Phase 2 Study of Afatinib Alone or Combined With Bevacizumab in Chemonaive Patients With Advanced Non–Small-Cell Lung Cancer Harboring *EGFR* Mutations: AfaBev-CS Study Protocol

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Abstract

Afatinib, a second-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), has demonstrated a significant survival benefit over platinum-based chemotherapy in a first-line setting in advanced non–small-cell lung cancer (NSCLC) harboring *EGFR* exon 19 deletion. In addition, we and other groups have shown there to be favorable progression-free survival (PFS) outcomes, with acceptable toxicity profiles, with bevacizumab and first-generation EGFR-TKI combination therapy. On the basis of the above, we hypothesized that a combination of bevacizumab and afatinib could potentially improve efficacy. In our phase 1 study, a daily 30 mg dose of afatinib and 15 mg/kg intravenous bevacizumab every 3 weeks was well tolerated and was defined as the recommended dose. We have initiated a randomized phase 2 trial comparing afatinib (30 mg daily) and bevacizumab (15 mg/kg every 3 weeks) with afatinib (40 mg daily) alone for nonsquamous NSCLC harboring *EGFR* common mutations as a first-line therapy. A total of 100 patients will be enrolled onto this study and randomized in a 1:1 ratio. Patients will continue to receive treatment until disease progression or unacceptable toxicity. The primary end point is PFS, and the secondary end points are overall survival, tumor response, and time to treatment failure. The power is greater than 50% under the assumptions of a median PFS of 12 months for the afatinib group and a hazard ratio of 0.6 for the combination group

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(2-sided $\alpha = 0.05$). We hypothesize that the combination therapy will be more efficacious than standard therapies for *EGFR*-mutant NSCLC patients.

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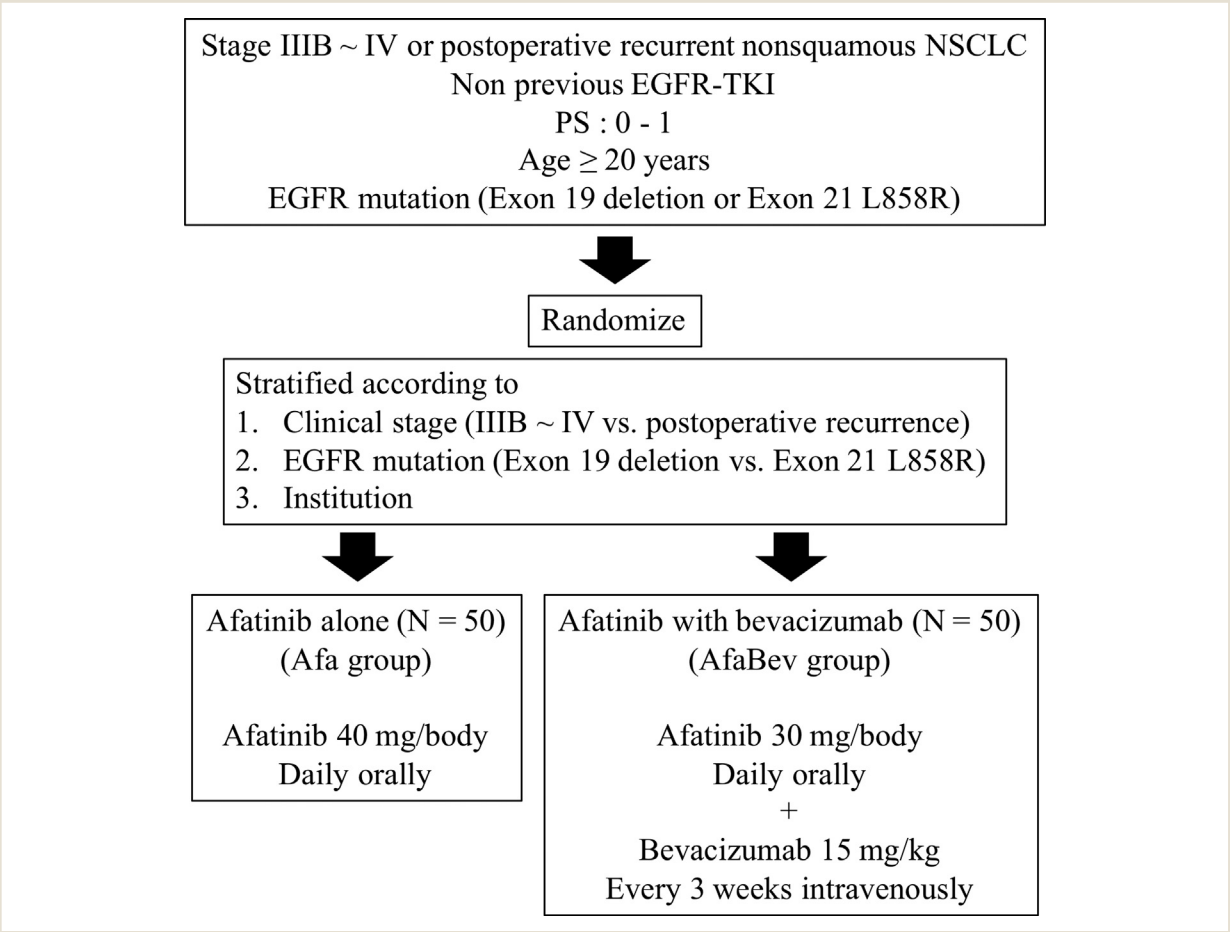
Introduction

