A Phase II Study of Nivolumab in Patients With Advanced Non–small-cell Lung Cancer who Responded to Prior PD-1/L1 Inhibitors: West Japan Oncology Group 9616L (WJOG9616L)

Hiroaki Akamatsu,[1] Shunsuke Teraoka,[1] Yasuhiro Koh,[1] Takeharu Yamanaka,[2] Nobuyuki Yamamoto,[1] Kazuhiko Nakagawa[3]

Abstract

Immune-checkpoint inhibitors (ICIs) play an important role in treatment for advanced non–small-cell lung cancer. Over one-half of patients, however, have relapse. Although rechallenge treatment of anti-cancer drugs that showed efficacy in prior lines of therapy has been broadly accepted in lung cancer, evidence of efficacy of rechallenge of ICIs has been limited to anecdotal case series. We therefore plan a phase II study. The primary endpoint is to assess the overall response rate of nivolumab in patients with advanced non–small-cell lung cancer who responded to prior ICIs. Secondary endpoints are disease control rate, progression-free survival, overall survival, and safety. Sixty patients will be enrolled in this trial. Programmed death-ligand 1 expression level in circulating tumor cells will be evaluated as a surrogate biomarker for the prediction of the efficacy.

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Introduction

Immune-checkpoint inhibitors (ICIs) play an important role in advanced non–small-cell lung cancer (NSCLC). Recent phase III trials of platinum-doublet chemotherapy combined with programmed cell death protein-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors have shown prolongation of overall survival.[1,2] Pembrolizumab monotherapy is another first-line treatment option in patients with NSCLC whose tumor expressed PD-L1 more than 50%.[3] However, more than one-half of the patients have relapse.

Rechallenge treatment of anti-cancer drugs that have shown efficacy in prior lines of therapy has been broadly accepted in lung cancer. Rechallenge with platinum doublet chemotherapy is one optional treatment in platinum-sensitive small-cell lung cancer. In patients with NSCLC who have driver oncogenes, rechallenge of tyrosine-kinase inhibitors are used based on the phase II trials.[4] Rechallenge treatment showed efficacy because a proportion of sensitive clones remain after initial treatment and regrow either during the drug-free period or during exposure to other treatment. On the other hand, evidence of rechallenge of ICIs has been limited. Several studies have reported potential efficacy of rechallenge treatment of melanoma,[5,6] but not NSCLC. We therefore begin this phase II study.

Study Protocol

Objectives. This study aims to assess the efficacy of nivolumab in patients with advanced NSCLC who previously responded to ICIs.

Study Design. This study is a single-arm prospective, phase II study, summarized in Figure 1.

Endpoints. The primary endpoint is to assess the overall response rate (ORR) of nivolumab. Secondary endpoints are disease control rate, progression-free survival, overall survival, and safety.

[1]Third Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan
[2]Department of Biostatistics, Yokohama City University School of Medicine, Yokohama, Japan
[3]Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka, Japan

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Address for correspondence: Hiroaki Akamatsu, MD, Third Department of Internal Medicine, Wakayama Medical University, 811-1, Kimiidera, Wakayama City, Wakayama, 641-8509, Japan
E-mail contact: h-akamat@wakayama-med.ac.jp

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Eligibility Criteria.

Key Inclusion Criteria

(1) Pathologically proven patients with NSCLC who received systemic anti-cancer treatment including ICIs.
(2) Clinical benefit was obtained by prior ICIs, and progressed. Clinical benefit is defined as complete response, partial response, or disease control rate $\geq$ 6 months. Any combination regimen is allowed if it includes ICIs.
(3) Prior ICIs were completed $\geq$ 60 days of registration.
(4) Age $\geq$ 20 years.
(5) Eastern Cooperative Oncology Group performance status of 0 to 1.
(6) Measurable lesion.
(7) Adequate organ function for 14 days prior to registration.
(8) Informed, documented consent to participate in the study.

Key Exclusion Criteria

(1) No symptomatic brain metastasis.
(2) History of severe immune-related adverse events during prior ICIs.
(3) Active autoimmune disease. Patients who have controlled thyroid dysfunction or skin disease that does not require systemic therapy are allowed.
(4) Exhibiting significant interstitial pneumonitis or pulmonary fibrosis on chest computed tomography. ICI-induced pneumonitis is allowed if patients' lung infiltration is stable and is free from systemic steroids $\geq$ 90 days.
(5) Pregnant or nursing women, or women unwilling to use contraception.
(6) Serious psychiatric condition that makes registration difficult.
(7) Known serious allergy.

