clinical trial updates

Updated Analysis of NEJ009: Gefitinib-Alone Versus Gefitinib Plus Chemotherapy for Non–Small-Cell Lung Cancer With Mutated *EGFR*

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abstract

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned coprimary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

In a randomized, open-label, phase III NEJ009 study, gefitinib plus chemotherapy significantly improved progression-free survival (PFS) and overall survival (OS) compared with gefitinib-alone in patients with untreated non–small-cell lung cancer harboring mutations in epidermal growth factor receptor. Herein, we report the updated survival outcome and long-term tolerability. Patients were randomly assigned to gefitinib (gefitinib 250 mg orally, once daily) and gefitinib combined with carboplatin plus pemetrexed (GCP in a 3-week cycle for six cycles followed by concurrent gefitinib and pemetrexed maintenance) groups. At the data cutoff (May 22, 2020), GCP demonstrated significantly better PFS2 (hazard ratio, 0.77; 95% CI, 0.62 to 0.97; $P = .027$) than gefitinib. However, the updated median OS was 38.5 months (95% CI, 31.1 to 47.1) and 49.0 months (95% CI, 41.8 to 56.7) in the gefitinib and GCP groups, respectively (hazard ratio, 0.82; 95% CI, 0.64 to 1.06; $P = .127$). The OS in both groups was similar for the overall patient population. No severe adverse events occurred since the first report. This updated analysis revealed that the GCP regimen improved PFS and PFS2 with an acceptable safety profile compared with gefitinib-alone. GCP is more efficient than gefitinib monotherapy as a first-line treatment for non–small-cell lung cancer with epidermal growth factor receptor mutations.

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INTRODUCTION

NEJ009 (UMIN000006340) was a multicenter, randomized, open-label, phase III study of gefitinib combined with carboplatin plus pemetrexed (GCP) versus gefitinib-alone for patients with non–small-cell lung cancer (NSCLC) harboring epidermal growth factor receptor (*EGFR*) mutations.[1] Herein, we updated the data for progression-free survival (PFS)2, overall survival (OS), and safety examined over a longer follow-up period and also assessed the impact of subsequent therapy on OS among patients with *EGFR*-mutated NSCLC.

PATIENTS AND METHODS

The complete details of the NEJ009 study have been published previously.[1] The primary end points included PFS, PFS2, and OS, which were analyzed using a preplanned hierarchical sequential testing method. In this study, preplanned PFS2 was defined as the period from random assignment until both platinum-based chemotherapy and gefitinib were ineffective, that is, not a true comparison of PFS2 in both groups (Appendix Fig A1A, online only). However, as reported previously, preplanned PFS2 was inappropriate because of the influence of the beyond-progressive disease (PD) treatment period that was included only in the gefitinib group.[1] Thus, we corrected the definition of PFS2 (corrected PFS2) in the gefitinib group to omit the beyond-PD period—duration since random assignment to PD after second-line therapy or death (Appendix Fig A1B). Notably, the corrected PFS2 was a comparison of PFS1 (GCP) and PFS2 (gefitinib). Moreover, we conducted an additional analysis by comparing the two groups for PFS2 with the same definition; events were the actual time for the second PD in both groups (Appendix Fig A1C). Survival and extended follow-up safety data were re-evaluated at the data cutoff of May 22, 2020.

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

The phase III NEJ009 study conducted in Japan showed benefits for combinatorial epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor and platinum-doublet chemotherapy with an acceptable safety profile for patients with non–small-cell lung cancer harboring *EGFR* mutations. We report updated survival outcomes and long-term tolerability.

Knowledge Generated

Gefitinib combined with carboplatin plus pemetrexed did not improve overall survival although progression-free survival and progression-free survival 2 showed significant improvements as compared with gefitinib-alone. No severe adverse events, including interstitial lung disease, occurred since the first report.

Relevance

A new treatment strategy, gefitinib combined with carboplatin plus pemetrexed regimen, is an effective treatment option for patients with untreated advanced non–small-cell lung cancer harboring *EGFR* mutations.