Lung cancer is a leading cause of death worldwide.[1] The major pathologic subtype of lung cancer is non–small-cell lung cancer (NSCLC), and a proportion of NSCLC patients have epidermal growth factor receptor (EGFR)-activating mutations.[2] In this subgroup of patients, EGFR–tyrosine kinase inhibitor (TKI) prolonged progression-free survival (PFS) compared to standard platinum-based chemotherapy.[3-8] While the median overall survival of this subgroup is almost 30 months after treatment with EGFR-TKI, the prognosis remains unfavorable.

Afatinib, a second-generation EGFR-TKI, is an irreversible ErbB family blocker that is expected to inhibit tumors with activating *EGFR* mutations more strongly than reversible EGFR-TKIs. Our preclinical study revealed that afatinib prolonged survival compared to gefitinib in an *EGFR*-driven lung cancer mouse model.[9] In a phase 2b clinical study, afatinib significantly improved outcomes in treatment-naive patients with NSCLC harboring *EGFR* mutations compared to gefitinib. In that study, the median PFS values were 11.0 and 10.9 months for afatinib and gefitinib, respectively; the hazard ratio (HR) was 0.73, and the 2-sided 95% confidence interval (CI) was 0.58 to 0.92.[10] Dacomitinib is also a second-generation irreversible EGFR-TKI that shows activity against all 3 kinase-active members of the ErbB family.[11] Dacomitinib also significantly improved PFS compared to gefitinib, with a median PFS of 14.7 versus 9.2 months, respectively, HR of 0.59, and 95% CI of 0.47 to 0.74.[12] Osimertinib is a third-generation irreversible EGFR-TKI that selectively inhibits both activating *EGFR* mutations and T790M resistance mutations.[13] It also improved PFS compared to gefitinib or

Figure 1 AfaBev-CS Study Design



Abbreviations: EGFR = epidermal growth factor receptor; NSCLC = non–small-cell lung cancer; PS = performance status; TKI = tyrosine kinase inhibitor.

erlotinib, with a median PFS of 18.9 versus 10.2 months, respectively, HR of 0.46, and 95% CI of 0.37 to 0.57.[14] The only EGFR-TKIs that significantly improved PFS compared to first-generation EGFR-TKIs in randomized clinical studies were these 3 agents.[10,12,14] Accordingly, the standard primary therapy for this subgroup of patients is scheduled to change.

Vascular endothelial growth factor (VEGF)-A, by binding to VEGF receptor 2, promotes angiogenesis in the tumor microenvironment and indirectly promotes tumor growth. We previously revealed the preclinical synergistic effect of afatinib and bevacizumab, a recombinant monoclonal antibody targeting VEGF-A.[9] In that study, the combination of bevacizumab and afatinib was more effective than afatinib alone in a xenograft model of NSCLC cells harboring *EGFR* mutations. Clinically, we and other groups have already reported favorable PFS data, with acceptable toxicity profiles, with combination therapy of bevacizumab and first-generation EGFR-TKIs in untreated *EGFR*-mutant tumors.[15,16] The median PFS values were 16.0 months and 14.4 months for erlotinib/bevacizumab therapy and gefitinib/bevacizumab therapy, respectively. In a phase 3 trial that compared bevacizumab and erlotinib combination therapy to erlotinib alone, the combination therapy yielded a greater improvement in PFS. The median PFS values of erlotinib plus bevacizumab versus erlotinib alone were 16.9 and 13.3 months, respectively; the HR was 0.605, and the 95% CI was 0.417 to 0.877.[17] The combination of EGFR-TKI with bevacizumab has attracted attention as a first-line therapy for patients with *EGFR*-mutant disease. However, clinically, a combination of bevacizumab and the second-generation EGFR-TKI afatinib remains to be investigated as a first-line therapy.

On the basis of these previous studies, we hypothesized that bevacizumab and afatinib in combination could potentially improve efficacy, and as a first step, we performed a phase 1 trial of this combination therapy in chemonaive patients with advanced NSCLC harboring *EGFR* mutations. In the trial, a daily 30 mg dose of afatinib and 15 mg/kg intravenous bevacizumab every 3 weeks was well tolerated and was defined as the recommended dose.[18] We have initiated a phase 2 randomized trial of afatinib, alone or with bevacizumab.

Patients and Methods

Study Design and Objectives

The AfaBev-CS study is designed as an open-label, randomized phase 2 study to evaluate the efficacy of afatinib with bevacizumab in chemonaive patients with advanced NSCLC harboring *EGFR* mutations. One hundred patients will be randomized in a 1:1 ratio to the experimental arm (afatinib with bevacizumab) or the control arm (afatinib alone), stratified according to clinical disease stage (IIIB to IV vs. postoperative recurrence), *EGFR* mutation (exon 19 deletion vs. exon 21 L858R), and institution (Figure 1). The primary end point is PFS, and the secondary end points are overall survival, tumor response, and time to treatment failure.

