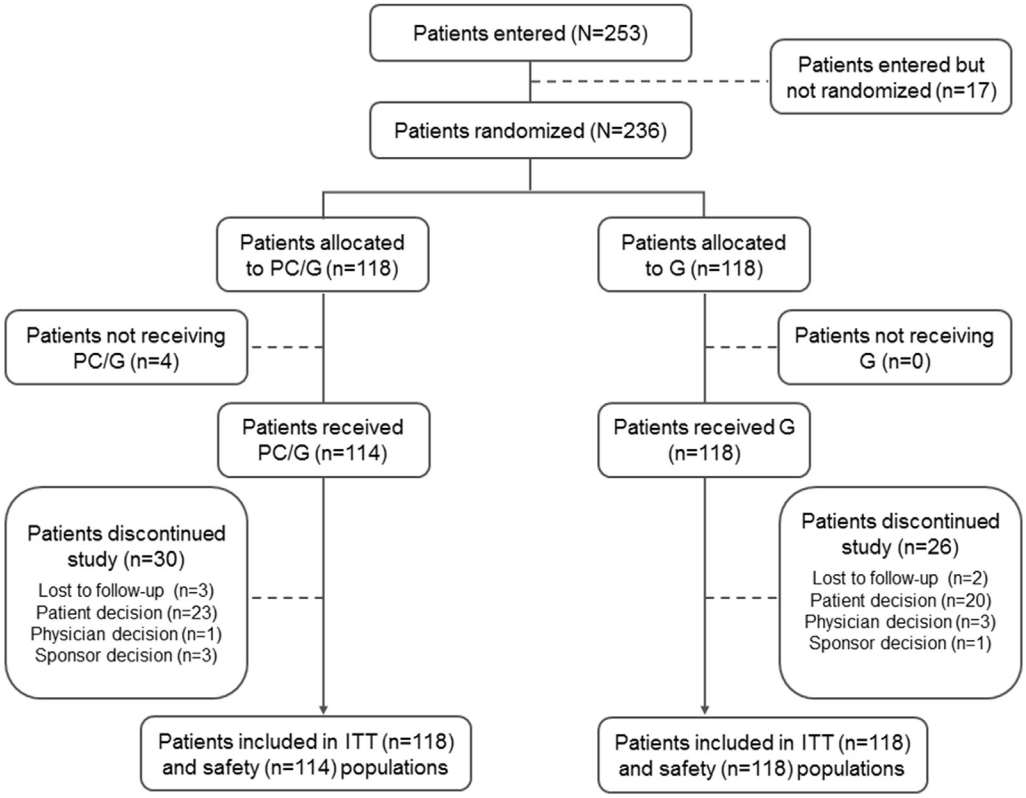

Figure 1. Patient flow. G, gefitinib monotherapy; ITT, intention-to-treat; PC/G, pemetrexed plus cisplatin followed by maintenance gefitinib.

OS

The censor rate was 40.7% and the median duration of follow-up in the ITT population was 43.5 months (95% CI: 39.3–47.3). There was no significant difference in OS between the PC/G and G groups in the ITT population (Table 2 and Fig. 2*A*). Median OS was longer in the PC/G group than in the G group in the *EGFR* wild-type subgroup (see Table 2 and Fig. 2*B*). In contrast, median OS was longer in the G group than in the PC/G group in the *EGFR*-mutated subgroup, the Ex19del subgroup, and the L858R subgroup (see Table 2). However, none of the observed differences in the OS Kaplan-Meier curves between treatment groups in the *EGFR* subgroups was statistically significant. In the *EGFR*-mutated subgroup (Fig. 2*C*) and the Ex19del subgroup (Fig. 2*D*), the Kaplan-Meier survival curves were separated, with the curve for the G group located above that for the PC/G group. In contrast, in the L858R subgroup (Fig. 2*E*), the Kaplan-Meier curves for the G and PC/G group overlapped somewhat.

PDT

Most patients (>60%) in both the PC/G and G groups received second-line PDT with systemic treatment (Table 3). The proportion of patients who received chemotherapy and a platinum doublet as second-line PDT was significantly higher ($p < 0.001$) in the G group than in the PC/G group (see Table 3). The proportion of patients who received an EGFR TKI as second-line PDT was significantly higher ($p = 0.002$) in the PC/G group than in the G group (see Table 3). In the G group, OS appeared to be longer in patients who received a pemetrexed platinum doublet as second-line PDT than in patients who received a nonpemetrexed platinum doublet (Fig. 2*F*). Median OS was 34.9 months (95% CI: 21.3–42.3) in patients who received a pemetrexed platinum doublet (Pem) and 26.9 months (95% CI: 12.0–40.6) in patients who received a nonpemetrexed platinum doublet (Non-Pem) (HR = 0.57, 95% CI: 0.29–1.14, $p = 0.108$).

