Final Overall Survival Results from a Phase III, Randomized, Placebo-Controlled, Parallel-Group Study of Gefitinib Versus Placebo as Maintenance Therapy in Patients with Locally Advanced or Metastatic Non–Small-Cell Lung Cancer (INFORM; C-TONG 0804)

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Background: The results of the Iressa in NSCLC for maintenance study (NCT00770588; C-TONG 0804), which compared gefitinib and placebo as maintenance therapy in patients with advanced non–small-cell lung cancer without disease progression after first-line chemotherapy, were published previously. The objective of this report is to provide a mature analysis of overall survival (OS) for Iressa in NSCLC for maintenance study in intention to treat (ITT) population and in subgroups according to epidermal growth factor receptor (EGFR) mutation status.

Patients and Methods: A total of 296 patients were randomly assigned. EGFR mutations were detected using an amplification mutation refractory system. Seventy-nine patients were assessable for EGFR mutations. OS was analyzed by a Cox proportional hazards model adjusted for the same covariates in ITT population and subgroups according to EGFR mutation status.

Results: OS was similar for gefitinib and placebo arm with no significant difference between treatments in ITT population (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.68–1.14; $p = 0.335$) and in subgroups with wild type EGFR (HR, 1.27; 95% CI, 0.7–2.3; $p = 0.431$) or unknown EGFR mutations (HR, 0.92; 95% CI, 0.68, 1.25; $p = 0.603$). In the EGFR mutation–positive subgroup, the gefitinib arm showed a higher OS than the placebo arm (HR, 0.39; 95% CI, 0.15, 0.97; $p = 0.036$).

Conclusion: EGFR mutation was the strongest predictive biomarker for OS benefit of gefitinib as maintenance treatment. The analyses of OS showed that patients achieve a clear and significant survival benefit if they receive EGFR tyrosine kinase inhibitors as maintenance treatment in EGFR mutation–positive patients.

Key Words: Gefitinib, Maintenance, NSCLC, INFORM, OS.

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For patients with advanced non–small-cell lung cancer (NSCLC), platinum-based combination first-line chemotherapy has been shown to prolong survival compared with best supportive care. However, the prognosis of these patients remains poor with a median survival time of 10 to 12 months.[1,2] Maintenance therapy is started immediately after first-line (induction) therapy and aims to prolong tumor response or stable disease (SD), thus improving progression-free survival (PFS) and overall survival (OS), which is usually administered until disease progression or unacceptable

toxicity. Previous phase III trials have reported the efficacy of maintenance therapy with minimal side effects for locally advanced or metastatic (stages IIIB–IV) NSCLC.[3–6] Switch maintenance, compared with continuation maintenance, means using a different drug for maintenance therapy instead of using the one that is used for induction. Some studies have showed that switch maintenance could improve PFS and OS.[7–10]

The epidermal growth factor receptor (EGFR) is typical for an important signaling pathway that regulates tumorigenesis and cell survival and is frequently overexpressed in the development and progression of NSCLC.[11,12] Previous studies have demonstrated the effectiveness of EGFR tyrosine kinase inhibitors (TKIs) as maintenance therapy.[5,10,13–15] Recent data showed that EGFR mutations are a predictor of response to EGFR TKIs in patients.[16–19] Patients with EGFR mutations have a significantly longer survival than those with wild-type EGFR when treated with EGFR TKIs.[20,21]

The Iressa in NSCLC FOR Maintenance study (INFORM; NCT00770588; C-TONG 0804) was a double-blind, randomized, placebo-controlled, parallel-group study of gefitinib (250 mg/day) as maintenance therapy in patients from China with locally advanced/metastatic NSCLC who had achieved disease control after first-line platinum-based doublet chemotherapy. As previously reported,[22] in INFORM trial, the primary end point of PFS was met and showed significantly longer PFS with gefitinib versus placebo overall (intention to treat [ITT]; HR, 0.42; 95% confidence interval [CI], 0.33–0.55; $p < 0.0001$; median PFS 4.8 vs. 2.6 months). In the subgroup of patients with EGFR mutation–positive tumor, PFS was significantly longer for gefitinib versus placebo (HR, 0.17; 95% CI, 0.07–0.42; $p = 0.0063$; median PFS 16.6 vs. 2.8 months). Secondary end points, safety analysis, and early survival data were presented in 2012.[22] Here, we report the final results of the survival analyses in the ITT population and in subgroups stratified by EGFR mutation from the INFORM study, on the

