Current Trial Report

Phase I/II Study of Osimertinib With Bevacizumab in EGFR-mutated, T790M-positive Patients With Progressed EGFR-TKIs: West Japan Oncology Group 8715L (WJOG8715L)

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Abstract

Osimertinib is a standard treatment for *epidermal growth factor receptor* (*EGFR*)-mutated, *T790M*-positive patients with progression during EGFR-tyrosine kinase inhibitor (TKI) therapy. Osimertinib, a third-generation EGFR-TKI, allows progression-free survival of around 10 months, but its toxicity is well-tolerated compared with other EGFR-TKIs. Preclinical and clinical evidence suggests that EGFR-TKI may work synergistically with vascular endothelial growth factor inhibitors.

We therefore plan a phase I/II study to investigate this possibility. In phase I, the primary endpoint is assessment of the tolerability of osimertinib and bevacizumab in 6 patients. Phase II then explores the efficacy of combined treatment compared with osimertinib monotherapy with progression-free survival as the primary endpoint. Secondary endpoints are overall response rate, time to treatment failure, overall survival, and safety. Eighty patients will be enrolled in phase II.

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Keywords: Bevacizumab, EGFR mutation, Osimertinib

Introduction

AURA3, a phase III trial, compared osimertinib with platinum doublet chemotherapy in *epidermal growth factor receptor (EGFR)*-mutated, *T790M*-positive patients with progression during EGFR-tyrosine kinase inhibitor (TKI) therapy. It demonstrated that osimertinib, a third-generation EGFR-TKI, is the standard treatment in this population.[1] Although its toxicity was well-tolerated, its efficacy was unsatisfactory (10 months of progression-free survival [PFS]). Preclinical study showed that EGFR-TKI and vascular endothelial growth factor (VEGF) inhibitors work synergistically in the cell lines to harbor *EGFR T790M* mutation.[2] Additionally, several studies conducted of patients with sensitive *EGFR* mutations demonstrated durable PFS prolongation.[3-5] At the time of planning this study, the feasibility of osimertinib plus bevacizumab has not been reported. Thus, we will assess the safety of this combination as a phase I study, and subsequently plan a randomized phase II study.

Study Protocol

Objectives. In phase I, the main objective is to assess the tolerability of osimertinib plus bevacizumab in 6 patients. Phase II aims to explore the efficacy of this combination compared with osimertinib monotherapy in 80 patients.

Study Design. This is a multi-center, prospective study consisting of a single-arm phase Ib and randomized phase II. The phase I part is planned as a safety lead-in cohort of 6 patients. Thus, we do not set any dose escalation cohort. If ≥ 2 patients of this lead-in cohort experience dose-limiting toxicity in their first cycle, we will

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terminate this study. The definition of dose-limiting toxicity is as follows: (1) non-hematological toxicity ≥ grade 3; (2) grade 4 hypertension; and (3) interstitial pneumonitis ≥ grade 2. Figure 1 shows the study schema.

Endpoints. In phase I, the primary endpoint is the assessment of tolerability of osimertinib with bevacizumab. In phase II, the primary endpoint is PFS. Secondary endpoints are overall response rate (ORR), time to treatment failure, overall survival, and safety.

Eligibility Criteria

Key inclusion criteria include: (1) pathologically proven advanced lung adenocarcinoma with *EGFR* mutation; (2) confirmed radiologic progression after EGFR-TKI (other than third-generation TKI) and confirmed *EGFR T790M* mutation; (3) Eastern Cooperative Oncology Group performance status 0 or 1; (4) Age ≥ 20 years; (5) adequate organ function within 14 days prior to registration; (6) measurable lesion per Response Evaluation Criteria in Solid Tumors V1.1 (phase II only); and (7) informed, documented consent to participate in the study.