Safety and Tolerability Measures

The safety results were similar to those reported at the time of the primary analysis.[11] Throughout the study period (the induction and maintenance periods combined), most of the patients in both groups in the safety population reported one or more possibly drug-related TEAEs (PC/G, 104 of 114 patients [91.2%]; G, 99 of 118 patients [83.9%]). A higher proportion of patients in

Table 1. Patient Demographics and Baseline Disease Characteristics

Characteristic	PC/G (n = 118)	G (n = 118)	Total (N = 236)
Sex, n (%)			
Male	30 (25.4)	29 (24.6)	59 (25.0)
Age, y			
Mean (SD)	58.5 (10.73)	59.4 (10.67)	59.0 (10.69)
Age group, n (%)			
<65	80 (67.8)	81 (68.6)	161 (68.2)
≥65	38 (32.2)	37 (31.4)	75 (31.8)
Smoking status, n (%)			
Never-smoker	109 (92.4)	109 (92.4)	218 (92.4)
Light ex-smoker	9 (7.6)	9 (7.6)	18 (7.6)
Pathological diagnosis, n (%)			
Adenocarcinoma	114 (96.6)	115 (97.5)	229 (97.0)
Nonadenocarcinoma	4 (3.4)	3 (2.5)	7 (3.0)
Stage of disease, n (%)			
IIIB	6 (5.1)	8 (6.8)	14 (5.9)
IV	112 (94.9)	110 (93.2)	222 (94.1)
ECOG performance status, n (%)			
0	49 (41.5)	49 (41.5)	98 (41.5)
1	69 (58.5)	69 (58.5)	138 (58.5)
Country of enrollment, n (%)			
Hong Kong	3 (2.5)	7 (5.9)	10 (4.2)
Republic of Korea	54 (45.8)	60 (50.8)	114 (48.3)
Singapore	1 (0.8)	1 (0.8)	2 (0.8)
Taiwan	39 (33.1)	28 (23.7)	67 (28.4)
Thailand	21 (17.8)	22 (18.6)	43 (18.2)
EGFR mutation status, n (%)			
EGFR wild type	13 (11.0)	11 (9.3)	24 (10.2)
EGFR mutated	27 (22.9)	25 (21.2)	52 (22.0)
Ex19del	15 (12.7)	11 (9.3)	26 (11.0)
L858R	10 (8.5)	14 (11.9)	24 (10.2)

ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor gene; Ex19del, deletion in exon 19; G, gefitinib monotherapy; L858R, point mutation in exon 21; PC/G, pemetrexed plus cisplatin followed by maintenance gefitinib; SD, standard deviation.

the PC/G group than in the G group reported one or more possibly drug-related grade 3/4 TEAEs (PC/G, 40 of 114 patients [35.1%]; G, 20 of 118 patients [16.9%]). The most commonly reported possibly drug-related TEAEs were nausea, vomiting, and decreased appetite in the PC/G group and rash, diarrhea, and pruritus in the G group.

Discussion

The final OS results from this randomized phase 3 study of chemonaive East Asian patients with advanced NSCLC and unknown *EGFR* mutation status at study entry showed that there was no significant difference in OS between patients receiving PC/G and those receiving G. When analyzed by *EGFR* mutation

Table 2. Overall Survival

Population (n)	Overall Survival, Median (95% CI), mo		PC/G vs. G HR (95% CI; *p* Value)
	PC/G	G	
ITT (236)	26.9 (20.8-35.1)	27.9 (21.3-32.4)	0.94 (0.68-1.31; 0.717)
EGFR wild type (24)	28.4 (11.3-50.6)	8.9 (0.7-NE)	0.62 (0.22-1.72; 0.356)
EGFR mutated (52)	32.4 (19.3-NE)	45.7 (25.8-NE)	1.57 (0.72-3.39; 0.255)
Ex19del (26)	32.4 (15.2-NE)	45.7 (18.7-NE)	2.36 (0.70-7.92; 0.166)
L858R (24)	35.7 (1.3-NE)	41.3 (13.6-NE)	1.23 (0.41-3.67; 0.709)

CI, confidence interval; *EGFR*, epidermal growth factor receptor gene; Ex19del, deletion in exon 19; HR, hazard ratio; G, gefitinib monotherapy; ITT, intention-to-treat; L858R, point mutation in exon 21; NE, not estimable; PC/G, pemetrexed plus cisplatin followed by maintenance gefitinib.