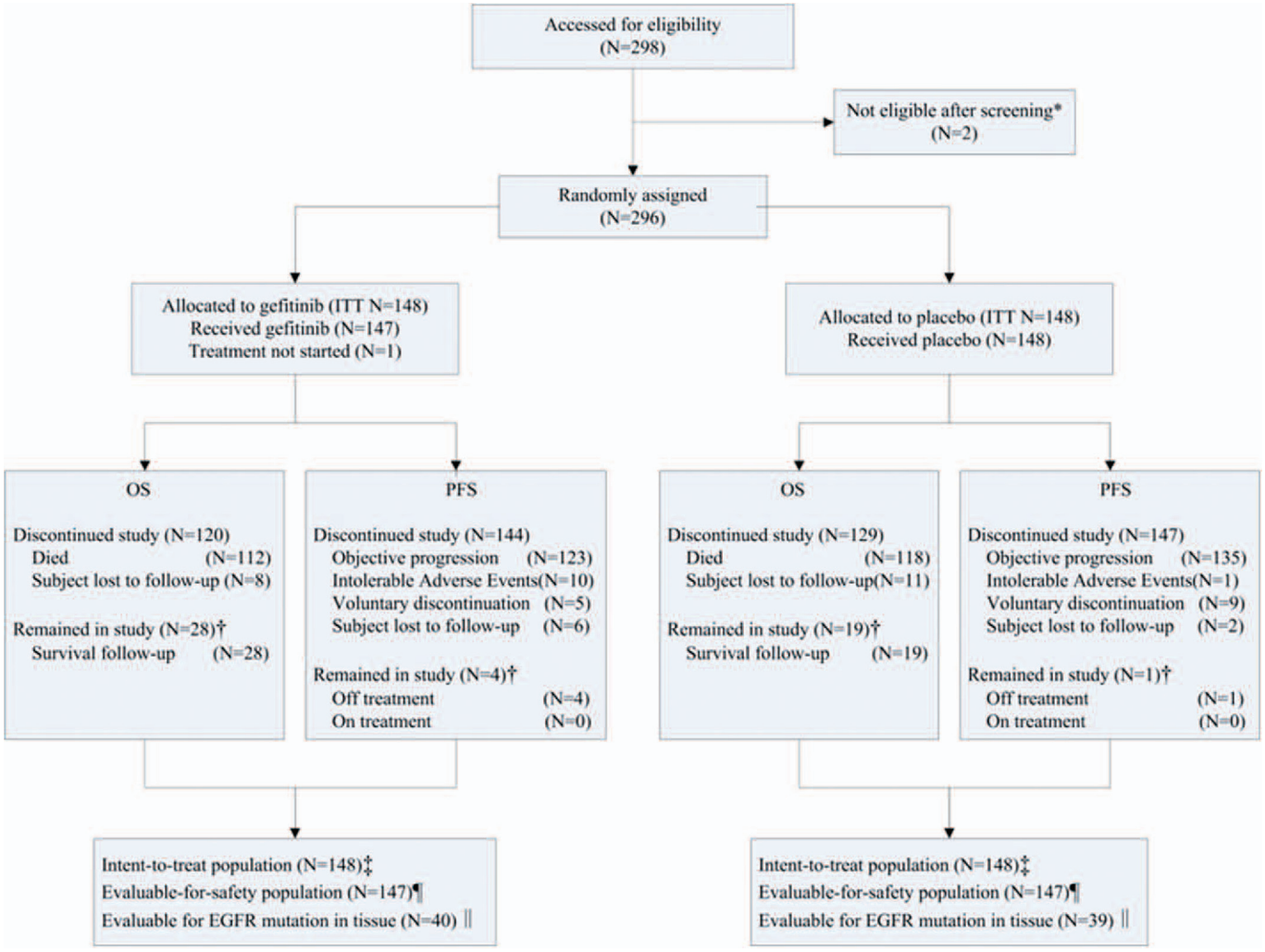

FIGURE 1. CONSORT diagram. †Cut off dates: June 17, 2014, for overall survival (OS) and progression-free survival. ‡All patients who were randomly assigned to a study group were included in the intent-to-treat analysis. ¶All patients who received at least one dose of study treatment were included in the safety analysis. ‖All patients in the intent-to-treat population with an evaluable tumor sample.

basis of 78% maturity and a follow-up period of up to 20.23 months (median 17.83 months).

PATIENTS AND METHODS

Study Design and Treatment

Chinese patients with locally advanced/metastatic NSCLC who had achieved disease control after first-line platinum-based doublet chemotherapy were eligible. Full details of the INFORM have been published previously.[22] Patients were randomized 1:1 to gefitinib (250 mg/day orally) or placebo (orally) administered 3–6 weeks postchemotherapy. Randomization was performed using dynamic balancing[23] with respect to histology (adenocarcinoma [including bronchioalveolar carcinoma] vs. nonadenocarcinoma) and smoking history (never-smoker vs. ever-smoker; where never-smoker was defined as <100 cigarettes/lifetime). Treatment continued until objective disease progression, intolerable toxicity, dose delay/interruption for more than 14 days, withdrawal of consent, or serious noncompliance with study protocol. The primary end point of INFORM was superiority of gefitinib relative to placebo in terms of PFS. Objective response rate (ORR) and OS were secondary end points. Evaluation of tumor EGFR mutation status and efficacy of gefitinib versus placebo was a preplanned exploratory objective.

All patients provided written, informed consent, with separate consent obtained for optional provision of tumor material for biomarker analyses. Study approval was obtained from independent ethics committees at each institution. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice, applicable regulatory requirements, and AstraZeneca's policy on bioethics.

Assessments

OS was assessed from the date of randomization to death from any cause. In a supplementary analysis, OS was assessed from the date of induction chemotherapy to death from any cause. The provision of tumor samples (cytology samples were not permitted) for exploratory biomarker analysis was not mandated. Tumor EGFR mutation status was determined by analyzing DNA extracted from formalin-fixed and paraffin-embedded archival tumor tissue at the AstraZeneca Innovation Centre China, Shanghai laboratory, using validated methods

TABLE 1. Demography and Baseline Characteristics in Intention to Treat Population and Subgroups Defined by *EGFR* Mutation Status

	ITT		EGFR Positive 19(+) 21(+)				EGFR Negative		EGFR Unknown	
Category	**Gefitinib (*n* = 148), *n* (%)**	**Placebo (*n* = 148), *n* (%)**	**Gefitinib (*n* = 10), *n* (%)**	**Placebo (*n* = 6), *n* (%)**	**Gefitinib (*n* = 5), *n* (%)**	**Placebo (*n* = 8), *n* (%)**	**Gefitinib (*n* = 25), *n* (%)**	**Placebo (*n* = 24), *n* (%)**	**Gefitinib (*n* = 108), *n* (%)**	**Placebo (*n* = 109), *n* (%)**
Median age (range)	55 (31–79)	55 (20–75)	43 (32–59)	51 (40–64)	53 (46–65)	52 (33–75)	55 (31–72)	51 (35–62)	55 (37–79)	55 (20–74)
Gender										
Male	83 (56)	92 (62)	4 (40)	3 (50)	1 (20)	6 (75)	17 (68)	14 (58)	61 (56)	67 (61)
Female	65 (44)	56 (38)	6 (60)	3 (50)	4 (80)	2 (25)	8 (32)	10 (42)	47 (44)	42 (39)
Histology type										
Adenocarcinoma	105 (71)	104 (70)	10 (100)	4 (67)	3 (60)	7 (88)	16 (64)	15 (63)	77 (71)	80 (74)
Squamous	27 (18)	30 (20)	0 (0)	1 (17)	1 (20)	1 (13)	7 (28)	7 (29)	19 (18)	21 (19)
Others	16 (11)	14 (10)	0 (0)	1 (17)	1 (20)	0 (0)	2 (8)	2 (8)	12 (11)	8 (7)
Disease stage										
IIIB	42 (39)	32 (30)	2 (20)	0 (0)	0(0)	1 (13)	6 (24)	7 (29)	34 (31)	24 (22)
IV	106 (61)	116 (70)	8 (80)	6(100)	5(100)	7 (88)	19 (76)	17 (71)	74 (69)	85 (78)
WHO PS										
0	69 (47)	72 (49)	6 (60)	2 (33)	3 (60)	4 (50)	11 (44)	12 (50)	49 (45)	54 (50)
1	76 (51)	72 (49)	3 (30)	4 (67)	2 (40)	4 (50)	14 (56)	11 (46)	57 (53)	52 (47)
2	3 (2)	4 (3)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	2 (2)	3 (3)
Smoking history										
Nonsmoker	79 (53)	81 (55)	7 (70)	2 (33)	4 (80)	5 (63)	10 (40)	11 (46)	58 (54)	63 (58)
Ex-smoker	57 (39)	55 (37)	3 (30)	4 (67)	0 (0)	2 (25)	13 (52)	11 (46)	41 (38)	37 (34)
Current smoker	12 (8)	12 (8)	0 (0)	0 (0)	1 (20)	1 (13)	2 (8)	2 (8)	9 (8)	9 (8)
Type of first chemotherapy										
Taxane	60 (41)	66 (45)	7 (70)	3 (50)	4 (80)	5 (63)	13 (52)	10 (42)	36 (33)	48 (44)
Nontaxane	88 (59)	82 (55)	3 (30)	3 (50)	1 (20)	3 (38)	12 (48)	14 (58)	72 (67)	61 (56)
Response to first chemotherapy										
PR or CR	58 (39)	51 (34)	1 (10)	2 (33)	2 (40)	4 (50)	11 (44)	10 (42)	44 (41)	35 (32)
SD	90 (61)	97 (66)	9 (90)	4 (67)	3 (60)	4 (50)	14 (56)	14 (58)	64 (59)	74 (68)

