JOURNAL OF CLINICAL ONCOLOGY

Gefitinib Versus Placebo in Completely Resected Non–Small-Cell Lung Cancer: Results of the NCIC CTG BR19 Study

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Processed as a Rapid Communication manuscript.

ABSTRACT

Purpose
Survival of patients with completely resected non–small-cell lung cancer (NSCLC) is unsatisfactory, and in 2002, the benefit of adjuvant chemotherapy was not established. This phase III study assessed the impact of postoperative adjuvant gefitinib on overall survival (OS).

Patients and Methods
Patients with completely resected (stage IB, II, or IIIA) NSCLC stratified by stage, histology, sex, postoperative radiotherapy, and chemotherapy were randomly assigned (1:1) to receive gefitinib 250 mg per day or placebo for 2 years. Study end points were OS, disease-free survival (DFS), and toxicity.

Results
As a result of early closure, 503 of 1,242 planned patients were randomly assigned (251 to gefitinib and 252 to placebo). Baseline factors were balanced between the arms. With a median of 4.7 years of follow-up (range, 0.1 to 6.3 years), there was no difference in OS (hazard ratio [HR], 1.24; 95% CI, 0.94 to 1.64; $P = .14$) or DFS (HR, 1.22; 95% CI, 0.93 to 1.61; $P = .15$) between the arms. Exploratory analyses demonstrated no DFS (HR, 1.28; 95% CI, 0.92 to 1.76; $P = .14$) or OS benefit (HR, 1.24; 95% CI, 0.90 to 1.71; $P = .18$) from gefitinib for 344 patients with epidermal growth factor receptor (*EGFR*) wild-type tumors. Similarly, there was no DFS (HR, 1.84; 95% CI, 0.44 to 7.73; $P = .395$) or OS benefit (HR, 3.16; 95% CI, 0.61 to 16.45; $P = .15$) from gefitinib for the 15 patients with *EGFR* mutation-positive tumors. Adverse events were those expected with an EGFR inhibitor. Serious adverse events occurred in ≤ 5% of patients, except infection, fatigue, and pain. One patient in each arm had fatal pneumonitis.

Conclusion
Although the trial closed prematurely and definitive statements regarding the efficacy of adjuvant gefitinib cannot be made, these results indicate that it is unlikely to be of benefit.

J Clin Oncol 31:3320-3326. © 2013 by American Society of Clinical Oncology

INTRODUCTION

Globally, lung cancer remains the most common cancer and is the leading cause of cancer-related mortality in men and women. In 2012, an estimated 20,100 Canadians and 160,340 Americans died of the disease.[1,2] Non–small-cell lung cancer (NSCLC) accounts for approximately 85% of all pulmonary neoplasms.[3] At initiation of the NCIC CTG BR19 (CTSUBR19) study in 2002, the results of the large platinum-based adjuvant chemotherapy studies in NSCLC were not available and the 5-year survival rate for stage I disease was 60% to 70%, decreasing to

40% for stage II.[4] Although some studies demonstrated a biologic effect, adjuvant chemotherapy was not considered standard of care, and practice patterns varied considerably.

It was known that in NSCLC increased epidermal growth factor receptor (EGFR) expression correlated with aggressive biology, poor response to therapy, and poor outcome.[5-8] The EGFR pathway was believed to be important in the development and progression of epithelial malignancies and to be a potential target for systemic therapeutics.[9] Gefitinib binds reversibly to the internal domain of EGFR and blocks downstream pathways, thereby

reducing proliferation, increasing apoptosis, and decreasing angiogenesis and invasion in NSCLC.[10] In phase II studies, dramatic responses and improved disease control were observed.[11,12] Given the poor survival of patients with completely resected NSCLC, only modest improvements with adjuvant chemotherapy, evidence of gefitinib activity in advanced NSCLC, and gefitinib's acceptable toxicity profile and oral route of administration, this study of adjuvant gefitinib in patients with completely resected NSCLC was undertaken.

PATIENTS AND METHODS

Study Design

This study was a North American, multicenter, prospective, randomized, double-blind, placebo-controlled trial of the EGFR antagonist gefitinib in patients with completely resected stage IB, II, and IIIA NSCLC (American Joint Committee on Cancer/International Union Against Cancer TNM classification, sixth edition)[4,13] conducted by NCIC CTG in collaboration with the Clinical Trials Support Unit of the US National Cancer Institute. Within 16 weeks after surgical resection, eligible patients were randomly assigned (1:1) to receive gefitinib or placebo. The study was activated in September 2002. Initially, patients were stratified by stage (IB, II, or IIIA), histologic subtype (squamous v others), postoperative radiotherapy (given v not), and sex. In October 2003, the study was amended to allow, and stratified for, adjuvant chemotherapy (given v not) with random assignment within 26 weeks of surgery. The primary study end point was overall survival (OS). Secondary end points included toxicity, disease-free survival (DFS), and establishment of a tumor bank for biomarker analysis. The protocol was approved by institutional review boards at all study sites, and all patients provided written informed consent. Data were collected, managed, and analyzed by the NCIC CTG.

