Current Trial Report

Rationale and Design of a Phase II Trial of Osimertinib Combined With Bevacizumab in Patients With Untreated Epidermal Growth Factor Receptor-mutated Non–small-cell Lung Cancer and Malignant Pleural and/or Pericardial Effusion (SPIRAL II Study)

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Abstract

Progression-free survival (PFS) of patients with non–small-cell lung cancer with pleural or pericardial effusion is expected to be prolonged with combination use of an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor plus bevacizumab compared with that with an EGFR-tyrosine kinase inhibitor alone. Phase I clinical trial data have been reported for combined treatment with osimertinib plus bevacizumab and demonstrated their safety, but the efficacy remains unclear, particularly in patients with pleural or pericardial effusion. This is an ongoing single arm, prospective, open-label, multicenter, phase II trial to evaluate the efficacy and safety of osimertinib plus bevacizumab combination therapy in EGFR mutation-positive patients with untreated or recurrent non–small-cell lung cancer and pleural and/or pericardial effusion. Osimertinib will be administered orally once daily at a dose of 80 mg. One cycle consists of 21 days. Bevacizumab 15 mg/kg will be administered by drip infusion on Day 1 of each cycle. Treatment will be continued until progressive disease or any of the discontinuation criteria are met. The primary endpoint will be the 1-year PFS rate. Secondary endpoints are response rate, PFS, overall survival, survival not requiring pleural/pericardial drainage, and safety. Osimertinib plus bevacizumab combination therapy is expected to prolong PFS and reduce adverse events. **Trial registration number:** UMIN000028071

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Introduction

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are drugs that block EGFR-mediated signaling and have shown good responses in patients with sensitizing EGFR mutations. EGFR-TKIs are classified into 3 generations based on their mechanisms of action. Gefitinib and erlotinib are first-generation EGFR-TKIs that reversibly bind to the ATP-binding site of the EGFR tyrosine kinase domain to block downstream signal transmission.[1,2] Afatinib is a second-generation EGFR-TKI that binds to EGFR, human epidermal growth factor receptor (HER)2, and HER4, and irreversibly inhibits dimer formation.[3] Osimertinib is a third-generation EGFR-TKI that irreversibly inhibits EGFR. Osimertinib exhibited inhibitory activity against tumor cells harboring

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Table 1 Eligibility Criteria

Inclusion Criteria

1. Histologically or cytologically documented non–small-cell lung cancer (excluding squamous cell carcinoma), either untreated stage IV or postoperative recurrent disease
   - Patients with postoperative recurrence given postoperative adjuvant chemotherapy may be enrolled $\geq$ 4 weeks after the last dosing of the chemotherapy
     - Radiotherapy: Definitive thoracic radiotherapy: Longer than 12 weeks after the last radiation date
     - Other radiation therapy: Longer than 2 weeks after the last radiation date
   - Surgery or therapeutic procedure (other than pleural or pericardial drainage): 4 weeks or longer after the last surgery/procedure date
   - Pleural or pericardial drainage: 2 weeks or longer after the date of drainage
2. Patients with concurrent malignant pleural or pericardial effusion (In principle, cytology should be performed, but even without malignant cytology, patients with imaging and clinical evidence of malignant pleural or malignant pericardial effusion are regarded eligible by this criterion)
3. EGFR mutation-positive
4. Patients capable of receiving oral drugs
5. With 1 or more measurable lesion according to RECIST v.1.1 criteria
6. ECOG performance status, 0-2
7. Patients who, in principle, can be hospitalized or placed under equivalent management for at least 2 weeks to undergo study procedures
8. Age $\geq$ 20 years at the time of providing informed consent
9. Patients with normal major organ functions (bone marrow, liver, kidney, etc.) and who satisfy the following criteria in a test conducted within 2 weeks prior to registration (testing on the same day of the week as the day 2 weeks before the registration is permitted)
   - Neutrophil count $\geq$ 1500/mm^3
   - Platelet count $\geq$ 100,000/mm^3
   - Hemoglobin $\geq$ 9.0 g/dL
   - AST $\leq$ 100 IU/L
   - ALT $\leq$ 100 IU/L
   - Serum bilirubin $\leq$ 1.5 mg/dL
   - Serum creatinine $\leq$ 2.0 mg/dL
   - SpO_2 (room air) $\geq$ 90%
   - Proteinuria $\leq$ 1+
10. Patients expected to survive for at least 3 months
11. Patients who provided written informed consent by their own free will