EGFR, epidermal growth factor receptor; ITT, intent to treat; WHO PS, World Health Organization performance status; PR, partial response; CR, complete response; SD, stable disease.

previously published by Fukuoka et al.[24] Briefly, samples underwent central, histopathologic review; only those deemed suitable for downstream biomarker analysis were used for further analysis (based on quality, sample source, and tumor content). EGFR mutations were detected using an amplification mutation refractory system-based EGFR mutation detection kit (DxS, Manchester, United Kingdom), with modified cutoff values and conditions.[24] Patients were considered EGFR mutation–positive if at least one of 29 EGFR mutations was detected[24] (see Supplemental Table, Supplemental Digital Content 1, http://links.lww.com/JTO/A766).

Statistical Analysis

In the ITT population (all randomized patients) and subgroups according to EGFR mutation status, the primary analysis compared OS with gefitinib versus placebo arm using a Cox proportional hazards model adjusted for the same covariates as for the primary PFS analysis (histology, adenocarcinoma vs. nonadenocarcinoma, smoking history, never-smokers vs. smokers, tumor *EGFR* mutation status, positive vs. negative vs. unknown, and previous response to chemotherapy, complete response/partial response vs. SD). The hazard ratio (HR; gefitinib:placebo) was estimated with 95% CIs and *p* value. Final analysis of OS was planned when 230 deaths (78%) had occurred in the ITT population and when the same level of maturity was reached for PFS.

RESULTS

Patients

From September 26, 2008 to August 10, 2009, 296 patients from 27 centers across China were randomized to gefitinib or placebo arm (ITT; *n* = 148 both arms). Patient disposition is presented in Figure 1. For the ITT population, demographics and baseline characteristics are presented in Table 1. Poststudy treatments by study arms in the overall population and in different EGFR mutation status subgroups are listed in Table 2.

OS (ITT Population)

The median duration of follow up for OS was 17.83 months (95% CI, 15.43–20.23). At the time of data cutoff for OS (June 17, 2014), 230 patients (78%) had died (Fig. 1). In the overall population, OS was similar for gefitinib and placebo with no significant difference between the two arms (112 and 118 events, respectively; HR, 0.88; 95% CI, 0.68–1.14; $p = 0.335$; median OS for gefitinib, 18.97 months vs. 16.00 months for placebo; Fig. 2*A*). A consistent effect of maintenance treatment with gefitinib was seen across all clinical subgroups, with the exception of EGFR mutation–positive subgroups (Fig. 3).

Subgroup Analyses

Of the 296 patients enrolled, 102 patients (34.5%) provided tissue samples for biomarker analyses, of which 23 were unsuitable for analysis due to insufficient quantity/quality as determined after pathologic review. A total of 79 (26.7%) samples were assessable for EGFR mutations, with 30 patients (38%) presenting with EGFR mutation–positive tumors. EGFR mutations detected in tumor tissue samples are summarized in Table (Supplemental Digital Content 1, http://links.lww.com/JTO/A766). For patients in subgroups stratified by EGFR mutation status, demographics and baseline characteristics were generally comparable to the ITT population (Table 1) and were also balanced between the treatment arms.

In the subgroup positive for EGFR mutation, a higher OS was observed in patients treated with gefitinib than that in the placebo arm (HR, 0.39; 95% CI, 0.15, 0.97; $p = 0.036$; median OS, 46.87 vs. 20.97 months; Fig. 2*B*). By contrast,

TABLE 2. Summary of Poststudy Treatments by Study Arms in the Overall Population and in EGFR Mutation Status Subgroups (ITT Population; Data from OS Data Cutoff)

	ITT Population		EGFR Mutation Positive		EGFR Mutation Negative		EGFR Mutation Unknown	
Treatment	Gefitinib, *n* (%)	Placebo, *n* (%)	Gefitinib, *n* (%)	Placebo, *n* (%)	Gefitinib, *n* (%)	Placebo, *n* (%)	Gefitinib, *n* (%)	Placebo, *n* (%)
Still in study	4 (3)	1 (1)	1 (7)	0 (0)	0 (0)	0 (0)	3 (3)	1 (1)
None	38 (26)	23 (16)	3 (20)	2 (13)	5 (20)	5 (21)	30 (28)	16 (15)
Chemotherapy only	65 (44)	54 (36)	4 (27)	4 (27)	14 (56)	7 (29)	47 (44)	43 (39)
Taxane	39	34	1	3	10	6	28	25
Nontaxane	21	17	3	1	4	1	14	15
Not-clear	5	3	0	0	0	0	5	3
EGFR TKIs involved	15 (10)	53 (36)	3 (20)	8 (53)	3 (12)	8 (33)	9 (8)	37 (34)
Gefitinib	8	30	0	3	1	3	7	24
Erlotinib	6	18	3	3	2	5	1	10
Other EGFR TKIs	1	5	0	2	0	0	1	3
Radiotherapy only	5 (3)	5 (3)	0 (0)	0 (0)	2 (8)	1 (4)	3 (3)	4 (4)
Lost to follow-up	21 (14)	12 (8)	4 (27)	1 (7)	1 (4)	3 (13)	16 (15)	8 (7)
Total	148	148	15	15	25	24	108	109

A patient may appear in more than one poststudy treatment group. Patients may have received the same second-line and third-line therapies.

"None" is defined as patients who did not receive any form of cancer treatment after discontinuation of randomly assigned treatment. Radiotherapy, surgery, medical procedures, and other treatments were excluded.