In this updated analysis, the survival differences in the mean expected time to death were calculated as the restricted mean survival time (RMST) up to 5 and 7 years for a complementary to the log-rank test for OS.[2,3] The RMST between the GCP and gefitinib groups represents the average gain in survival time within a time window from 0 to a specific threshold time point; the time was based on the areas under the survival curves for each group.

RESULTS

Patients and Treatment

NEJ009 included 345 randomly assigned patients (gefitinib, n = 173; GCP, n = 172) from 47 institutions in Japan (Appendix Fig A2, online only). The median follow-up duration, which was defined as a median duration from patients' study enrollment dates to the cutoff date, was 84 months. Patient demographics and baseline clinical characteristics were generally well balanced between the groups (Table 1).

Patients in both groups received one or more subsequent chemotherapies after the protocol therapy. The regimens administered after the protocol treatment are summarized in Appendix Table A1 (online only). As osimertinib has been approved for treating patients with metastatic *EGFR* T790M mutation–positive NSCLC, 40 patients (23.3%) in the gefitinib group and 37 patients (21.8%) in the GCP group received osimertinib in any treatment line. In the gefitinib group, 46 patients (26.7%) did not receive platinum-based chemotherapy in any treatment line.

Updated PFS2

In the 341 evaluated patients, the updated median PFS2 (corrected PFS2) was 18.0 months (95% CI, 16.3 to 20.7) and 20.9 months (95% CI, 18.0 to 24.0) in the gefitinib and GCP groups, respectively (hazard ratio [HR], 0.77; 95% CI, 0.62 to 0.97; $P = .027$; Fig 1A). In addition, we performed an analysis to compare PFS in the two groups with the same definition (events are true for the second PD in both groups) as

TABLE 1. Patient Demographic and Disease Characteristics at Baseline

Characteristic	Gefitinib (n = 172)	GCP (n = 170)
Sex, No. (%)		
Male	64 (37.2)	56 (32.9)
Female	108 (62.8)	114 (67.1)
Age, years		
Mean (range)	64 (37-75)	65 (34-75)
Smoking status, No. (%)		
Never	97 (56.4)	97 (56.5)
Previous/current	75 (43.6)	73 (42.9)
ECOG PS, No. (%)		
0	107 (62.2)	98 (57.6)
1	65 (37.8)	72 (42.4)
Histology, No. (%)		
Adenocarcinoma	170 (98.8)	168 (98.8)
Others	2 (1.2)	2 (1.2)
Clinical stage, No. (%)		
IIIA	1 (0.6)	0 (0.0)
IIIB	4 (2.3)	6 (3.5)
IV	137 (79.7)	139 (81.8)
Postoperative recurrence	30 (17.4)	25 (14.7)
Brain metastasis, No. (%)		
Yes	38 (22.1)	50 (29.4)
No	134 (77.9)	120 (70.6)
Liver metastasis, No. (%)		
Yes	12 (7.0)	17 (10.0)
No	160 (93.0)	153 (90.0)
Type of *EGFR* mutation, No. (%)		
Exon 19 deletion	95 (55.2)	93 (54.7)
L858R	67 (39.0)	69 (40.6)
Others	10 (5.8)	8 (4.7)

Abbreviations: ECOG PS; Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; GCP, gefitinib combined with carboplatin plus pemetrexed.

that used for reference. The updated median PFS2 with the same definition was 20.7 months (95% CI, 17.9 to 24.6) in the gefitinib group and 32.5 months (95% CI, 29.0 to 36.6) in the GCP group (HR, 0.58; 95% CI, 0.46 to 0.73; $P < .001$; Fig 1B).