Eligibility Criteria

Patients ≥ 18 years old with completely resected, histologically proven stage IB, II, or IIIA NSCLC and an Eastern Cooperative Oncology Group performance status of 0 to 2 were eligible. All patients had a presurgical computed tomography (CT) or magnetic resonance imaging scan of the chest and complete mediastinal lymph node resection or nodal sampling (biopsy of nodes ≥ 1.5 cm on presurgical scans was mandatory). A period of no more than 16 weeks between surgery and random assignment was permitted for patients receiving study drug only, and a period of no more than 26 weeks was permitted for those receiving adjuvant chemotherapy. Patients were ineligible if they had undergone only segmentectomy or wedge resection or had prior malignancies within 5 years, clinically significant or untreated ophthalmologic or GI conditions, mixed tumors with small-cell or carcinoid components, more than one discrete area of primary cancer, clinically significant cardiac dysfunction, active infection, or neurologic or psychiatric disorders.

Random Assignment and Treatment Regimen

Patients received either gefitinib 250 mg or placebo orally daily for 2 years. A 50% dose reduction was allowed that, when necessary, was accomplished by alternate-day dosing. No dose reductions less than 50% were allowed. Patients requiring more than 21 days of continuous drug withholding for toxicity were taken off study medication permanently.

Follow-Up

Patients were observed at 1 and 3 months, then every 3 months until 30 months, then every 6 months for years 3, 4, and 5, and then yearly. During the 2 years of drug administration and for 6 months thereafter, patients underwent history, physical examination, hematology, biochemistry, chest x-ray, and adverse event evaluation.

Exploratory Molecular Analyses

DNA was isolated from sections cut from formalin-fixed, paraffin-embedded blocks. Either macrodissection or laser capture microdissection was used to ensure DNA preparations had ≤ 10% contamination with non-cancer cell DNA. KRAS mutation analysis was performed using a nested polymerase chain reaction procedure.[14] EGFR analyses were performed on all adequate specimens at two different institutions.[15,16] When results lacked concordance, the DNA was tested at a third institution.[17] Results from the latter laboratory were taken as final (Appendix, online only).

Statistical Analysis

Assuming 60% of patients with stage IB and II disease, the corresponding median survival for patients with stage IB to IIIA was calculated to be approximately 32 months (2.7 years). To have 90% power to detect a hazard ratio (HR) of 0.75 using a one-sided 2.5% level test, a total of 1,242 patients were to be accrued in 3.5 years with 1.8 years of follow-up to reach 537 required events (Appendix).

Primary End Points and Analysis

OS and DFS were defined as the time from random assignment to time of death from any cause and time of documented local or distant recurrence of the initial cancer, respectively. All randomly assigned patients were included in survival analyses on an intent-to-treat basis. Survival was described using the Kaplan-Meier method. A stratified log-rank test was used to compare OS and DFS between arms adjusting for stratification factors. An unadjusted analysis was also performed. For exploratory analyses, a Cox proportional hazards model was derived using a stepwise model-building procedure. All patients receiving one dose of study treatment were included in the safety analysis.
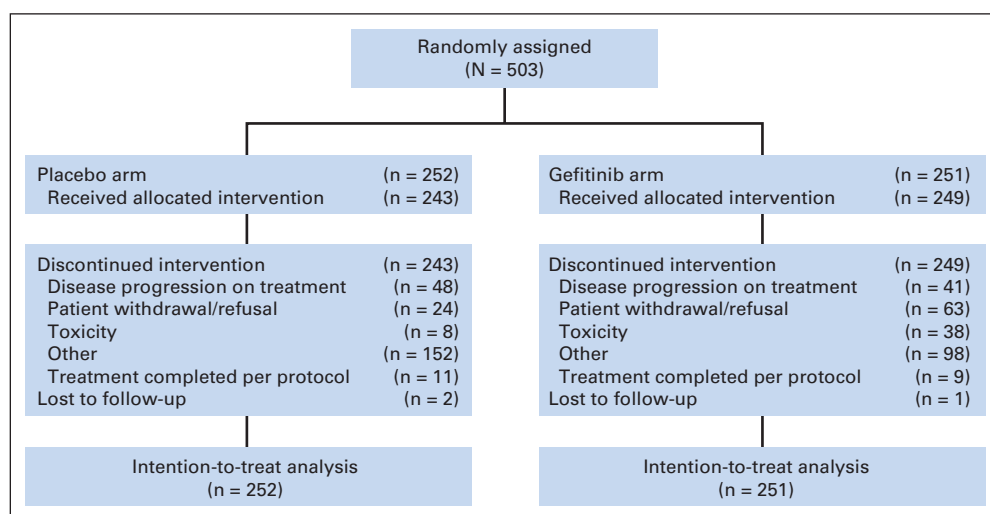

Fig 1. CONSORT diagram for BR19.

Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) and summarized by type and severity. Fisher's exact test was used to compare toxicities between arms. For interim analyses, see the Appendix.