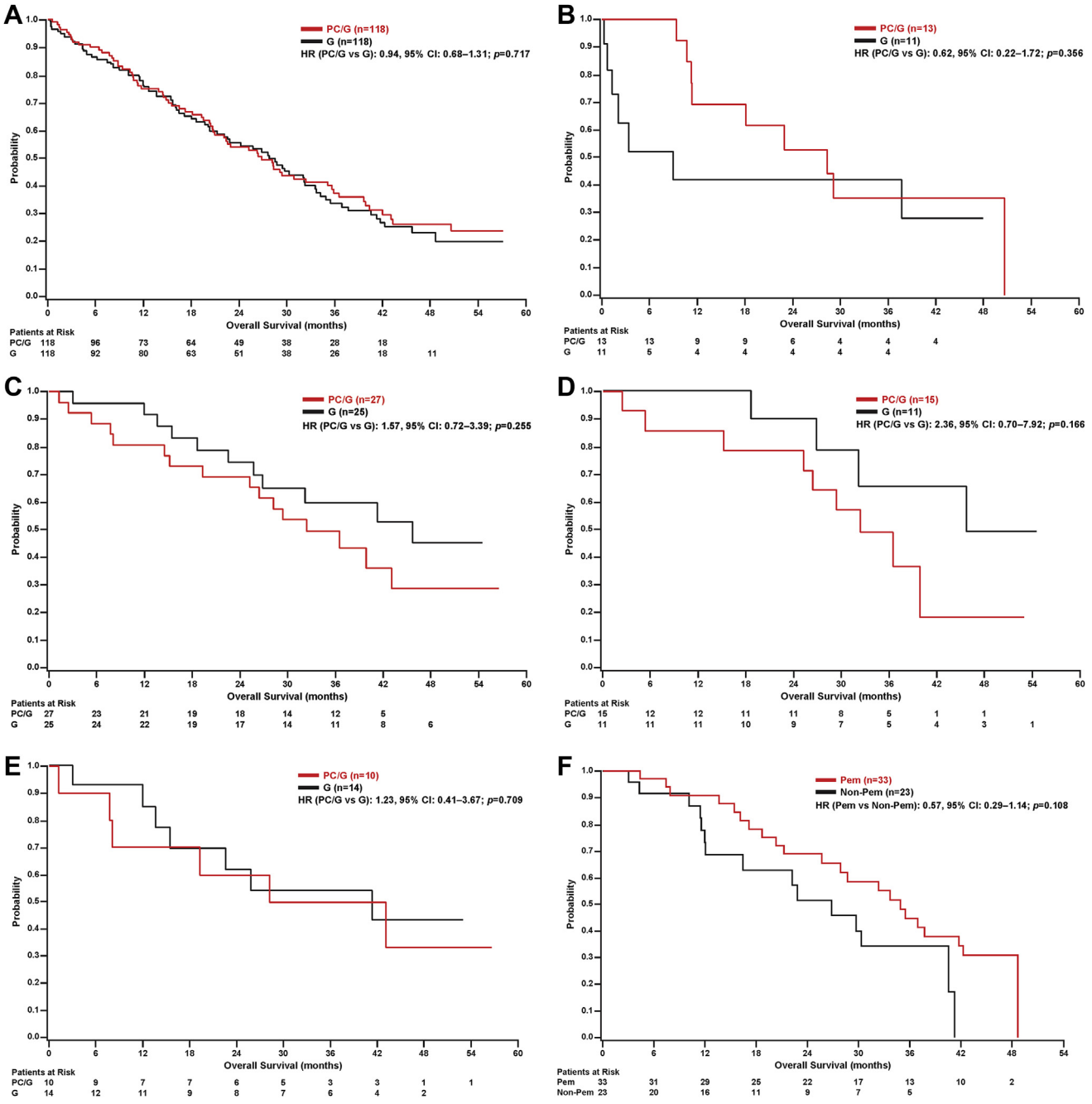

Figure 2. Kaplan-Meier analysis of OS in the ITT population by *EGFR* mutation status and by postdiscontinuation therapy. OS in the PC/G and G groups in the ITT population (*A*), *EGFR* wild-type subgroup (*B*), *EGFR*-mutated subgroup (*C*), Ex19del subgroup (*D*), and L858R subgroup (*E*). OS in the G group for patients receiving a pemetrexed platinum doublet as second-line PDT and those receiving a nonpemetrexed platinum doublet (*F*). *EGFR*, epidermal growth factor receptor gene; Ex19del, deletion in exon 19; G, gefitinib monotherapy; ITT, intention-to-treat; L858R, point mutation in exon 21; non-Pem, non-pemetrexed platinum doublet; OS, overall survival; PC/G, pemetrexed plus cisplatin followed by maintenance gefitinib; PDT, postdiscontinuation therapy; Pem, pemetrexed platinum doublet.

status, OS was longer with PC/G in patients with *EGFR* wild-type tumors and longer with G in patients with *EGFR*-mutated tumors, although these differences in OS were not statistically significant. For patients who progressed while receiving first-line G, OS appeared to be longer in patients who received a pemetrexed platinum doublet as second-line treatment than in those who received a nonpemetrexed platinum doublet. As observed at the time of the primary analysis, both treatment regimens were associated with a manageable safety profile. The results from this study provide further support for *EGFR* mutation

Table 3. Postdiscontinuation Therapy

PDT	PC/G (n = 118) n (%)	G (n = 118) n (%)	*p* Value
Second-line PDT with systemic treatment	71 (60.2)	85 (72.0)	0.074
Chemotherapy	41 (34.7)	73 (61.9)	<0.001
Platinum doublet	15 (12.7)	56 (47.5)	<0.001
Pemetrexed platinum doublet	4 (3.4)	33 (28.0)	NA
Nonpemetrexed platinum doublet	11 (9.3)	23 (19.5)	NA
Single agent	24 (20.3)	17 (14.4)	0.303
Nonplatinum doublet	2 (1.7)	0 (0)	0.498
EGFR TKI	27 (22.9)	9 (7.6)	0.002
Afatinib	0 (0)	1 (0.8)	1.000
Erlotinib	12 (10.2)	1 (0.8)	0.003