Updated OS

At data cutoff, 243 death events were recorded. The death event rate increased from 57% (195 events) in the previous report to 71% (243 events) in the current study. However, there was no significant difference in OS between the groups. The mean survival time, 2-year survival rate, and 5-year survival rate were 38.5 months, 69%, and 34% for the gefitinib group and 49.0 months, 77.1%, and 39% for the GCP group, respectively (HR, 0.822; 95% CI, 0.639 to 1.058; $P = .127$; Fig 1C). In the subgroup analysis, the OS benefit for GCP and gefitinib was comparable in the overall patient population, including the type of *EGFR* activation mutation and metastatic sites (Fig 2). However, larger numerical between-group differences in the HRs for OS were observed between male and female patients.

The RMST was calculated to further compare survival between the groups (Appendix Table A2, online only). The 5-year RMST for the GCP group was longer than those for the gefitinib group (43.6 *v* 38.6 months, $P = .017$). Over a 5-year period, RMST analysis demonstrated that GCP was indeed associated with a 5-month OS benefit. In addition, this tendency was still detectable when the 7-year period was selected. The 7-year RMST for the GCP group was longer than those for the gefitinib group (51.6 *v* 45.3 months, $P = .037$). RMST analysis indicated a

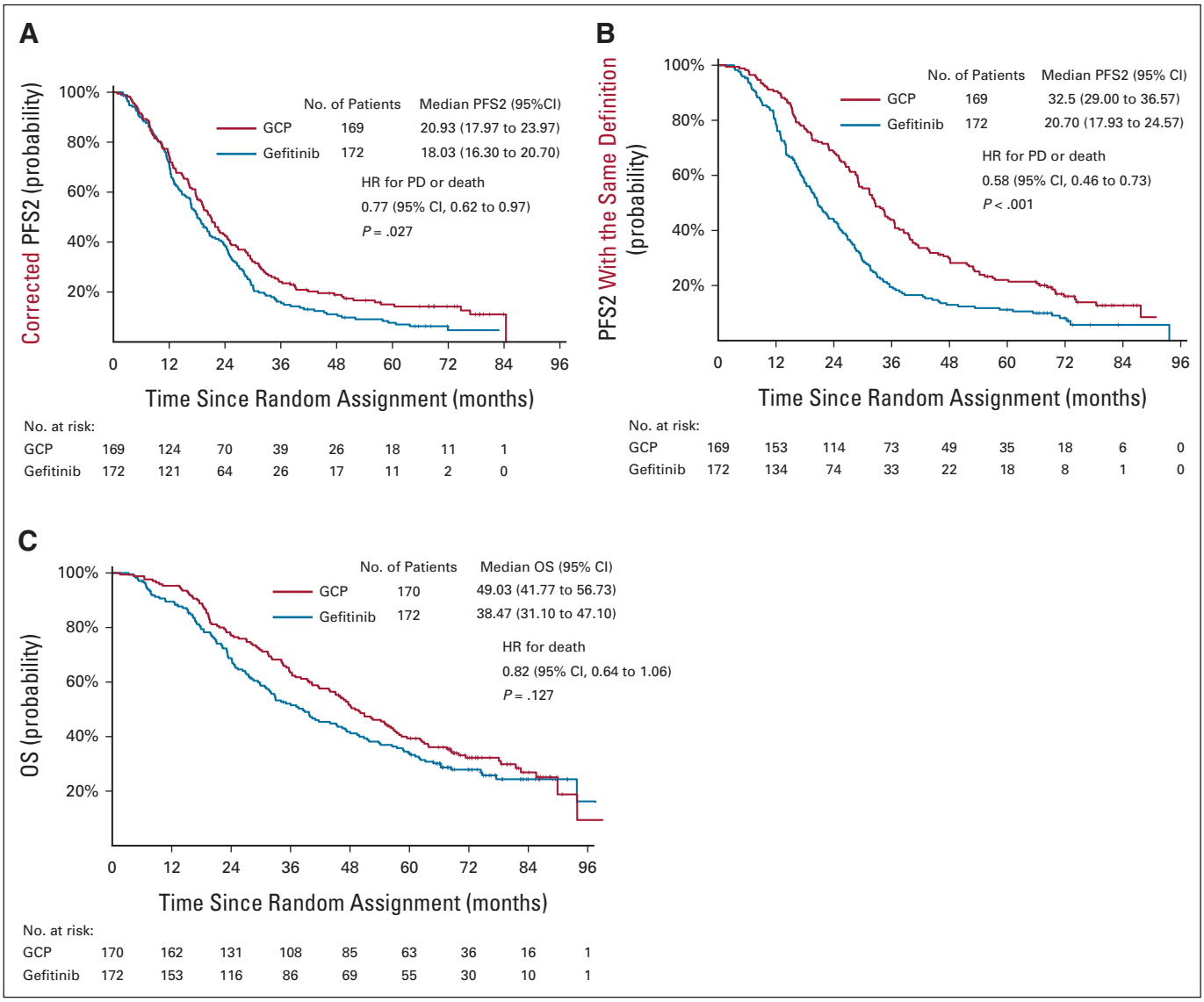

FIG 1. Updated PFS2 and OS. Kaplan-Meier curves for (A) corrected PFS2, (B) PFS2 with the same definition (events are true for the second PD in both groups), and (C) OS in patients treated with GCP and those treated with gefitinib-alone are shown. Plus symbols indicate censored patients at the data cutoff point. GCP, gefitinib and carboplatin plus pemetrexed; HR, hazard ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