Accrual and Time of Analysis

In December 2004, the phase III study, Iressa Survival Evaluation in Lung Cancer (ISEL), comparing gefitinib with placebo in advanced NSCLC, failed to demonstrate a significant survival benefit.[18] In addition, an unplanned interim analysis of trial S0023 demonstrated that maintenance gefitinib after chemoradiation in patients with stage III NSCLC did not improve OS and was potentially detrimental.[19] In April 2005, based on these results, the BR19 Data and Safety Monitoring Committee recommended study closure and discontinuation of study medication. The trial committee elected to perform the final analysis once all patients were followed for at least 4 years.

RESULTS

Patient Characteristics

Between September 2002 and April 2005, 503 patients were randomly assigned (251 to gefitinib and 252 to placebo; Fig 1). Eleven patients were ineligible (gefitinib, n = 4; placebo, n = 7) but were included in the intent-to-treat analysis. Reasons included preoperative CT over the deadline (n = 1), stage 1A disease (n = 4), two separate tumors (n = 2), serum creatinine ≥ 1.5× upper limit of normal (n = 1), metastases (n = 1), prior cancer (n = 1), and no preoperative CT (n = 1). Three patients were lost to follow-up. The median follow-up time for all patients was 4.7 years (range, 0.1 to 6.3 years). Baseline characteristics were balanced between arms (Table 1). Only 17% of patients (n = 87) received adjuvant chemotherapy, and 5% (n = 23) received adjuvant radiotherapy. Fifty-two percent, 35%, and 13% of patients had stage IB, II, and IIIA NSCLC, respectively, and 60% and 28% had adenocarcinoma and squamous carcinoma, respectively.

Delivery and Toxicity of Therapy

Of 503 randomly assigned patients, 249 received at least one dose of gefitinib, and 243 received one dose of placebo. Median duration of treatment was 4.8 months (range, 1 day to 25 months) for gefitinib and 8.9 months (range, 1 day to 26 months) for placebo. Dose adjustment occurred in 39% of gefitinib-treated patients (96 of 249 patients) and 20% of placebo-treated patients (49 of 243 patients). Drug was held temporarily for 23% of patients on gefitinib and 11% on placebo, with 60% and 35%, respectively, a result of toxicities. Treatment was discontinued as a result of toxicity in 15.3% of patients on gefitinib and 3.3% of patients on placebo. Patient refusal or withdrawal rate after beginning therapy was 24% on gefitinib and 7% on placebo.

Gefitinib patients had a higher incidence of rash, dry skin, diarrhea, anorexia, and nausea but less chest pain, muscle pain, and dyspnea. Adverse events generally were grade 1 to 2. Grade 3 to 4 diarrhea, skin effects, and chest pain were reported in 5% to 8% of both gefitinib- and placebo-treated patients (Table 2). The most common serious adverse event in both cohorts was dyspnea, occurring in 13% and 7% of patients on gefitinib and placebo, respectively. Other serious adverse events were less frequent and occurred in ≤ 5% of patients, with the exception of infection and pain. One patient in each cohort had fatal pneumonitis. Five gefitinib and four placebo patients died of fatal adverse event; three of five deaths in the gefitinib arm were considered drug related.

Table 1. Baseline Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	Gefitinib (n = 251)		Placebo (n = 252)	
	No. of Patients	%	No. of Patients	%
Median age, years	66		67	
Sex				
Female	116	46	116	46
Male	135	54	136	54
Race				
White	233	93	235	93
Asian	6	2	3	1
Other	12	5	14	6
Histology				
Adenocarcinoma	150	60	149	59
Squamous carcinoma	69	27	71	28
Other	32	13	32	13
Smoking history				
Yes	224	89	223	88
No	23	9	19	8
Missing	4	2	10	4
ECOG PS				
0-1	244	97	244	97
2	7	3	8	3
Stage				
IB	133	53	127	50
II	87	35	88	35
IIIA	31	12	36	14
Unknown	0	0	1	0
Type of surgery				
Pneumonectomy	30	12	41	16
Other	221	88	221	84
Prior adjuvant chemotherapy*				
Yes	43	17	44	17
No	208	83	208	83
Prior radiotherapy				
Yes	11	4	12	5
No	240	96	240	95

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.
*Adjuvant chemotherapy included cisplatin 100 mg/m^2 on day 1 and vinorelbine 30 mg on days 1 and 8.

DFS and OS

Among 503 patients, recurrence was documented in 225 (121 patients on gefitinib and 104 patients on placebo). Patterns of disease recurrence were similar between treatment arms for both local (gefitinib, 49.5%; placebo, 49.1%) and distant (gefitinib, 42.1%; placebo, 41.3%) recurrences. The specific sites of disease recurrences are listed in Appendix Table A1 (online only). The median DFS was 4.2 years (95% CI, 3.2 years to not calculable) on gefitinib and not reached on the placebo arm (HR for recurrence, 1.22; 95% CI, 0.93 to 1.61; P = .15; Fig 2A). The stratified Cox regression model found only tumor size ≥ 4 cm (P < .001) to be associated with poor DFS, whereas gefitinib remained not significant and potentially harmful (HR, 1.27; 95% CI, 0.96 to 1.69; P = .096). At data cutoff, 219 of 503 patients had died (116 on gefitinib and 103 on placebo), 72% from progressive disease, 9% from unknown causes, and 19% from other causes. Eighty-five patients (73%) on gefitinib and 73 patients (71%) on placebo died of disease progression. The median survival time on