ITT, intent to treat; OS, overall survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

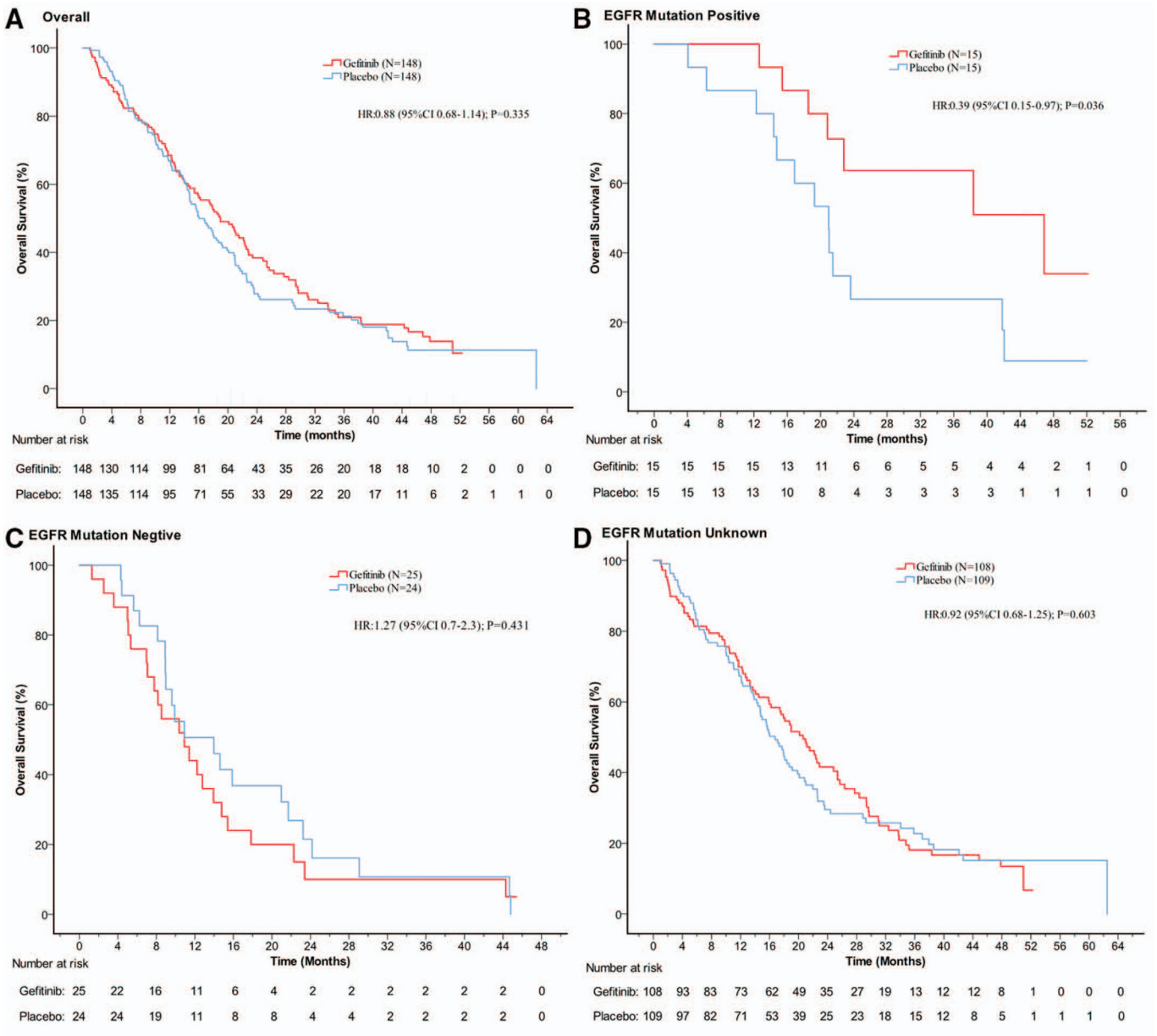

FIGURE 2 Kaplan–Meier curves for overall survival in the overall population and by epidermal growth factor receptor (EGFR) mutation status (intent-to-treat population). Hazard ratio less than 1 implies a lower risk of death for patients treated with gefitinib. *A*, Overall population. *B*, Patients with EGFR mutation–positive tumors. *C*, Patients with EGFR mutation-negative tumors. *D*, Patients with EGFR mutation status unknown tumors.

there was no significant difference in OS for gefitinib versus placebo in patients negative for EGFR mutations (HR, 1.27; 95% CI, 0.7–2.3; $p = 0.431$; median OS, 10.9 vs. 14.0 months; Fig. 2*C*). In the subgroup with unknown EGFR mutation, OS was numerically but not statistically longer with gefitinib versus placebo (HR, 0.92; 95% CI, 0.68, 1.25; $p = 0.603$; median OS, 20.6 vs. 16.8 months; Fig. 2*D*).

Exploratory Analysis: Impact of Subsequent EGFR TKIs Treatments on OS

Treatments after discontinuation of trial in the ITT population are presented in Table 2. We observed no significant differences between the two treatment arms in patients treated with chemotherapy poststudy. However, in the placebo arm, a higher rate of patients (36%) received EGFR TKIs treatment after discontinuation of the study compared with patients in study arm (10%, $p = 0.001$).

To assess the effect of subsequent EGFR TKIs treatment on OS, we divided patients into two groups. Group A included patients who received EGFR TKIs as either maintenance or subsequent treatment, whereas group B included patients who had never received any EGFR TKIs during the treatment process before randomization into the study. We examined demographic factors and rates of subsequent chemotherapy used in these two treatment