Gefitinib	14 (11.9)	7 (5.9)	0.169
Gefitinib + investigational agent	1 (0.8)	0 (0)	1.000

EGFR, epidermal growth factor receptor; G, gefitinib monotherapy; NA, not applicable; PC/G, pemetrexed plus cisplatin followed by maintenance gefitinib; PDT, postdiscontinuation therapy; TKI, tyrosine kinase inhibitor.

testing before selecting first-line treatment for patients with advanced NSCLC, rather than relying solely on clinical characteristics to select the most appropriate treatment.

OS in the Overall Study Population

As observed for the primary analysis of PFS,[11] there was no significant difference in OS between PC/G and G in the overall population in this study. These OS results are consistent with those of two randomized phase 3 studies of chemotherapy versus gefitinib in chemonaive patients who were clinically selected to respond to gefitinib (i.e., East Asian never-smokers or light ex-smokers with adenocarcinoma).[16,17] Specifically, the IPASS found no significant difference in OS between patients receiving up to six cycles of carboplatin-paclitaxel (n = 608, median OS 17.4 months) and patients receiving gefitinib (n = 609, median OS 18.8 months).[16] Likewise, the First-SIGNAL study found no significant difference in OS between patients receiving up to nine cycles of gemcitabine-cisplatin (n = 150, median OS 22.9 months) and patients receiving gefitinib (n = 159; median OS 22.3 months).[17] The authors of these two studies stated that the high proportions of patients in the chemotherapy and gefitinib groups receiving the alternative treatment as PDT may have confounded the true effect of the first-line treatment on OS.[16,17] In the current study, it should be noted that in addition to second-line PDT being common in the two treatment groups, patients who had not progressed after six cycles of chemotherapy received maintenance gefitinib, which may also have contributed to the lack of difference in OS between the two treatment groups in the overall study population.