Key exclusion criteria are: (1) interstitial lung disease; (2) high risk of bleeding or embolism; (3) uncontrolled hypertension; (4) leptomeningeal disease (Brain metastasis is allowed if the patient is asymptomatic at the time of registration. Patients who received radiotherapy to the brain can participate, but are required to have an interval ≥ 14 days between the last days of radiotherapy and study treatment.); and (5) positive for hepatitis B virus antigen.

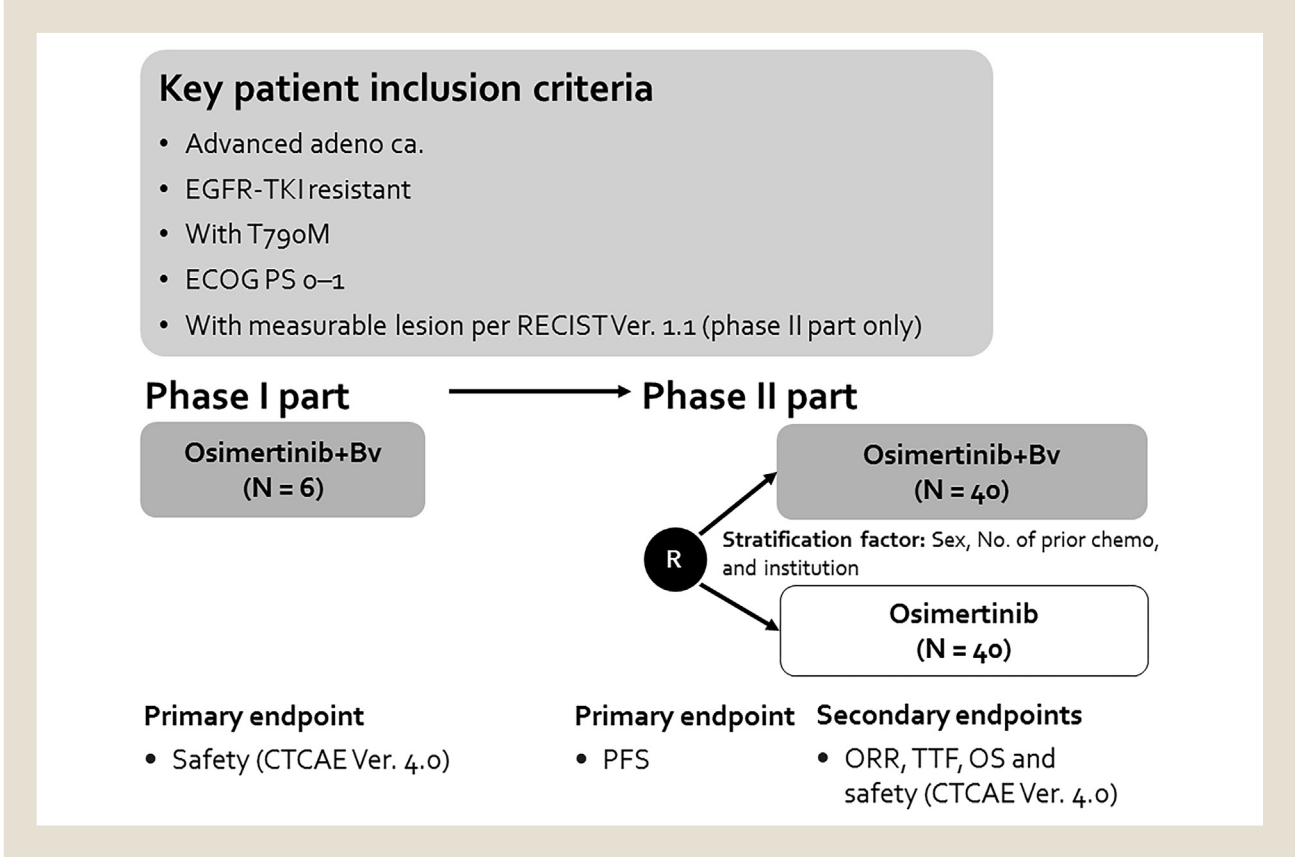
Treatment. Osimertinib (80 mg) is orally administered every day until disease progression. Patients in phase I and patients allocated to the combination arm in phase II are administered osimertinib plus bevacizumab (15 mg/kg intravenously on day 1, every 3 weeks) until disease progression.