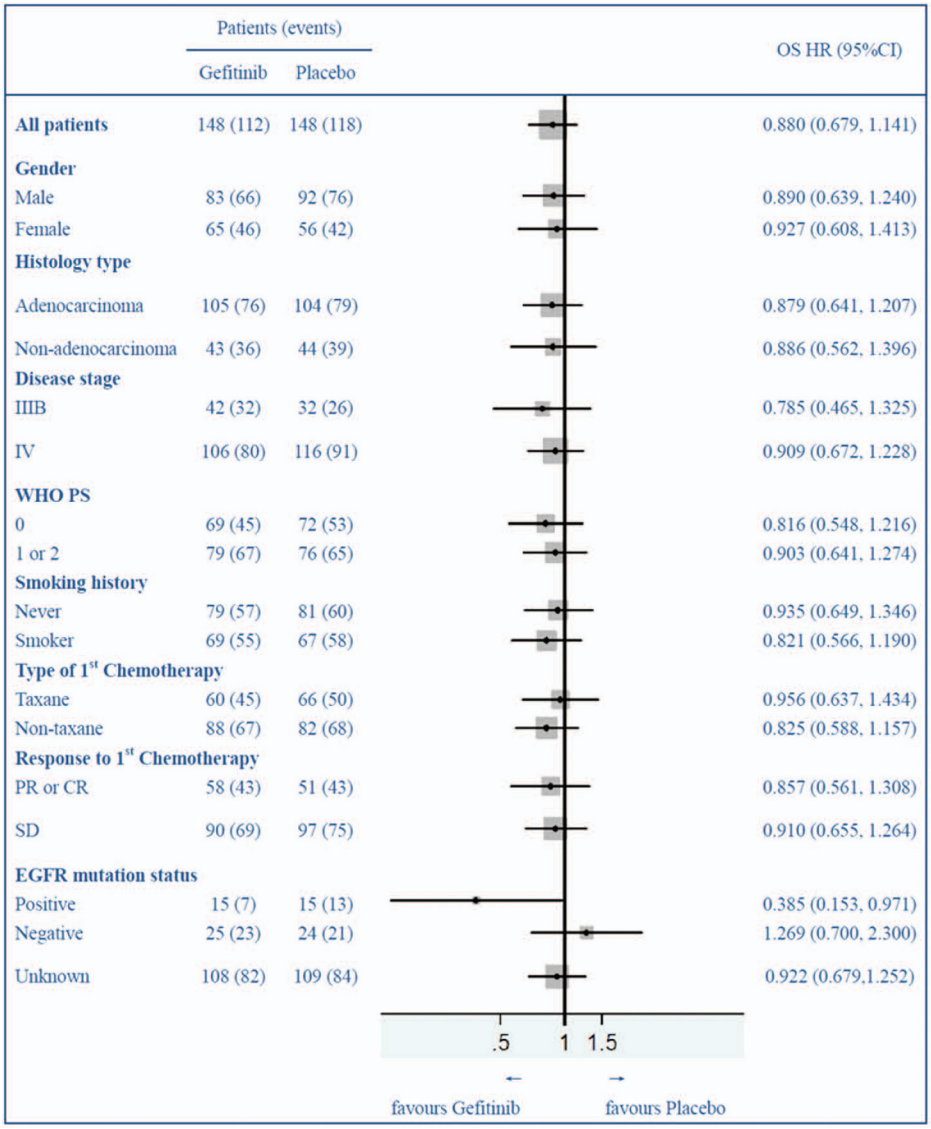

FIGURE 3. Forest plot of overall survival by clinical subgroup and epidermal growth factor receptor mutation status (intent-to-treat population). Hazard ratio less than 1 implies a lower risk of death for patients treated with gefitinib. The size of the point estimate reflects the number of events in the subgroup, with a larger circle indicating more events. Cox analysis with covariates (histology [adenocarcinoma vs. nonadenocarcinoma]; World Health Organization performance status [0, 1, vs. 2]; smoking history [never-smokers vs. smokers]; tumor epidermal growth factor receptor mutation status [positive vs. negative vs. unknown]; type of first-line chemotherapy [taxane vs. nontaxane]; previous response to chemotherapy [complete or partial response vs. stable disease]; sex; and disease stage at screening [IIIb vs. IV]). CR, complete response; PR, partial response; SD, stable disease; OS, overall survival; HR, hazard ratio.

groups. Both treatment groups exhibited similar demographics and rates of subsequent chemotherapy (Table 3). However, we did observe a significantly longer OS for patients in group A than in group B (HR, 0.66; 95% CI, 0.50–0.88; $p = 0.004$; median OS, 19.9 vs. 14.7 months; Fig. 4*A*). Significant difference in OS was also observed in the subgroup of patients who were positive for EGFR mutations (HR, 0.40; 95% CI, 0.16–1.00; median OS, 38.4 vs. 19.3 months; Fig. 4*B*). In the subgroup whose EGFR mutation status is unknown, patients receiving TKIs either as maintenance or as subsequent had a lower risk of death compared with patients who did not receive TKIs since maintenance (HR, 0.68; 95% CI, 0.49–0.88). A similar OS benefit was seen across most of the subgroups, with the exception of male, nonadenocarcinoma, smoker and EGFR mutation–negative subgroups (Fig. 5).

DISCUSSION

INFORM was the first phase III randomized maintenance study to be conducted solely in patients from East Asian with advanced NSCLC. Previous reports showed significantly longer PFS, higher ORR and disease control rate, and better symptomatic control with gefitinib than placebo. However, maintenance gefitinib therapy showed no survival benefit over placebo based on a survival analysis of 59% (176 of 296) of deaths events.[22]

Unfortunately in current report, with a more mature follow-up data, longer PFS was not associated with the difference in OS between the two treatment arms in the ITT population. The final OS analyses of INFORM trial were consistent with previous studies reporting on maintenance treatment.[5,13,14] Gaafar et al.[14] reported a phase III study (EORTC 08021) of similar design to INFORM that found no statistical significance in OS (primary end point) in Caucasians (median follow up of 41 months; HR, 0.83; 95% CI, 0.60–1.15; *p*, 0.2; median survival for gefitinib and placebo, 10.9 vs. 9.4 months, respectively). Furthermore, in a randomized Japanese phase III WJTOG0203 study,[13] OS (primary end point) was not statistically different in patients treated with gefitinib or on placebo

TABLE 3. Demography and Baseline Characteristics in Patients Defined by the Usage of EGFR TKIs since randomization

Characteristics	Patients Treatment from Randomization (%)		
	TKIs Treatment[a]	No TKIs Treatment[b]	*P*
All patients	201	83	
Gender			
Male	118 (59)	48 (58)	*0.892*
Female	83 (41)	35 (42)	
Histology type			
Adenocarcinoma	145 (72)	57 (69)	*0.558*
Nonadenocarcinoma	56 (28)	26 (31)	
Disease stage			
IIIB	52 (26)	18 (22)	*0.457*
IV	149 (74)	65 (78)	
WHO PS			
0	96 (48)	37 (45)	*0.625*
1 or 2	105 (52)	46 (55)	
Smoking history			
Never	106 (53)	48 (58)	*0.433*
Smoker	95 (47)	35 (42)	
Type of first chemotherapy			
Taxane	83 (41)	34 (41)	*0.959*
Nontaxane	118 (59)	49 (59)	
Response to first chemotherapy			
PR or CR	81 (40)	25 (30)	*0.107*
SD	120 (60)	58 (70)	
EGFR mutation status			
Positive	23 (11)	7 (8)	*0.701*
Negative	33 (16)	13 (16)	
Unknown	145 (72)	64 (77)	

[a]TKIs treatment indicates patients received EGFR TKIs as maintenance or subsequent treatment since randomization.

[b]No TKIs treatment indicates patients never received any EGFR TKIs since randomization.

EGFR, epidermal growth factor receptor; WHO PS, World Health Organization performance status; PR, partial response; CR, complete response; SD, stable disease.