Exclusion Criteria

1. Patients who underwent pleurodesis for pleural effusion (Pleural drainage is permitted)
2. Complications of pulmonary disorders such as idiopathic pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, active radiation pneumonitis, drug-induced pneumonia, etc.
3. Patients with hemoptysis (expectoration of fresh blood $\geq$ 2.5 mL at a time, owing to non–small-cell lung cancer) or patients with current or past history of bloody sputum meeting the following:
   - Persistent bloody sputum (lasting 1 week or longer)
   - Bloody sputum requiring chronic use of oral hemostatic medication (eg, recurrence requiring repeated use of oral hemostatic medication after improvement with prior use of oral hemostatic medication)
   - Bloody sputum requiring administration of injectable hemostatic medication
4. Patients with tumor invasion to a cavitary lesion or a major blood vessel
5. Complications of infectious diseases requiring intravenous administration of antibacterial or antifungal agents
6. Patients with corneal ulceration
7. Patients who have any of the following QTc-prolongation risks:
   1. Mean corrected QT interval at rest of >470 msec (Fridericia's correction: QTc)
   2. Clinically important abnormalities (for example, complete left bundle branch block, third-degree heart block, second-degree heart block) in the rhythm, conduction, or waveform of electrocardiogram at rest.
   3. Any factors that increase the risk of QTc prolongation or arrhythmia (for example, cardiac failure, hypokalemia, congenital long QT syndrome, a family history of long QT syndrome or unexplained sudden death in first-degree relatives aged 40 years or younger, or any concomitant drug that is known to prolong QT interval)
8. Pregnant, lactating, or possibly pregnant women
9. Symptomatic brain metastasis
10. Active multiple cancer
11. Uncontrolled diabetes
12. Clinically important complications (such as uncontrolled heart disease, severe arrhythmia requiring medication, persistent watery diarrhea, and so on)
13. Systemic disease that is severe or uncontrollable in the opinion of the investigator (eg, uncontrollable hypertension, active bleeding diathesis, hepatitis B, hepatitis C, human immunodeficiency virus [HIV] infection or other active infections that would preclude participation in the study or prevent compliance with the protocol in the opinion of the investigator). Tests for these conditions are not mandatory.
14. Patients with intractable nausea and vomiting, chronic gastrointestinal disease, or inability to swallow drugs, or a history of gastrointestinal resection or other procedures that may markedly affect absorption of osimertinib

15. Patients without confirmed wound healing
16. Patients who are unwilling to use contraception or whose partner plans to become pregnant during the study period
17. Judged as ineligible to participate in this study by the investigator

Abbreviations: ALT = alanine aminotransferase; AST = aspartate amino transferase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; RECIST = Response Evaluation Criteria In Solid Tumors; SpO_2 = peripheral capillary oxygen saturation.

sensitizing EGFR mutations and also had selective inhibitory activity against tumor cells harboring the TKI-resistant mutation, T790M.[4] Osimertinib is a first-line treatment for EGFR mutation-positive non−small-cell lung cancer (NSCLC).[5]

First- and second-generation EGFR-TKIs have been suggested to have reduced efficacy in patients with malignant pleural effusion.[6,7] In addition, vascular endothelial growth factor (VEGF) expression, which may play a role in the onset of pleural effusion, is potentially related to resistance to EGFR-TKIs.[8,9] Thus, as with earlier generation EGFR-TKIs, osimertinib may also have reduced efficacy in patients with pleural effusion.

VEGF-A, which promotes angiogenesis and increases vascular permeability, is a critical mediator in the formation of pleural effusion in patients with lung cancer.[10] Bevacizumab, a human monoclonal antibody targeting VEGF, blocks the binding of VEGF-A to its receptor and thus inhibits the activation of downstream signaling pathways. This suppresses the formation of pleural effusion, and also decreases vascular permeability, thereby reducing the incidence of pleural effusion.[10,11]

Clinically, study JO25567[12] in EGFR mutation-positive patients compared erlotinib alone versus erlotinib plus bevacizumab. The results of this study demonstrated that the median progression-free survival (PFS) was 6.3 months longer with erlotinib plus bevacizumab than with erlotinib alone (16.0 vs. 9.7 months; hazard ratio [HR], 0.54; $P = .0015$), indicating the additive effect of bevacizumab to the EGFR-TKI. In addition, an exploratory subgroup analysis of results from this study showed that, in patients with pleural or pericardial effusion (n = 66), the median PFS was significantly longer by 9.7 months with erlotinib plus bevacizumab (n = 30) than with erlotinib alone (n = 36) (15.4 vs. 5.7 months; HR, 0.45; 95% confidence interval [CI], 0.25-0.82).[13] In patients without pleural or pericardial effusion (n = 86), the median PFS was non-significantly longer by 5.3 months with erlotinib plus bevacizumab (n = 45) than with erlotinib alone (n = 41) (16.4 vs. 11.1 months; HR, 0.62; 95% CI, 0.37-1.04).