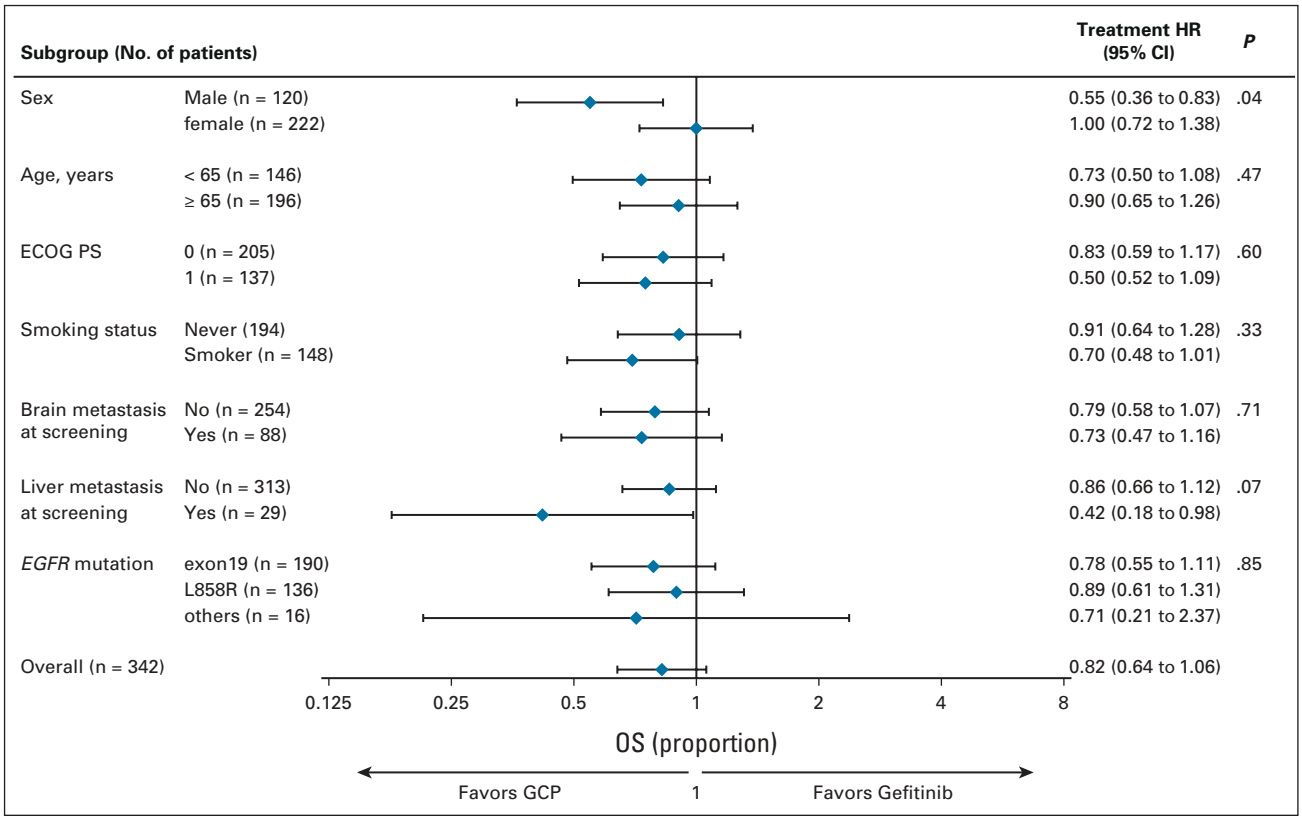

FIG 2. Subgroup analysis of OS. Forest plots for OS are shown. A HR < 1 implies a lower risk of death with the GCP regimen than with gefitinib-alone. The Cox proportional hazards regression model includes randomly assigned treatments, subgroup covariates of interest, and treatment-by-subgroup interaction. ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; GCP, gefitinib and carboplatin plus pemetrexed; HR, hazard ratio; OS, overall survival.

statistically significant 6.3-month survival advantage associated with GCP over a 7-year follow-up period.

Safety

In the extended follow-up analysis, fewer patients reported grade ≥ 3 treatment-related adverse events in the gefitinib group than those in the GCP group (31.0% *v* 66.5%; odds ratio, 0.23; 95% CI, 0.15 to 0.36; $P < .001$; Appendix Table A3, online only). One grade 5 treatment-related adverse event (infection) was observed in the GCP group. No new severe interstitial lung disease occurred during the extended follow-up since the first report.

DISCUSSION

In the first report of NEJ009, PFS benefit in the GCP group was consistent with the results from other phase III trials with EGFR tyrosine kinase inhibitors (TKIs), such as the FLAURA study.[1,4-20] Of note, this updated analysis demonstrated a significantly prolonged corrected PFS2 in the GCP group. These persistent survival benefits confirmed that combination therapy with EGFR-TKI and chemotherapy boosted the tumor response and duration of response than EGFR-TKI monotherapy in patients with *EGFR*-mutated NSCLC.