Table 2. Serious Adverse Events Graded According to National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0

Serious Adverse Events	Gefitinib (n = 249)				Placebo (n = 243)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Infection, other	7	3	0	0	3	1	0	0
Rash/acne	21	8	0	0	1	< 1	0	0
Dehydration	2	1	0	0	2	1	0	0
Diarrhea	18	7	0	0	5	2	0	0
Nausea	6	2	0	0	1	< 1	0	0
Fatigue	15	6	2	1	6	2	1	< 1
Dyspnea	24	10	7	3	18	7	1	< 1
Vomiting	3	1	0	0	0	0	0	0
Pneumonitis	2	1	2	1	2	1	0	0

gefitinib was 5.1 years (95% CI, 4.4 years to not calculable) and had not been reached for placebo patients (HR, 1.24; 95% CI, 0.94 to 1.64; $P = .14$; Fig 2B). The stratified Cox regression model found age ≥ 65 years (HR, 1.42; 95% CI, 1.05 to 1.91; $P = .02$) and tumor size ≥ 4 cm (HR, 1.72; 95% CI, 1.28 to 2.30; $P = .003$) to be associated with shorter survival, whereas gefitinib remained not significant and potentially harmful (HR, 1.27; 95% CI, 0.96 to 1.69; $P = .097$).

Exploratory Subgroup Analyses

EGFR. Among 503 patients, *EGFR* mutation status was determined successfully in 359 tumors (71%; gefitinib, n = 173; placebo, n = 186). Baseline factors were balanced between those with and without *EGFR* mutation data, except patients who had undergone pneumonectomy ($P = .02$), and males ($P = .06$) were more likely to have mutation data. Among patients with known *EGFR* status, 344 had wild-type status, whereas only 15 (4%) had mutations (all adenocarcinoma). *EGFR* mutations were more frequent in women ($P = .004$), nonsmokers ($P < .001$), and Asians ($P = .03$). For the 186 patients on placebo, the median DFS and OS (Fig 3) for *EGFR* wild-

type (n = 178) and the *EGFR* mutant (n = 8) tumors were not reached. *EGFR* mutation positivity was not a significant prognostic factor for DFS (HR, 0.95; 95% CI, 0.300 to 3.01; $P = .93$) or OS (HR, 0.57; 95% CI, 0.14 to 2.33; $P = .43$), but analyses were limited by the low mutation rate. In multivariable Cox regression modeling, *EGFR* mutation status was not a significant prognostic factor for DFS (HR, 0.92; 95% CI, 0.29 to 2.96; $P = .89$) or OS (HR, 0.52; 95% CI, 0.13 to 2.12; $P = .36$). For 344 patients with *EGFR* wild-type tumors (166 patients on gefitinib and 178 patients on placebo), gefitinib demonstrated no beneficial effect on DFS (HR, 1.28; 95% CI, 0.92 to 1.76; $P = .14$) or OS (HR, 1.24; 95% CI, 0.90 to 1.71; $P = .18$; Fig 4). For the 15 patients with *EGFR*-mutated tumors (seven on gefitinib and eight on placebo), gefitinib demonstrated no beneficial effect on DFS (HR, 1.84; 95% CI, 0.44 to 7.73; $P = .40$; Fig 5A) or OS (HR, 3.16; 95% CI, 0.61 to 16.45; $P = .15$; Fig 5B). Cox regression models with gefitinib, *EGFR* mutations, and their interaction demonstrated no significant interaction for DFS and OS in univariate ($P = .60$ and $P = .25$, respectively) or adjusted multivariable analysis ($P = .57$ and $P = .27$, respectively).