These findings indicate that the PFS of patients with pleural or pericardial effusion is expected to be prolonged with combination use of an EGFR-TKI plus bevacizumab compared with that with an EGFR-TKI alone. However, although phase I clinical trial data have been reported for the combination of osimertinib plus bevacizumab and demonstrated their safety, the efficacy remains unclear,[14] particularly in patients with pleural or pericardial effusion.

Study Design and Treatment

Objective and Endpoints

With the above background, the present study is underway to prospectively evaluate the efficacy and safety of combination therapy with osimertinib plus bevacizumab in EGFR mutation-positive patients with untreated or recurrent NSCLC (excluding squamous cell carcinoma) with malignant pleural effusion and/or malignant pericardial effusion. The primary endpoint is the 1-year PFS rate. Secondary endpoints are response rate, PFS, overall survival, survival not requiring pleural/pericardial drainage, and safety.

Study Design

This is a single arm, prospective, open-label, multicenter, phase II trial.

Ethical Consideration and Registration

The study received ethical approval from the Clinical Research Network, Fukuoka Certified Review Board, Fukuoka, Japan. The trial is subject to the supervision and management of the Ethics Committee. Written informed consent will be obtained from all patients before registration, in accordance with the Declaration of Helsinki. Results of the study will be disseminated via publications in peer-reviewed journals.

Eligibility Criteria

The inclusion and exclusion criteria are shown in Table 1.