(78% maturity, HR, 0.86; 95% CI, 0.72, 1.03; $p = 0.11$; median survival for chemotherapy followed by gefitinib and chemotherapy alone, 13.7 vs. 12.9 months, respectively). The phase III study of IFCT-GFPC 0502[5] also demonstrated that maintenance treatment with erlotinib was not statistically different from the observation group (HR, 0.87; 95% CI, 0.68, 1.13; $p = 0.3043$; median survival for erlotinib and observation, 11.4 vs. 10.8 months, respectively). Clearly, our study results, combined with other similar studies, do not support the routine use of gefitinib for maintenance treatment as standard of care in all advanced NSCLC patients who achieved disease control after treatment with platinum-based chemotherapy.

Previous studies[25–27] have demonstrated that EGFR mutation status is a strong predictor for treatment response. In IPASS[26] and First-SIGNAL[27] studies, molecular analyses suggested that the benefit of gefitinib was limited to patients exhibiting EGFR mutations. In this study, a significant prolongation of PFS in EGFR mutation–positive subgroup of the gefitinib arm was observed, which was associated with a significantly longer OS compared with placebo (HR, 0.39; 95% CI, 0.15, 0.97; $p = 0.036$). Because of the lack of subgroup analyses based on EGFR mutation status from previous gefitinib maintenance studies,[13,14] we could not make direct comparisons in the INFORM IPASS, NEJ002 study. SATURN study[28] had the same design as INFORM, but the recent biomarker analysis of the SATURN study[10] failed to report the OS benefit for patients with EGFR mutation–positive tumors, probably due to the high degree of censoring and the 67% crossover rate to second-line EGFR TKI therapy in the placebo group for this population. In the INFORM study, the subgroup with EGFR mutation–positive tumors had a crossover rate of 53% (8 of 15). Reviewing first-line trials,[19,24,29] which failed to find improved OS for patients with EGFR mutation–positive, the crossover rate in IPASS, NEJ002, and the European Tarceva versus Chemotherapy (EURTAC) study was 64.3%, 95%, and 76%, respectively. In the present study, although the number of tumor samples evaluable for EGFR mutation status was small, it is notable that median OS was 46.87 months in the gefitinib maintenance arm compared with 20.97 months in placebo ($p = 0.036$). Our study indicated that EGFR mutation is an important predictor of OS in patients treated with gefitinib for maintenance compared with placebo, so our data emphasize the importance of selecting patients who could benefit from EGFR TKIs by EGFR genetic testing, especially in an Asian lung cancer population. As we know, the current standard of care is to test EGFR mutation first and to give EGFR TKIs as front line if the result for EGFR mutation testing is positive. However, if mutation testing results are unavailable for whatever reason, the chemotherapy had been employed initially, for patients whose tumors have confirmed EGFR activating mutations and have achieve partial response/SD response from first-line chemotherapy, and EGFR TKIs should be used as maintenance therapy on the basis of this study.

Subsequent treatments that patients received are likely to have confounding effects when evaluating the OS of patients on first line or maintenance treatment. Our previous meta-analysis of East Asian patients[30] showed that advanced NSCLC patients treated with both platinum-based doublet chemotherapy and EGFR-TKIs in any order were superior to chemotherapy alone. In this study, higher incidence of EGFR mutations was observed in the East Asian population compared with patients of other ethnicities; we also observed that more patients in the placebo arm received subsequent therapy (84%) compared with patients in the gefitinib arm (74%) ($p = 0.031$, Table 2). Further analysis showed that although chemotherapy/radiotherapy used in the poststudy setting is similar between the two treatment arms (Table 2), there was a difference in the use of EGFR TKIs, which could affect OS. Therefore, we conducted an exploratory analysis based on whether the patient received EGFR TKIs treatment or not after randomization. We found that patients receiving EGFR TKIs as maintenance or subsequent treatment had a longer OS than patients who never received any EGFR TKIs in the ITT population. Furthermore, most of the clinical