KRAS. Of 503 patients, *KRAS* mutation status was determined in 350 tumors (gefitinib, n = 169; placebo, n = 181). For the 181 patients on placebo, the median DFS and OS for 128 patients with *KRAS* wild-type tumors and 53 patients with *KRAS* mutant tumors were not reached. *KRAS* mutation status was not a significant prognostic factor for either DFS (HR, 1.09; 95% CI, 0.66 to 1.82; $P = .74$) or OS (HR, 1.12; 95% CI, 0.67 to 1.86; $P = .66$). The multivariable Cox regression model adjusted for confounding and prognostic factors found that *KRAS* mutation status was not associated with DFS (HR, 0.96; 95% CI, 0.57 to 1.61; $P = .87$) or OS (HR, 0.94; 95% CI, 0.56 to 1.59; $P = .83$). Among 254 patients with *KRAS* wild-type tumors (gefitinib, n = 126; placebo, n = 128), gefitinib demonstrated no beneficial effect on DFS (HR, 1.08; 95% CI, 0.74 to 1.59; $P = .69$) or OS (HR, 1.13; 95% CI, 0.78 to 1.65; $P = .51$). For 96 patients with *KRAS* mutated tumors (gefitinib, n = 43; placebo, n = 53), gefitinib demonstrated significant detrimental effect on DFS (HR, 1.77; 95% CI, 1.00 to 3.13; $P = .05$) and lack of benefit on OS (HR, 1.51; 95% CI, 0.84 to 2.70; $P = .16$). Cox regression modeling with gefitinib, *KRAS* status,
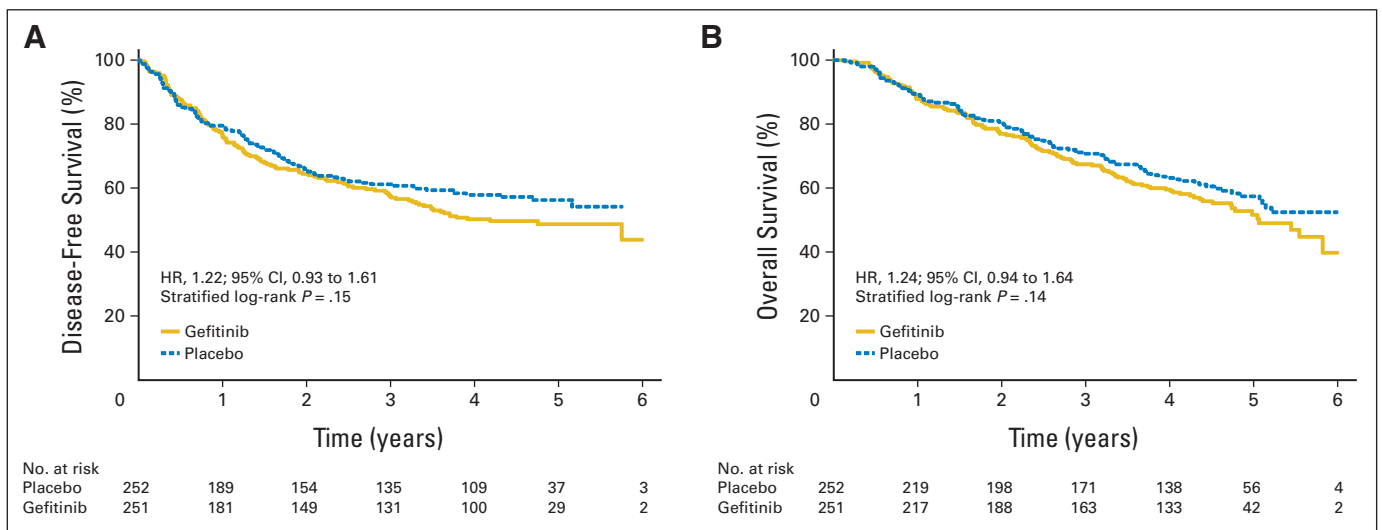

HR, 1.22; 95% CI, 0.93 to 1.61
Stratified log-rank $P = .15$

No. at risk
Placebo	252	189	154	135	109	37	3
Gefitinib	251	181	149	131	100	29	2

HR, 1.24; 95% CI, 0.94 to 1.64
Stratified log-rank $P = .14$

No. at risk
Placebo	252	219	198	171	138	56	4
Gefitinib	251	217	188	163	133	42	2

Fig 2. (A) Disease-free survival. (B) Overall survival. HR, hazard ratio.
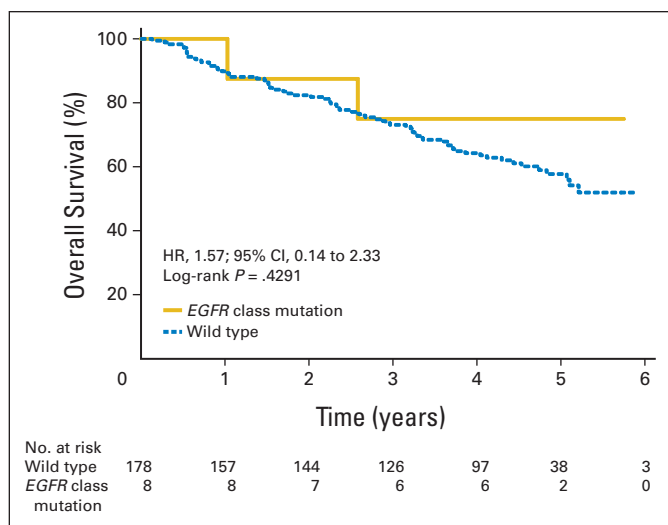
Fig 3. Overall survival in placebo arm in patients with *EGFR* wild-type versus *EGFR*-mutant tumors. HR, hazard ratio.

and their interaction term demonstrated no significant interaction effect (DFS, $P = .15$; OS, $P = .36$) and remained nonsignificant in multivariable adjusted models (DFS, $P = .12$; OS, $P = .5$).