By contrast, improvements in PFS and PFS2 did not translate to an OS benefit in the present analysis. One possible reason for this was the availability of osimertinib as the subsequent therapy. The long-term survival post-progression diluted the OS differences between treatment groups; nevertheless, we observed consistently favorable survival benefit (HR, 0.82; OS) in the GCP group than in the gefitinib group. With contrast analyses using RMST for 5 years in both treatment groups, the GCP appeared to have a clinically meaningful survival benefit compared with gefitinib.[2,3,21-24]

Previous studies have demonstrated that exon 19 deletion and exon 21 L858R mutations can distinguish clinical characteristics among patients.[25-30] In this study, GCP was found to confer more survival benefits than gefitinib-alone in a subgroup of patients regardless of their *EGFR* mutation type. A consistent result was reported in a similar phase III trial in India.[5] In addition, male patients demonstrated a more evident OS benefit in GCP in the subgroup analysis; however, no clear explanation exists for the differences observed.

In conclusion, to our knowledge, NEJ009 is the first phase III study to evaluate the efficacy of a combination of EGFR-TKI and platinum-doublet chemotherapy in patients with untreated advanced NSCLC with *EGFR* mutations. The

GCP regimen improved PFS and PFS2 with an acceptable safety profile than with gefitinib-alone. Clinical trials are ongoing to compare efficacy of osimertinib monotherapy with osimertinib combined with platinum plus pemetrexed as first-line treatment for patients with untreated NSCLC with *EGFR* mutations.[31,32]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Honoraria: AstraZeneca, Boehringer Ingelheim, Lilly Japan, Chugai Pharma, Ono Pharmaceutical, Bristol Myers Squibb Japan, Shionogi, Daiichi Sankyo, Kyowa Hakko Kirin, Nippon Kayaku, Mundipharma, Novartis, Pfizer
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APPENDIX