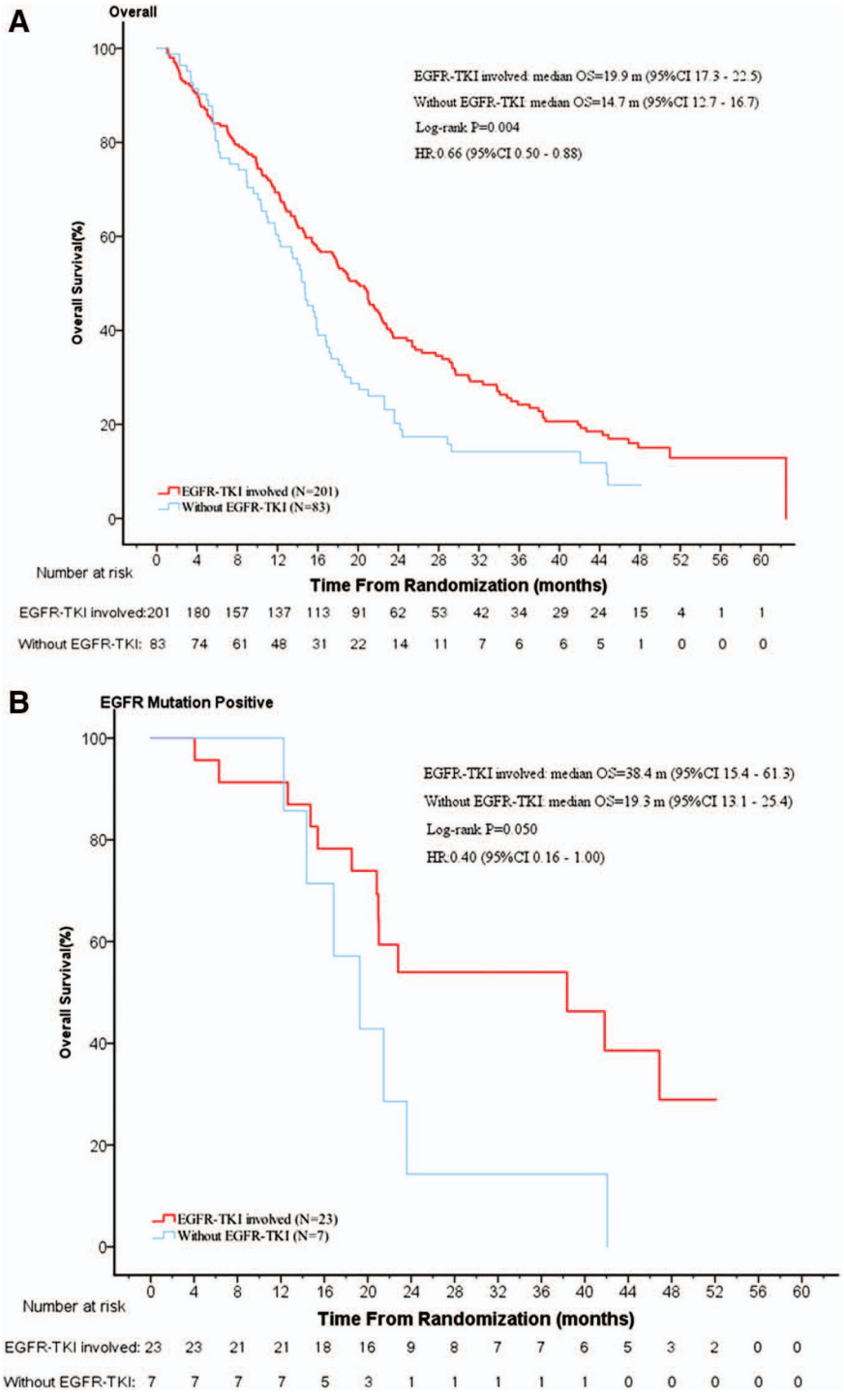

FIGURE 4. Kaplan–Meier curves for overall survival in the overall population and epidermal growth factor receptor (EGFR) mutation subgroup. Hazard ratio less than 1 implies a lower risk of death for patients treated with gefitinib. EGFR-TKI involved means patients received EGFR TKIs as maintenance or subsequent treatment since randomization; without EGFR TKI means patients never received any EGFR TKIs since randomization. *A*, Overall population. *B*, Patients with EGFR mutation–positive tumors.

subgroups, such as female, adenocarcinoma, nonsmoker and EGFR mutation–positive subgroups, but not in EGFR-mutation negative subgroup, also demonstrated a longer OS. Although this exploratory analysis was an unplanned subgroup analysis, our observations of the effects of OS based on subsequent EGFR TKIs treatment are consistent with our previous meta-analysis and OPTIMAL study.[31] In addition, we are aware of the limitations of this exploratory analysis, a small number of patients (23%,16 of 148) in placebo arm did not received any subsequent treatment, some of them may die early and lose their chance to receive EGFRTKIs or chemotherapy, thus the OS results could be affected. Larger phase III trials are needed to evaluate the effects of subsequent treatment on OS for this subpopulation of patients.

In this study, patients in the gefitinib arm demonstrated a numerically longer OS than patients in the placebo

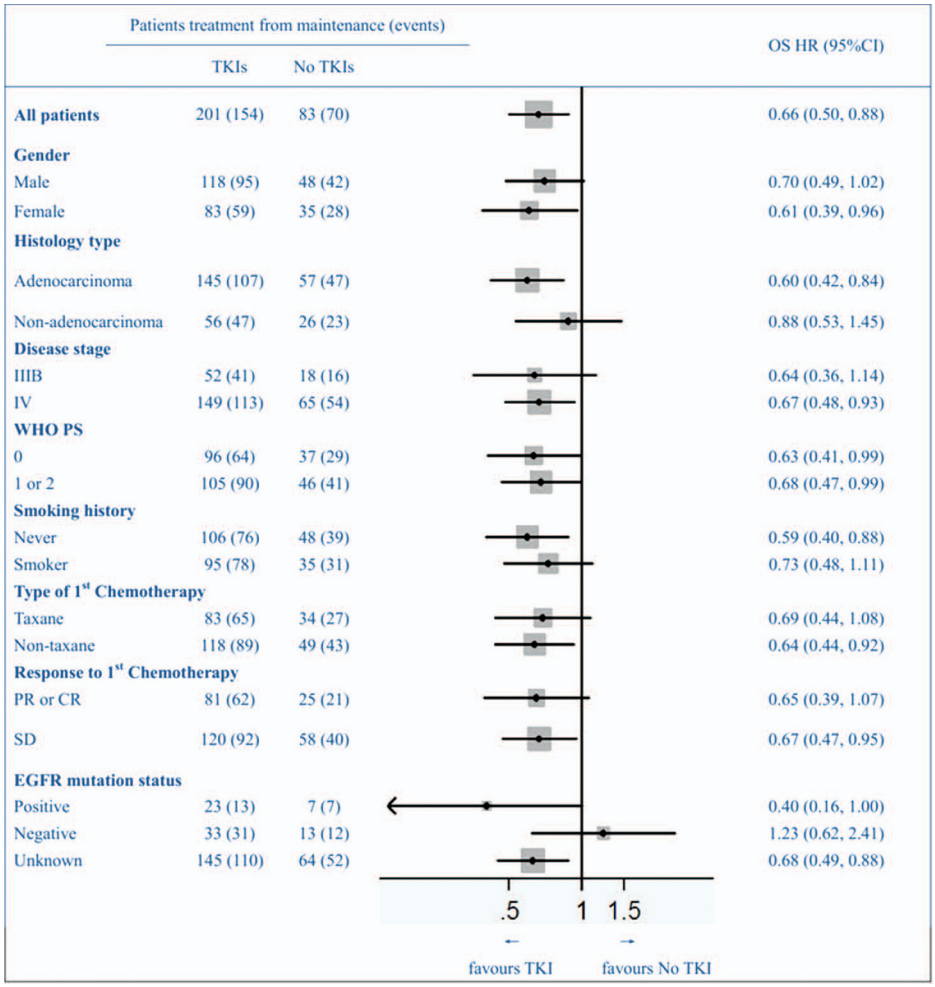

FIGURE 5. Forest plot of overall survival (OS) in two groups by clinical subgroup and epidermal growth factor receptor (EGFR) mutation status (intent-to-treat population). Hazard ratio less than 1 implies a lower risk of death for patients treated with gefitinib. The size of the point estimate reflects the number of events in the subgroup, with a larger circle indicating more events. Cox analysis with covariates (histology [adenocarcinoma vs. nonadenocarcinoma]; World Health Organization performance status [0, 1, vs. 2]; smoking history [never-smokers vs. smokers]; tumor EGFR mutation status [positive vs. negative vs. unknown]; type of first-line chemotherapy [taxane vs. nontaxane]; previous response to chemotherapy [complete or partial response vs. stable disease]; sex; and disease stage at screening [IIIb vs. IV]). CR, complete response; PR, partial response; SD, stable disease; OS, overall survival since randomization; HR, hazard ratio; TKIs, patients received EGFR TKIs as maintenance or subsequent treatment since randomization; no TKIs, patients never received any EGFR TKIs since randomization.

arm (median OS for gefitinib, 18.97 vs. 16.00 months for placebo). Because of the relative low number of patients included in our study significant differences between the two treatment arms were not observed. In the exploratory analysis, of the ITT population randomly assigned to the placebo arm, 36% (53 of 148) of patients received EGFR TKIs as subsequent therapy, which is significantly higher than study arm (10%, 15 of 148; $p = 0.001$) and may be a reason why no difference in OS was observed. In addition, no molecular selection for patient's enrolment in our study can be another explanation for the absence of OS benefit. When we initiated this double-blind, randomized trial, the clinical advantage of large-scale screening for EGFR mutations in patients with NSCLC had not been emphasized in Asian and in the world, we did not select patients by EGFR mutation status, and the collection of tumor material was not mandatory or feasible in all patients, so INFORM has big proportion of patients without tumor samples (73%). But it is worth to know that East-Asian patients have greater frequency of EGFR mutations compared with Caucasia patients,[16,32,33] almost one in three East-Asian patients could have EGFR mutation, and therefore, could benefit from EGFR TKI therapy. Nevertheless, the INFORM study does demonstrate the unprecedented median OS (exceeding 18 months) in gefitinib arm compared with previous switch maintenance studies,[3,5,10,13,14] indicating further exploration into this treatment strategy is warranted, especially in EGFR mutation–positive population.