Impact of Early Trial Closure

To examine the impact of early trial closure on the study results an unplanned subgroup analysis limited to the 397 patients randomly assigned at least 6 months before trial closure (198 on gefitinib and 199 on placebo) was undertaken. Similar to the overall population, gefitinib showed no potential treatment effect over placebo on OS (HR, 1.28; 95% CI, 0.96 to 1.71; $P = .097$). Similarly, for the 264 patients randomly assigned at least 1 year before trial closure (132 on placebo and 132 on gefitinib), gefitinib showed no potential treatment effect over placebo (HR, 1.24; 95% CI, 0.88 to 1.73; $P = .22$). The study results do not seem to be related to nonprotocol treatment received after disease progression, which was balanced between arms (Appendix Table A2, online only). Finally, based on a full intent-to-treat
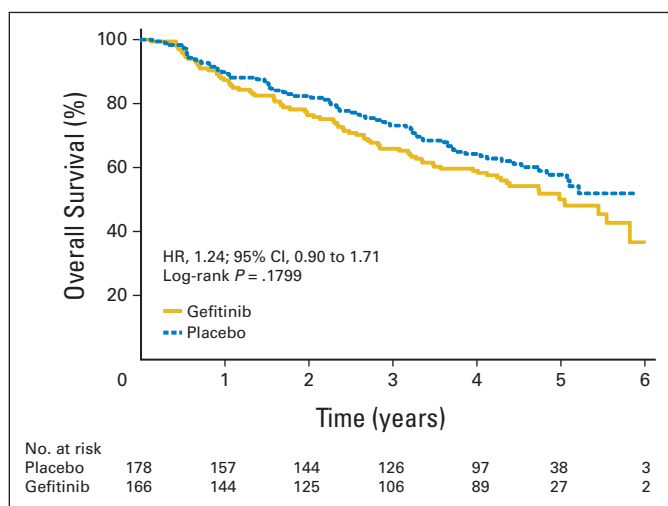

Fig 4. Overall survival by treatment arm in patients with *EGFR* wild-type tumors. HR, hazard ratio.

analysis, the conditional power of observing a beneficial effect of gefitinib had the study reached its target accrual was only 17.5%.

To our knowledge, NCIC CTG BR19 is the first randomized, double-blind, placebo-controlled trial of a targeted agent delivered in the adjuvant setting in completely resected NSCLC. Unfortunately early termination of the study does not allow for statistically robust conclusions. Nevertheless, the sample size is large (503 patients), and the study arms were balanced for the major prognostic factors

Gefitinib was well tolerated with an expected adverse event profile characteristic of EGFR inhibitors, namely rash, dry skin, diarrhea, anorexia, and nausea. The serious adverse event rate was low in both study arms (except dyspnea, which occurred in 7% to 13% of patients and was thought to be a result of surgery), with the majority reported by less than 5% of patients. Although more patients on gefitinib discontinued therapy as a result of treatment toxicity compared with patients on placebo (15.3% v 3.3%, respectively), prolonged administration of gefitinib in the adjuvant setting is tolerable in a majority of patients, although dose adjustments or temporary withholding may be required.

The median follow-up time for all patients accrued was 4.7 years (range, 0.1 to 6.3 years). The median duration of treatment was different between treatment arms (gefitinib, 4.8 months; placebo, 8.9 months) and was attributable to higher treatment toxicity withdrawals, greater number of patients refusing treatment, and greater disease progression and death observed in the gefitinib arm, as compared with placebo. Our results differ from those achieved in both the second-/third-line metastatic (BR.21)[20] and maintenance settings (Sequential Tarceva in Unresectable NSCLC [SATURN])[21] in biomarker unselected populations, where EGFR inhibition resulted in significant survival improvement. When BR19 was initiated, it was unknown that activating mutations of *EGFR* were oncogenic drivers and biomarkers of efficacy for EGFR inhibition.[22,23] However, the protocol allowed for exploratory analyses, and therefore, *KRAS* mutation analysis and *EGFR* analysis of the common exon 19 deletion and exon 21 (L858R) point mutation were undertaken on tissue available from 350 (*KRAS*) and 359 (*EGFR*) patients. Baseline characteristics were balanced between those with and without mutation data, suggesting a representative sample of the intent-to-treat population. Having a tumor with a *KRAS* mutation was not significantly prognostic for DFS or OS, and wild-type *KRAS* status was not predictive of gefitinib effect on DFS or OS. Patients with *KRAS* mutation-positive tumors receiving gefitinib had significantly worse DFS, whereas there was no statistically significant effect on OS.