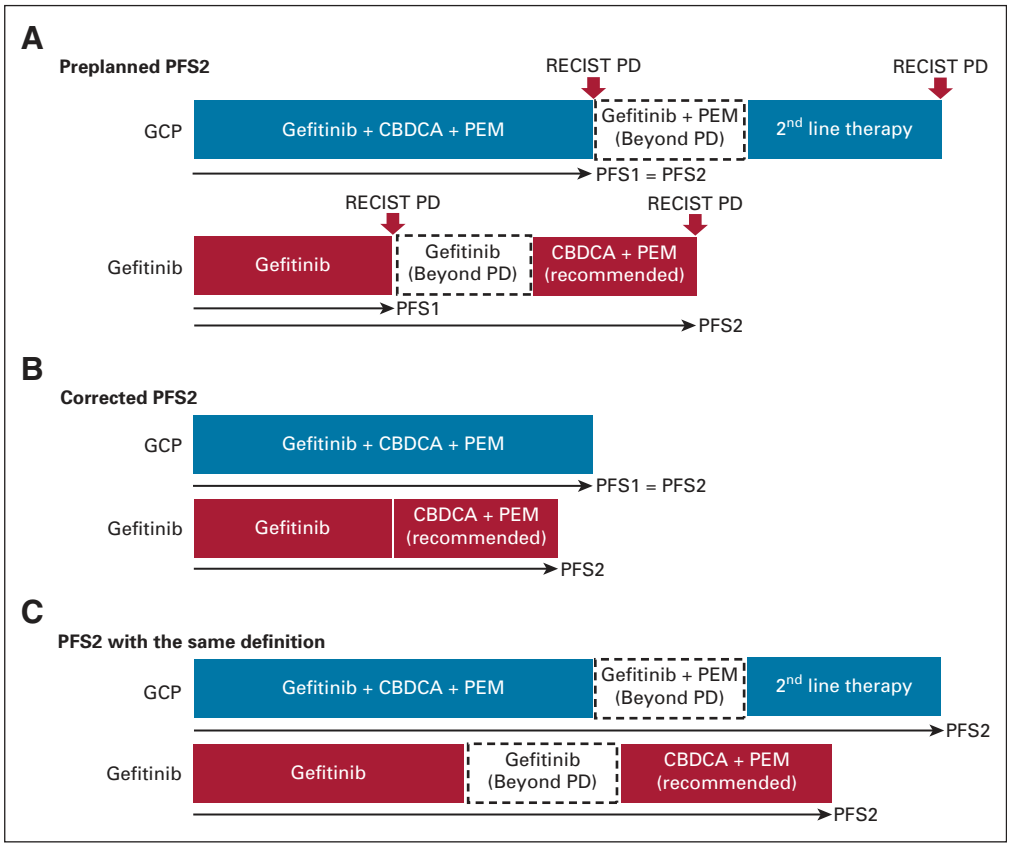

FIG A1. Definition of (A) preplanned PFS2, (B) corrected PFS2, and (C) PFS2 with the same definition. CBDCA, carboplatin; GCP, gefitinib combined with carboplatin plus pemetrexed; PD, progressive disease; PEM, pemetrexed; PFS, progression-free survival.