OS in Patients with EGFR *Wild-Type Tumors*

In the current study, median OS was longer with PC/G than with G in the subgroup of patients with *EGFR* wild-type tumors. This finding is in line with the PFS results of the primary analysis,[11] the IPASS,[12] and the First-SIGNAL study,[17] all of which demonstrated longer PFS (significantly longer in the primary analysis and the IPASS) with chemotherapy (plus maintenance gefitinib in the current study) than with gefitinib in patients with *EGFR* wild-type tumors. Unlike in the current study, however, OS was similar between treatment groups in patients with *EGFR* wild-type tumors in the IPASS and First-SIGNAL study.[16,17] In the IPASS, median OS was 12.7 months in patients with *EGFR* wild-type tumors who received carboplatin-paclitaxel (n = 85) and 11.2 months in patients receiving gefitinib (n = 91).[16] In the First-SIGNAL study, median OS was 21.9 months in patients with *EGFR* wild-type tumors who received gemcitabine-cisplatin (n = 27) and 18.4 months in patients receiving gefitinib (n = 27).[17] The lack of significant difference in OS in the *EGFR* wild-type subgroups in these two studies was attributed to the use of PDT. For instance, 75.8% of patients with *EGFR* wild-type tumors who received gefitinib in the IPASS subsequently received chemotherapy as PDT.[16]

OS in Patients with EGFR*-Mutated Tumors*

In the current study, median OS was longer with G than with PC/G in the subgroup of patients with *EGFR*-mutated tumors. In contrast, OS was similar between chemotherapy and gefitinib in the subgroups of patients with *EGFR*-mutated tumors in the IPASS and First-SIGNAL study.[16,17] Specifically, in the IPASS, median OS was 21.9 months in patients with *EGFR*-mutated tumors who received carboplatin-paclitaxel (n = 129) and 21.6 months in patients receiving gefitinib (n = 132).[16] In the First-SIGNAL study, median OS was 25.6 months in patients with *EGFR*-mutated tumors who received gemcitabine-cisplatin (n = 16) and 27.2 months in patients receiving gefitinib (n = 26).[17] In addition, two randomized phase 3 studies of chemonaive patients with advanced NSCLC (WJTOG3405 [N = 172] and NEJ002 [N = 228]), which enrolled only patients with *EGFR*-mutated tumors, found no significant difference in OS between chemotherapy and gefitinib.[18–21] Again, the frequent use of PDT in these

studies likely contributed to the lack of significant difference in OS between chemotherapy and gefitinib in patients with *EGFR*-mutated tumors. It is possible that the *EGFR* testing method, the proportion of patients receiving PDT, and the prevalence of pemetrexed treatment may have influenced the variation in outcomes between the current study and the other studies described here.

The current study assessed sequential administration of chemotherapy and an EGFR TKI; however, another possible treatment strategy for patients with NSCLC and *EGFR*-mutated tumors is concurrent administration of chemotherapy and EGFR TKI. Cheng et al.[22] recently assessed concurrent administration of pemetrexed and gefitinib in 191 patients with nonsquamous NSCLC with *EGFR*-mutated tumors, reporting a significant improvement in PFS with pemetrexed plus gefitinib versus with G (median PFS was 15.8 months for pemetrexed plus gefitinib versus 10.9 months for G; HR = 0.68, 95% CI: 0.48–0.96, one-sided $p = 0.014$; two-sided $p = 0.029$). Further investigation of different combinations and timing of chemotherapy and EGFR TKIs may expand the treatment strategies available for patients with NSCLC and *EGFR*-mutated tumors.

OS in Patients with Exon 19 Deletions or the L858R Point Mutation

Analysis of OS by the two most common *EGFR* mutations revealed longer OS with G than with PC/G in patients with exon 19 deletions and in patients with the L858R point mutation; however, the difference in OS between the two treatment regimens appeared to be more marked for the exon 19 deletion than for the L858R point mutation. A similar pattern was observed for PFS in the IPASS, in which PFS was significantly longer for gefitinib than for carboplatin-paclitaxel in both the exon 19 deletion and L858R subgroups, with a slightly greater advantage in the exon 19 deletion subgroup.[16] In addition, preplanned analyses of two randomized phase 3 studies of the EGFR TKI afatinib versus chemotherapy (LUX-Lung 3 [N = 345] and LUX-Lung 6 [N = 364]) showed significantly longer OS with afatinib than with chemotherapy in patients with exon 19 deletions, but not in patients with the L858R point mutation.[23] These results suggest that patients with exon 19 deletions may be more responsive to EGFR TKI treatment compared with chemotherapy than are patients with the L858R point mutation. Direct comparisons of the effect of exon 19 deletions and the L858R point mutation on treatment outcomes in patients with advanced NSCLC have yielded different results. Reports from retrospective analyses, phase 2 studies, a database of five studies from the United States and Europe, and a meta-analysis have noted longer PFS and/or OS after treatment with an EGFR TKI in patients with exon 19 deletions than in patients with the L858R point mutation.[10,24–27] However, other studies, including the phase 3 studies IPASS, WJTOG3405, and NEJ002, found no significant difference in PFS after gefitinib treatment in patients with exon 19 deletions compared with patients having the L858R point mutation.[16,18,21] The individual effects of exon 19 deletions and the L858R point mutation on treatment outcomes with EGFR TKIs remain to be fully elucidated and may depend on the individual EGFR TKI.[23] Nevertheless, the current study provides further evidence for improved outcomes in patients with exon 19 deletions and highlights the need for prospective research in this field.