This study is conducted in compliance with the principles of the Declaration of Helsinki and is registered in the University Hospital Medical Information Network database (UMIN000027432).

Key Eligibility Criteria

To be included in the study, patients are required to fulfill all of the inclusion criteria, while those who meet the exclusion criteria will be excluded. The main inclusion and exclusion criteria are listed in Table 1.

Table 1 Patient Eligibility Criteria

Inclusion Criteria
• Histologically or cytologically proven nonsquamous non—small-cell lung cancer.
• *EGFR* mutation (exon 19 deletion or exon 21 L858R).
• Disease unresectable or not suitable for radical radiotherapy.
• Clinical stage IIIB to IV or postoperative recurrence.
• EGFR tyrosine kinase inhibitor naive.
• No radiotherapy for tumor in lung.
• Aged 20 years or above.
• ECOG performance status 0-1.
• Adequate organ function, defined as: neutrophil count $\geq$ 1500/μL, hemoglobin $\geq$ 9.0 g/dL, platelets $\geq$ 100,000/μL, total bilirubin $\leq$ 1.5 mg/dL, aspartate aminotransferase/alanine transaminase levels $<$ 2.5$\times$ institutional ULN, creatinine $\leq$ 1.5 mg/dL, pulse oximetry oxygen saturation $\geq$ 94% on room air, activated partial thromboplastin time $\leq$ institutional ULN, prothrombin time international normalized ratio $\leq$ 1.5, and proteinuria $\leq$ 1+.
• Life expectancy of 3 months or more.
• Provision of written informed consent.
Exclusion Criteria
• *EGFR* mutation (T790M in exon 20).
• Symptomatic brain metastases.
• Leptomeningeal carcinomatosis.
• Active double cancer.
• History or presence of hemoptysis or bloody sputum.
• Any coagulation disorder.
• History or present receipt of anticoagulant drugs.
• Uncontrolled hypertension.
• Tumor invading or abutting major blood vessels.
• Lung tumor cavity.
• Effusion (pleural, pericardial, or ascites) that required treatment.
• Superior vena cava syndrome.
• Coexistence or history of interstitial lung disease.
• Gastrointestinal disturbance.
• Severe allergic history.
• Pregnant or lactating woman or woman of childbearing potential.
• Inappropriate patient as determined by a physician.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; ULN = upper limit of normal.

Treatment Plan

Patients enrolled onto this study will be randomized to receive either afatinib plus bevacizumab (AfaBev group) or afatinib alone (Afa group). The AfaBev group patients receive 15 mg/kg bevacizumab by intravenous infusion on day 1 of a 21-day cycle, and afatinib orally once daily at 30 mg, starting from day 1 of cycle 1. The Afa group patients receive afatinib orally once a day at 40 mg. Patients continue to receive treatment until disease progression or unacceptable toxicity.

Statistical Design

The primary end point of this study is PFS, defined as the time between the date of randomization and the date of disease

progression or death from any cause (whichever is earlier). As the primary analysis, a log-rank test will be applied to the full analysis set, which is defined as the set of all randomized patients receiving at least one medication. The cumulative survival rate will be estimated by the Kaplan-Meier method, with 95% CI given by the Greenwood method. The median PFS and 95% CI will be estimated where possible. As the secondary analysis, HR and 95% CI will be estimated by the Cox proportional hazard model. The secondary end points are overall survival, tumor response, and time to treatment failure. The interim data monitoring will be limited to reviewing the safety data. The statistical significance level was set at .05 (2 sided).

A total of 100 patients will be enrolled in a proof-of-concept study. The power is greater than 50% under the assumptions of a median PFS of 12 months for the Afa group and HR of 0.6 for the AfaBev group. The expected total number of events is 81 within the planned trial period (enrollment, 2.5 years; follow-up, 2-4.5 years).

Participating Institutions

The participating institutions include 28 hospitals in the Chugoku-Shikoku region and Hyogo, Japan.

Discussion

Almost all large-scale studies of EGFR-TKI plus angiogenesis inhibitors (bevacizumab or ramucirumab) excluded patients with brain metastasis. One phase 2 study of erlotinib with bevacizumab, the BELIEF study, and one phase 3 study using the same drug combination, NEJ026, included patients with asymptomatic brain metastasis. In the BELIEF study, no severe central nerve toxicities occurred, but there were only 21 patients with brain metastasis (of 109 total patients).[19] Therefore, the efficacy and safety of EGFR-TKI plus bevacizumab therapy in patients with brain metastasis has not been confirmed. The current study also permits patients with asymptomatic brain metastasis, and may help to confirm the efficacy and safety of EGFR-TKI plus bevacizumab therapy in patients with brain metastasis.

Conclusion

The AfaBev-CS study will provide important clinical data on the efficacy of afatinib and bevacizumab, which is important in light of new first-line treatment options, such as osimertinib, dacomitinib, and erlotinib plus bevacizumab, in *EGFR*-mutant NSCLC patients.

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Disclosure

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