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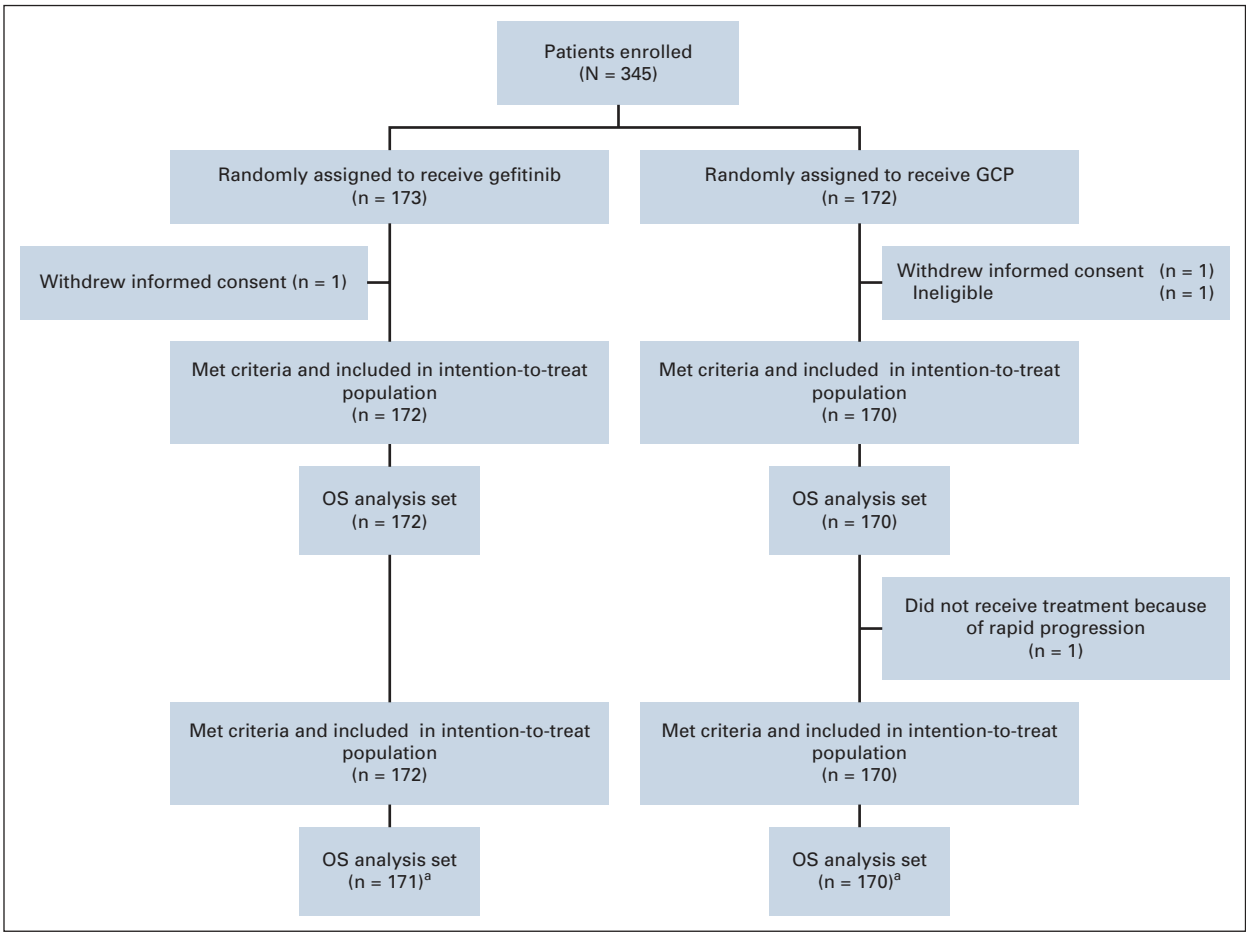

FIG A2. CONSORT diagram. All patients except one ineligible patient and two who withdrew consent were randomly assigned to the gefitinib group or GCP group. One patient in the gefitinib group did not receive gefitinib-alone but was treated with the GCP regimen at the patient's request; thus, this patient's safety data were evaluated as if the patient was in the GCP group, whereas the PFS and OS data were evaluated as if the patient was in the gefitinib group on the basis of the intention to treat. One patient in the GCP group was excluded from the PFS analysis because the patient did not receive any protocol treatment; this patient was included in the OS analysis only. [a]One patient received GCP instead of gefitinib monotherapy with a breach of allocation. GCP, gefitinib combined with carboplatin plus pemetrexed; OS, overall survival; PFS, progression-free survival.