The number of patients with *EGFR* mutation-positive tumors was low, with only 15 positive tumors (4%) identified despite confirmatory analyses in three different laboratories. Why the mutation rate is low is unknown. A possible explanation is a lower mutation rate in early-stage compared with advanced-stage disease. The small numbers necessitate cautious interpretation of the data. Nevertheless, in this study, the common activating *EGFR* mutations were not prognostic for DFS (HR, 0.95) but did demonstrate a noticeable prognostic effect on OS (HR, 0.57; 95% CI, 0.14 to 2.33). Gefitinib showed no beneficial effect on DFS (HR, 1.28) or OS (HR, 1.24) for patients with wild-type tumors or on
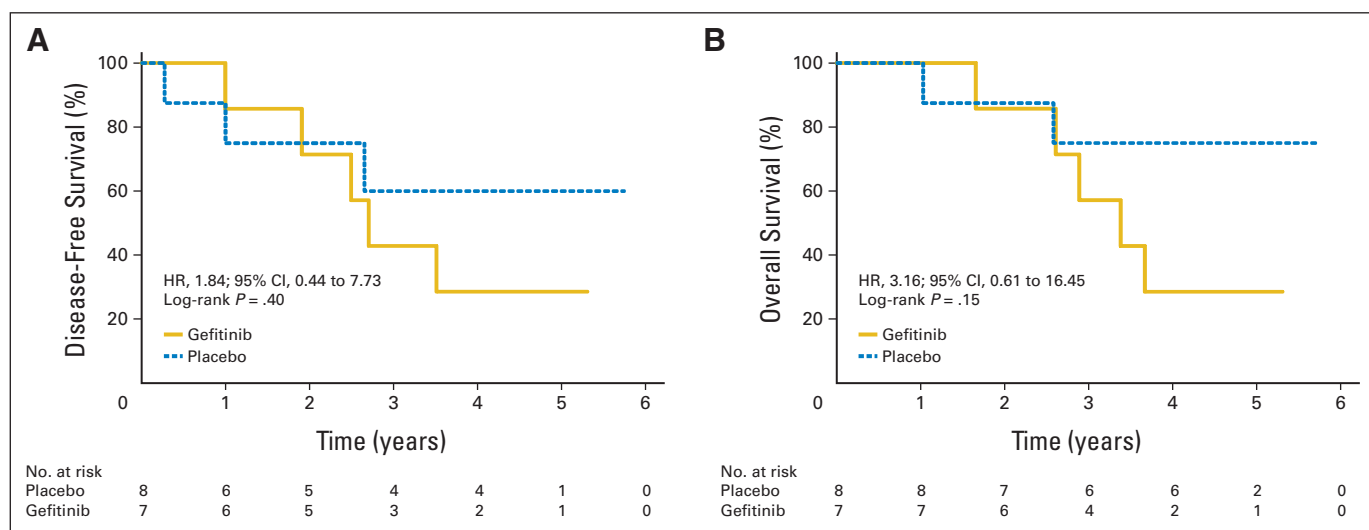
Fig 5. (A) Disease-free survival and (B) overall survival by treatment arm in patients with *EGFR* exon 19 and 21 mutations. HR, hazard ratio.

DFS (HR, 1.84) or OS (HR, 3.6) for patients with *EGFR* mutated tumors. Again, this is surprising because in the metastatic setting the common activating mutations are both prognostic[24-26] and predictive of EGFR tyrosine kinase inhibitor effect.[27-30] This apparent detrimental effect is not an isolated result confined to this trial. In the Southwest Oncology Group S003 trial, a detrimental effect on OS was seen in the arm receiving adjuvant gefitinib after chemoradiotherapy, and in the Iressa Pan-Asia Study (IPASS) in the metastatic setting, patients with wild-type tumors receiving gefitinib had significantly inferior DFS. What is the possible explanation? First, it is possible that because the study is underpowered, the gefitinib arm did poorly by chance alone. However, the detrimental effect is consistent across all subgroups. Second, because of the small number of mutation-positive patients, they were unable to exert a sufficiently powerful effect on the study results, and therefore, it is merely underpowered with mutation-positive patients. This would negate the effect of EGFR inhibition on the wild-type population seen in both the BR.21 and SATURN studies. Third, duration of treatment with gefitinib may have been too short to see therapeutic benefit; however, our results were not sensitive to treatment duration in patient groups randomly assigned 6 months or more before trial closure. Finally, it may be that the EGFR pathway plays a less important role in early disease and tumors are not as dependent on this pathway as an oncogenic driver as later disease states. These are intriguing questions but none can be answered, even with further analysis. BR19 has left us with unanswered questions, and we look forward to the results of the erlotinib adjuvant trial RADIANT (NCT 00373425) and two adjuvant studies in *EGFR* mutation-positive patients, the Chinese study (NCT01405079) and the ongoing Japanese study of adjuvant gefitinib versus chemotherapy.

AUTHOR CONTRIBUTIONS

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Appendix

KRAS *and* EGFR *Analysis*

DNA was isolated from sections cut from formalin-fixed, paraffin-embedded blocks. Either macrodissection or laser capture microdissection was used to ensure that DNA preparations had less than 10% contamination with noncancer cell DNA. *KRAS* mutation analysis was performed using a nested polymerase chain reaction (PCR) procedure.[14] Second-round PCR products were screened for the presence of mutations using high-resolution melting analysis on a Corbett Rotorgene 6000 (Qiagen, Venlo, the Netherlands). All samples that were positive for mutations by high-resolution melt analysis were then analyzed by Sanger sequencing on a separate PCR product, both to confirm the presence of the mutation and to determine the codon affected. *EGFR* mutation analysis was also performed using high-resolution melting screens for exon 19 and 21 mutations, followed by confirmation by Sanger sequencing.[15] Because this analysis gave a low frequency of mutations (5%), *EGFR* mutation analysis was repeated in a second laboratory, using the PCR-restriction fragment length polymorphism and fragment length analyses method for screening and using Sanger sequencing for conformation.[16] For samples that were discordant between the two laboratories, reanalysis was performed in a third College of American Pathologists–accredited clinical diagnostic laboratory using the PCR-restriction fragment length polymorphism and fragment length analyses method.[17] Results from the latter laboratory were taken as final.