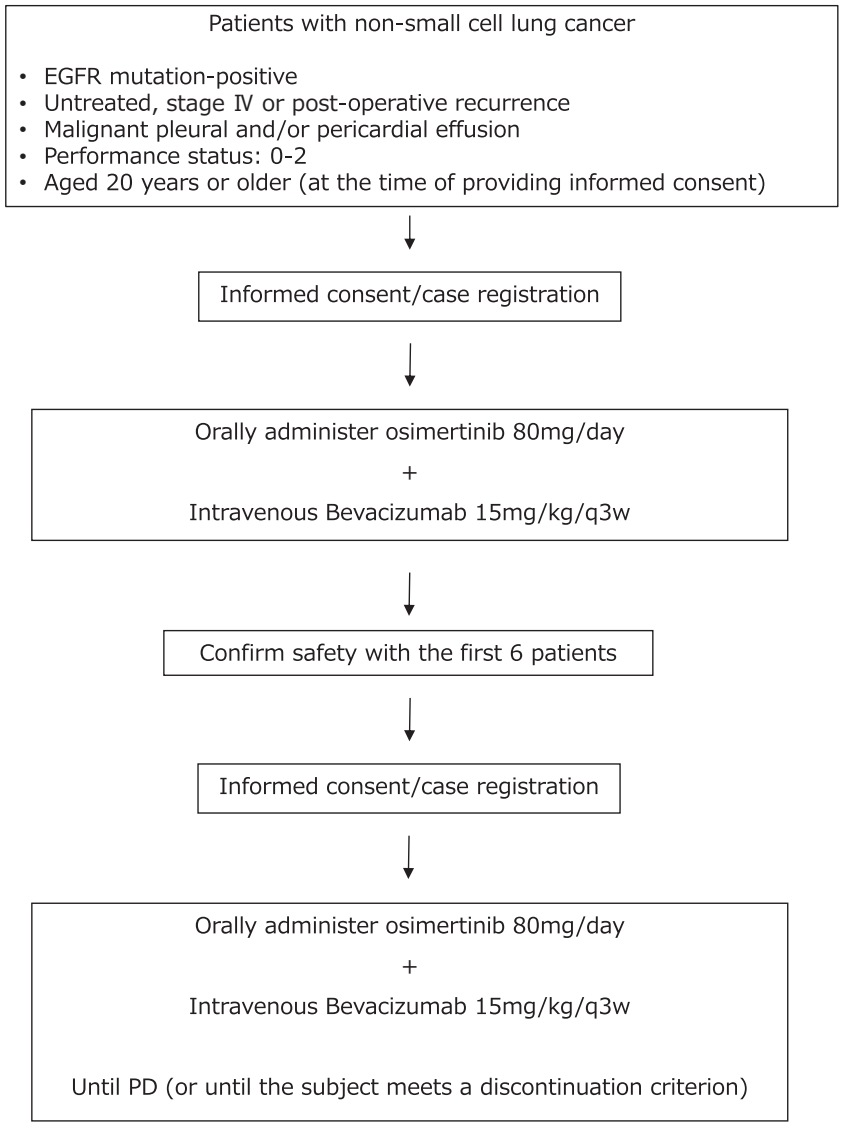
Dosages and Treatment Regimen

Osimertinib will be administered orally once daily at a dose of 80 mg, regardless of food intake, and must be taken at the same time every day at approximately 24-hour intervals. One cycle consists of 21 days. Bevacizumab 15 mg/kg will be administered by drip infusion on Day 1 of each cycle. Once the first 6 cases are registered, registration will be stopped and the safety of this regimen confirmed. Once safety is verified, registration of the seventh patient onward will be started. Treatment will be continued until progressive disease or any of the discontinuation criteria specified in "Criteria for discontinuation of protocol treatment," of the protocol are met. A schematic illustration of the study is provided in Figure 1.

Rationale for Setting the Number of Enrolled Subjects

The FLAURA study in untreated EGFR mutation-positive patients (n = 279) reported an overall response rate of 80% (95% CI, 75%-85%) and a median PFS of 18.9 months (95% CI, 15.2-21.4 months).[15] A pooled analysis by Atagi et al of results from 2 phase II studies (JO22903 and JO25567) conducted in Japan to evaluate the efficacy of erlotinib in untreated EGFR mutation-positive patients reported that the median PFS with erlotinib alone was 8.0 months (95% CI, 5.6-9.7 months) in patients with and 15.3 months (95% CI, 12.3-17.8 months) in patients without pleural or pericardial effusion.[6] In addition, an analysis of a subset of patients with pleural or pericardial effusion in Study JO25567 reported a median PFS of 15.4 months with the combination of erlotinib plus bevacizumab.[13] Based on these data, the increased risk of erlotinib monotherapy in patients with pleural or pericardial effusion can be interpreted as

Figure 1 Figure Study Profile



Abbreviations: EGFR = epidermal growth factor receptor; PD = progressive disease.

having an HR of 1.91, and the add-on effect of bevacizumab plus erlotinib in patients with pleural or pericardial effusion can be interpreted as having an HR of 0.52.

Assuming the risk of osimertinib monotherapy, and the add-on effect of bevacizumab plus osimertinib, in patients with pleural or pericardial effusion are similar to the above, the median PFS in patients with pleural or pericardial effusion can be assumed to be approximately 10 months with osimertinib alone and approximately 19 months with osimertinib plus bevacizumab. With these assumptions, the threshold 1-year PFS rate was set to 43.5% (converted from the threshold PFS of 10 months) and the expected 1-year PFS rate was set to 64.8%. With a significance level of 10% (1-sided) and 80% power, the required sample size was calculated to be 27. To allow for some dropouts, 30 patients will be enrolled.

Population to Be Analyzed

All subjects enrolled in this study, excluding those in whom a serious protocol violation (informed consent has yet to be obtained, consent withdrawal prior to the protocol treatment, etc.) is applicable, will be included in the full analysis set. The per-protocol set will include the remaining subjects from the full analysis set, after excluding those for whom the following protocol violations are applicable: violation of inclusion/exclusion criteria or concomitant drugs/therapies. The safety analysis set will include the subjects who received the protocol treatment at least once.

Statistical Methods

The Kaplan-Meier method will be used to estimate the PFS, overall survival, 1-year survival rate, pleural/pericardial drainage-free

survival, survival curves, medians, and yearly rates. The Brookmeyer and Crowley method will be used to calculate median CIs. The Greenwood method will be used to estimate standard errors of yearly rates. The Wilson method will be used to estimate 2-sided 95% CIs for response rate.

Conclusion

In EGFR mutation-positive patients with untreated or recurrent NSCLC, and with pleural or pericardial effusion, osimertinib plus bevacizumab combination therapy is expected to prolong PFS and reduce adverse events.

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Disclosure

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