TABLE A1. Subsequent Therapy After Protocol Treatment and Tumor Response

	Second-Line Therapy		Third-Line Therapy	
Chemotherapy Regimen	**Gefitinib (n = 172), No. (%)**	**GCP (n = 170), No. (%)**	**Gefitinib (n = 172), No. (%)**	**GCP (n = 170), No. (%)**
Any treatment	153 (89.0)	125 (73.5)	114 (66.3)	88 (51.8)
Platinum-based with or without bevacizumab	102 (59.3)	16 (9.4)	18 (10.5)	6 (3.5)
Pemetrexed	0 (0.0)	0 (0.6)	6 (3.5)	2 (1.2)
Docetaxel with or without ramucirumab	4 (2.3)	37 (21.8)	26 (15.1)	13 (7.6)
Tegafur, gimeracil, and oteracil	0 (0.0)	1 (0.6)	4 (2.3)	4 (2.4)
Osimertinib	10 (5.8)	11 (6.5)	6 (3.5)	9 (5.3)
Gefitinib or erlotinib	22 (12.8)	29 (17.1)	20 (11.6)	21 (12.4)
Afatinib	3 (1.7)	15 (8.8)	15 (8.7)	19 (11.2)
Immune checkpoint inhibitors	0 (0.0)	3 (1.8)	6 (3.5)	8 (4.7)
Others	12 (7.0)	13 (7.6)	13 (7.6)	6 (3.5)
Response rate (95% CI)	34.0 (26.5 to 41.5)	20.8 (13.7 to 27.9)	16.7 (9.8 to 23.5)	19.3 (11.1 to 27.6)
Disease control rate (95% CI)	72.5 (65.5 to 79.6)	66.4 (58.1 to 74.7)	64.0 (55.2 to 72.8)	58.0 (47.6 to 68.3)

Abbreviation: GCP, gefitinib and carboplatin plus pemetrexed.

TABLE A2. Restricted Mean Survival Time

Group	**Gefitinib (n = 172)**	**GCP (n = 170)**	***P***
5-Year RMST			
Mean (95% CI)	38.6 (35.6 to 41.6)	43.6 (40.8 to 46.3)	
SE	1.5	1.4	
Difference in RMST (95% CI)	Reference	5.0 (0.9 to 9.0)	.017
7-Year RMST			
Mean (95% CI)	45.3 (41.0 to 49.5)	51.6 (47.5 to 55.6)	
SE	2.2	2.1	
Difference in RMST (95% CI)	Reference	6.3 (0.4 to 12.2)	.037

Abbreviations: GCP, gefitinib and carboplatin plus pemetrexed; RMST, restricted mean survival time.

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TABLE A3. Adverse Events (National Cancer Institute-Common Toxicity Criteria grade ≥ 3)

Event	Gefitinib (n = 171) Grade ≥ 3 (n = 53), No. (%)	GCP (n = 170) Grade ≥ 3 (n = 113), No. (%)
Leukopenia	1 (0.6)	36 (21.2)
Neutropenia	1 (0.6)	53 (31.2)
Anemia	4 (2.3)	36 (21.2)
Thrombocytopenia	0 (0.0)	29 (17.1)
Liver dysfunction	38 (22.2)	21 (12.4)
Blood bilirubin increased	1 (0.6)	0 (0.0)
Hyponatremia	1 (0.6)	5 (2.9)
Diarrhea	2 (1.2)	7 (4.1)
Vomiting	1 (0.6)	4 (2.4)
Stomatitis	0 (0.0)	1 (0.6)
Rash	5 (2.9)	7 (4.1)
Nail changes	2 (1.2)	5 (2.9)
Anorexia	2 (1.2)	12 (7.1)
Edema limbs	0 (0.0)	3 (1.8)
Fatigue	0 (0.0)	8 (4.7)
Infection	0 (0.0)	8 (4.7)
Pneumonia	2 (1.2)	3 (1.8)

Abbreviation: GCP, gefitinib and carboplatin plus pemetrexed.