Follow-up and Assessment. To assess efficacy, chest and upper abdominal computed tomography is taken every 6 weeks. Gadolinium-enhanced magnetic resonance imaging of the brain is performed at baseline for all patients prior to registration, and taken every 6 weeks thereafter if the patient has brain metastasis. If patients had a known metastatic site other than these areas, appropriate radiologic assessment is also taken every 6 weeks. Adverse events are graded using the Common Terminology Criteria for Adverse Events, V4.0.

Statistical Analysis

Previous clinical data of EGFR-TKI plus bevacizumab marked a hazard ratio of 0.44 to 0.54 in PFS compared with EGFR-TKI

Figure 1 Study Schema



Abbreviations: Adeno ca = adenocarcinoma; Bv = bevacizumab; chemo = chemotherapy; CTCAE = Common Terminology Criteria for Adverse Events; ECOG PS = Eastern Cooperative Oncology Group performance status; EFGR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; R = randomized; RECIST = Response Evaluation Criteria in Solid Tumors; TTF = time to treatment failure.

monotherapy.[3,5] The calculation of sample size for phase II is based on the hypothesis that hazard ratio of osimertinib plus bevacizumab will enable a 0.55 improvement in PFS over osimertinib monotherapy with a median PFS of 9 months. Seventy-four eligible patients are required to ensure a statistical power of 0.80 at a 2-sided alpha error of 0.20. Assuming a drop-out rate of 8%, 80 patients need to be enrolled in the study.

The primary endpoint, PFS, will be estimated using the Kaplan-Meier curves. Median PFS with 95% confidence interval (CI) will be reported for each treatment arm. The difference in PFS between the 2 treatment arms will be examined at the significance level of 0.20 using a stratified log-rank test using the stratification factors. A Cox regression model will also be used to estimate the hazard ratio and its 80% and 95% CIs. All tests for the secondary endpoints will be carried out at a 5% alpha level. Time to treatment failure and overall survival will be analyzed in a similar way to PFS. For the ORR, the point estimates and the 95% CI with Pearson-Clopper method will be provided. The difference in the ORR and the associated 95% CIs will also be estimated. The Fisher exact test will also be performed.

Ethical Considerations

The study is conducted in compliance with the principles of the Declaration of Helsinki, and the institutional review board of each participating institution has approved the protocol. Written informed consent is obtained from all patients before any screening or inclusion procedure. This protocol was registered in the University Hospital Medical Information Network, Japan (protocol identification no. UMIN000023761).

Discussion and Conclusion

VEGF inhibition enhances the efficacy of EGFR-TKI in *EGFR*-muted cells.[2] A recent phase III trial comparing erlotinib plus bevacizumab against erlotinib monotherapy demonstrated statistically significant prolongation of PFS (16.9 vs. 13.3 months; $P = .01573$) with manageable toxicity, which consisted of EGFR- and VEGF-mediated adverse events.[5] Considering the safety profile of osimertinib, combination therapy of osimertinib plus bevacizumab may be promising.

WJOG8715L is the first randomized study to assess the efficacy of osimertinib plus VEGF inhibitors. The results of the phase III FLAURA trial allows us to use osimertinib as first-line treatment,[6] so the West Japan Oncology Group is conducting another randomized phase II trial of osimertinib plus bevacizumab in a first-line setting (WJOG9717L, UMIN000030206). The results of these 2 studies (WJOG8715L and 9717L) will show the clinical implications of EGFR-TKI plus VEGF inhibition in *EGFR*-mutated patients.

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