Second-Line PDT

As expected, significantly more patients in the PC/G group received an EGFR TKI as second-line PDT and significantly more patients in the G group received chemotherapy. Analysis of OS by PDT in the G group revealed longer OS in patients who received second-line treatment with a pemetrexed platinum doublet than in those who received a nonpemetrexed platinum doublet. As patients were not randomly assigned to the type of second-line chemotherapy, definitive conclusions cannot be drawn from this small, retrospective post hoc analysis and the p value should be interpreted with caution. Nevertheless, these results are in keeping with pemetrexed being a recommended treatment for chemotherapy-naive and pretreated patients with nonsquamous NSCLC,[3–5] and they suggest that pemetrexed-based chemotherapy may be superior to nonpemetrexed-based chemotherapy after progression during administration of an EGFR TKI. In addition, recent results from a randomized phase 3 study (Iressa Mutation Positive Multicentre Treatment Beyond Progression Study) have shown that the pemetrexed-cisplatin doublet is active in patients with advanced NSCLC with *EGFR* mutations who have progressed while receiving first-line gefitinib treatment and that continuation of gefitinib in combination with pemetrexed-cisplatin does not improve outcomes in patients with acquired resistance to gefitinib.[28]

Safety

The updated safety results reported from this analysis are similar to those reported at the time of the primary analysis[11] and are consistent with the known safety profiles of pemetrexed, cisplatin, and gefitinib.[29–31]

Study Limitations

The requirement that patients have unknown tumor *EGFR* mutation status at study entry was intended to reflect clinical practice, in which *EGFR* mutation status is not always known when treatment decisions are made. *EGFR* mutation testing after study entry allowed assessment of OS by *EGFR* mutation status. However, a limitation of the study was that tumor *EGFR* mutation status could be determined for only a small proportion of patients, which should be kept in mind when interpreting the OS results for these subgroups, as should the retrospective nature of these analyses. The challenges of sample acquisition and *EGFR* mutation testing further highlight the importance of selecting the appropriate treatment strategy in patients with unknown tumor *EGFR* mutation status. On the basis of the HR for PFS favoring PC/G in the overall study population[11] and the wild-type *EGFR* subgroup not benefitting from treatment with G,[11] we suggest that chemotherapy is the preferred treatment option in patients with unknown tumor *EGFR* mutation status, including those patients with clinical characteristics associated with response to an EGFR TKI. However, the patient's *EGFR* mutation status is of the utmost importance in making this treatment decision and should be determined whenever possible. In considering the limitations of this study, it should also be noted that the study was not powered to evaluate the difference in OS between the two treatment regimens.

Conclusions

In this population of patients with advanced NSCLC who were clinically selected to respond to gefitinib, OS was not prolonged by PC/G compared with by G. This fact is consistent with the primary analysis finding that there was no significant difference in PFS between the two treatment regimens in this patient population.[11] Notably, OS appeared to be longer with PC/G in patients with *EGFR* wild-type tumors and with G in patients with *EGFR*-mutated tumors, especially in those patients with exon 19 deletions. In patients who progressed while receiving first-line gefitinib treatment, OS appeared to be longer in patients who received a pemetrexed platinum doublet as second-line treatment than in those who received a non-pemetrexed platinum doublet. In conjunction with the PFS results from the primary analysis, the final OS data from this randomized phase 3 study further demonstrate the importance of determining *EGFR* mutation status to guide selection of the most appropriate first-line treatment for patients with advanced NSCLC.

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