Statistical Analysis

Sample size and duration of study. The 3-year survival rate for the 60% of patients with stage 1B and II disease together is approximately 63%. The corresponding median survival time for this subgroup of patients is about 54 months (4.5 years). The 3-year survival rate for the 40% of patients with stage IIIA disease is approximately 33%. The corresponding median survival time is about 23 months (1.9 years). To have 90% power to detect a hazard ratio of 0.75, using a one-sided 2.5% level test, after stratifying by the previously mentioned two subgroups, a total of 1,242 patients in 3.5 years with 1.8 years of follow-up were to be accrued. The total number of events required was 537 deaths, and the absolute calculated differences at 3 years were approximately 7% and 10% for the first and second subgroups, respectively.

Primary end points and analysis. Overall survival, the primary end point of this study, was defined as the time from random assignment to the time of death from any cause. Disease-free survival was defined as the time from random assignment to the time of documented recurrence of the initial cancer. All randomly assigned patients were included in survival analyses based on the intent-to-treat principle. The survival distributions of patients in both treatment groups were described using the Kaplan-Meier method. A stratified log-rank test was used as the primary method to compare the overall survival and disease-free survival between the two arms adjusting for the stratification factors. An unadjusted analysis was also performed. For exploratory analyses, a Cox proportional hazards model was used to adjust the observed treatment effect for the influence of various prognostic factors at study entry and identify factors significantly related to survival outcomes. The final Cox model was determined using a stepwise model-building procedure. All patients who received at least one dose of study treatment were included in the safety analysis. Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). The incidence of toxicities was summarized by type of adverse event and severity. A Fisher's exact test was used to compare toxicities between the two arms.

Interim Analysis

Two interim analyses (the first after 179 deaths and the second after 358 deaths) were planned to determine whether early termination of the study was necessary if results were extreme. The trial would be stopped if the comparison between the treatment arm and control arm was significant in favor of treatment at a significance level of $P = .001$ and $P = .005$ for the first and second interim analyses, respectively. The significance value of $P = .023$ was used for the final analysis to assure the overall type I error of 0.025 based on the O'Brien-Fleming design truncated at a significant level of $P = .001$.

Exploratory Analyses: EGFR *and* KRAS *Mutations*

Exploratory analyses were performed to characterize the relationships between patients' mutation status and baseline characteristics and outcomes. The χ^2 test or Fisher's exact test were used to assess the association between categorical variables. Kaplan-Meier curves were used to estimate the distributions of time-to-event outcomes, the log-rank test was used to test difference between groups, and the Cox regression model was used to correlate mutation status while adjusting baseline characteristics to time-to-event outcomes.

Table A1. Sites of Disease Recurrence						
	Gefitinib (n = 121)		Placebo (n = 104)		Total (N = 225)	
Type of Recurrence	No. of Patients	%	No. of Patients	%	No. of Patients	%
Local recurrence						
Local lung recurrence	32	26.4	31	29.8	63	28.0
Pleural effusion recurrence	5	4.1	6	5.8	11	4.9
Regional lymph node recurrence	23	19.0	14	13.5	37	16.4
Total	60	49.5	51	49.1	111	49.3
Distant recurrence						
Bone recurrence	11	9.1	12	11.5	23	10.2
Brain recurrence	12	9.9	20	19.2	32	14.2
Distant lung recurrence	20	16.5	8	7.7	28	12.4
Liver recurrence	8	6.6	3	2.9	11	4.9
Total	51	42.1	43	41.3	94	41.7
Other						
Other recurrence	8	6.6	8	7.7	16	7.1
Death as a result of cancer without documented recurrence	2	1.7	2	1.9	4	1.8
Total	10	8.3	10	9.6	20	8.9

Table A2. Nonprotocol Cancer Therapy Received After Disease Progression					
	Gefitinib		Placebo		
Therapy	No. of Patients	%	No. of Patients	%	Total No. of Patients*
All patients	119	53.9	102	46.1	221
Hormonal therapy	0	0	1	1.0	1
Chemotherapy	59	49.6	48	47.1	107
Immunotherapy	0	0	1	1.0	1
EGFR inhibitor	16	13.4	19	18.6	35
BRM	4	3.4	2	2.0	6
HDC/autologous stem-cell transplantation	0	0	0	0	0
Radiation therapy	59	49.6	53	52.0	112
Surgery	15	12.6	18	17.6	33
Other therapy	10	8.4	15	14.7	25

Abbreviations: BRM, biologic response modifier; HDC, high-dose chemotherapy.
*Four patient deaths were attributable to lung cancer without documented disease progression.