In summary, the final OS analysis of the INFORM data confirms the PFS finding, which translates into a significant OS benefit for patients with EGFR mutation–positive tumors, but not for patients with EGFR mutation–negative or unknown. EGFR mutation was the strongest predictive biomarker for benefit of gefitinib over placebo on PFS, ORR, and OS. Patients receiving EGFR TKIs as maintenance or subsequent treatment had longer OS than patients who had never received any EGFR TKIs (overall and EGFR mutation–positive subgroups). The positive results from INFOM, together with those from other maintenance therapy studies, demonstrated that gefitinib in the maintenance setting leads to significantly improved outcomes for patients with EGFR-mutated advanced NSCLC.

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REFERENCES

1. Schiller JH, Harrington D, Belani CP, et al.; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
2. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007;18:317–323.
3. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009;374:1432–1440.
4. Brodowicz T, Krzakowski M, Zwitter M, et al.; Central European Cooperative Oncology Group CECOG. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. *Lung Cancer* 2006;52:155–163.
5. Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2012;30:3516–3524.
6. Gridelli C, Maione P, Rossi A, et al. Potential treatment options after first-line chemotherapy for advanced NSCLC: maintenance treatment or early second-line? *Oncologist* 2009;14:137–147.
7. Azzoli CG, Temin S, Aliff T, et al.; American Society of Clinical Oncology. 2011 Focused update of 2009 American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 2011;29:3825–3831.
8. Fidias P, Novello S. Strategies for prolonged therapy in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:5116–5123.
9. Behera M, Owonikoko TK, Chen Z, et al. Single agent maintenance therapy for advanced stage non-small cell lung cancer: a meta-analysis. *Lung Cancer* 2012;77:331–338.
10. Coudert B, Ciuleanu T, Park K, et al.; SATURN Investigators. Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC) according to response to first-line chemotherapy. *Ann Oncol* 2012;23:388–394.
11. Sato M, Shames DS, Gazdar AF, Minna JD. A translational view of the molecular pathogenesis of lung cancer. *J Thorac Oncol* 2007;2:327–343.
12. Tang X, Shigematsu H, Bekele BN, et al. EGFR tyrosine kinase domain mutations are detected in histologically normal respiratory epithelium in lung cancer patients. *Cancer Res* 2005;65:7568–7572.
13. Takeda K, Hida T, Sato T, et al. Randomized phase III trial of platinum-doublet chemotherapy followed by gefitinib compared with continued platinum-doublet chemotherapy in Japanese patients with advanced non-small-cell lung cancer: results of a west Japan thoracic oncology group trial (WJTOG0203). *J Clin Oncol* 2010;28:753–760.
14. Gaafar RM, Surmont VF, Scagliotti GV, et al.; EORTC Lung Cancer Group and the Italian Lung Cancer Project. A double-blind, randomised, placebo-controlled phase III intergroup study of gefitinib in patients with advanced NSCLC, non-progressing after first line platinum-based chemotherapy (EORTC 08021/ILCP 01/03). *Eur J Cancer* 2011;47:2331–2340.
15. Xu JM, Han Y, Li YM, Zhao CH, Wang Y, Paradiso A. Phase II trial of sequential gefitinib after minor response or partial response to chemotherapy in Chinese patients with advanced non-small-cell lung cancer. *BMC Cancer* 2006;6:288.
16. Rosell R, Moran T, Queralt C, et al.; Spanish Lung Cancer Group. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med* 2009;361:958–967.
17. Zhu CQ, da Cunha Santos G, Ding K, et al.; National Cancer Institute of Canada Clinical Trials Group Study BR.21. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol* 2008;26:4268–4275.
18. Mitsudomi T, Morita S, Yatabe Y, et al.; West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010;11:121–128.
19. Maemondo M, Inoue A, Kobayashi K, et al.; North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380–2388.
20. Mitsudomi T, Kosaka T, Endoh H, et al. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. *J Clin Oncol* 2005;23:2513–2520.
21. Han SW, Kim TY, Hwang PG, et al. Predictive and prognostic impact of epidermal growth factor receptor mutation in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol* 2005;23:2493–2501.
22. Zhang L, Ma S, Song X, et al.; INFORM Investigators. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial. *Lancet Oncol* 2012;13:466–475.
23. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975;31:103–115.
24. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol* 2011;29:2866–2874.
25. Jackman DM, Miller VA, Cioffredi LA, et al. Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non-small cell lung cancer patients: results of an online tumor registry of clinical trials. *Clin Cancer Res* 2009;15:5267–5273.
26. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
27. Han JY, Park K, Kim SW, et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol* 2012;30:1122–1128.
28. Cappuzzo F, Ciuleanu T, Stelmakh L, et al.; SATURN Investigators. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010;11:521–529.
29. Rosell R, Wannesson L. A genetic snapshot of small cell lung cancer. *Cancer Discov* 2012;2:769–771.
30. Zhang JW, Zhao YY, Guo Y, et al. The impact of both platinum-based chemotherapy and EGFR-TKIs on overall survival of patients with advanced non-small cell lung cancer. *Chin J Cancer* 2014;33:105–114.
31. Zhou C, Wu YL, Liu X, et al. Overall survival (OS) results from OPTIMAL (CTONG0802), a phase III trial of erlotinib (E) versus carboplatin plus gemcitabine (GC) as first-line treatment for Chinese patients with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC). *ASCO Meeting Abstracts* 2012;30:7520.
32. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* 2005;97:339–346.
33. Wu YL, Zhong WZ, Li LY, et al. Epidermal growth factor receptor mutations and their correlation with gefitinib therapy in patients with non-small cell lung cancer: a meta-analysis based on updated individual patient data from six medical centers in mainland China. *J Thorac Oncol* 2007;2:430–439.