Treatment

Treatment will consist of nivolumab monotherapy. Nivolumab 240 mg will be administered intravenously every 2 weeks until disease progression.

Follow-up and Assessment

To assess efficacy, chest computed tomography will be taken every 6 weeks up to 40 weeks, and then every 12 weeks thereafter. Gadolinium-enhanced magnetic resonance imaging of the brain will be performed at baseline for all patients prior to registration. Tumor assessments will be based on Response Evaluation Criteria in Solid Tumors, version 1.1. Adverse events will be graded using Common Terminology Criteria for Adverse Events, version 4.0.

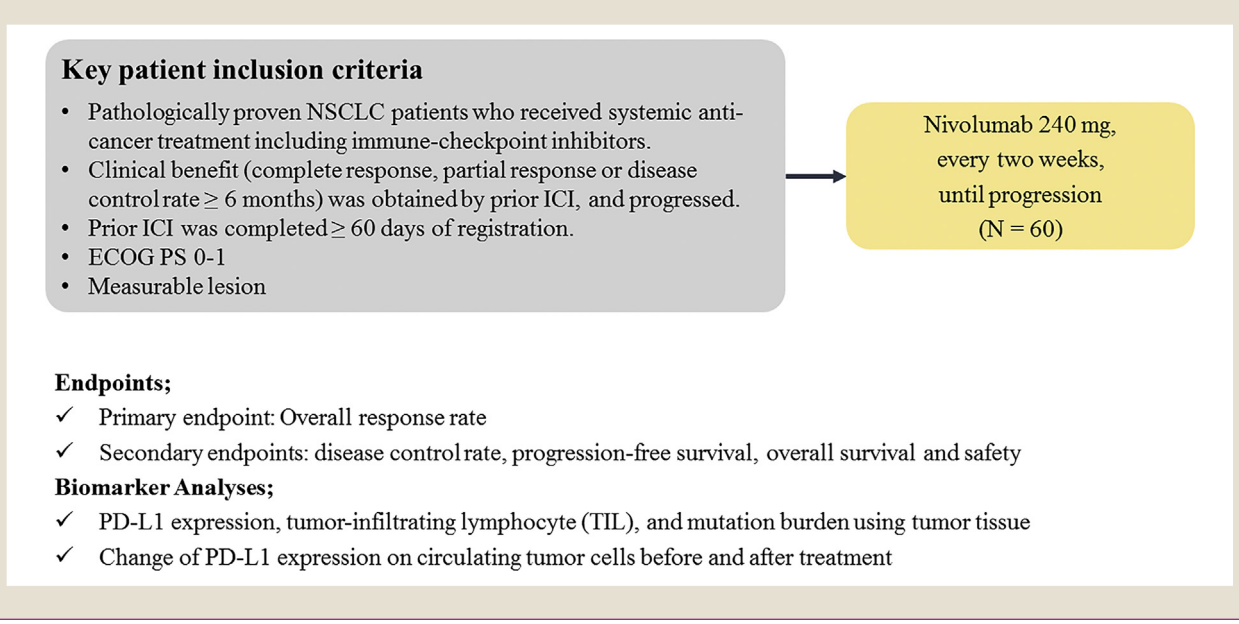
Statistical Analysis

After progression of ICIs, chemotherapy is the standard treatment. Sample size calculation is based on the hypothesis that re-administration of nivolumab will improve ORR from 10% to 20% in the second- or later-line setting. Sixty eligible patients are required to ensure a statistical power of 0.79 at a 1-sided alpha error of 0.05.

Biomarker Analyses

We plan correlation analysis of predictive biomarkers (PD-L1 expression, tumor-infiltrating lymphocyte, and mutation burden using tumor tissue at baseline). Change of PD-L1 expression on circulating tumor cells (CTCs) before and after treatment will also be analyzed. CTCs will be detected, and their PD-L1 expression levels will be evaluated using microcavity array (Hitachi Chemical Co. Ltd, Chikusei, Japan).[7] Tissue mutational analyses will be conducted using NextSeq 500 and MiSeq sequencer (Illumina, San Diego, CA).

Figure 1 Study Diagram



Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; ICI = immune-checkpoint inhibitor; NSCLC = non–small-cell lung cancer; PD-L1 = programmed death ligand 1; TIL = tumor-infiltrating lymphocyte.

Ethical Considerations

The study will be 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 procedures. This protocol was registered in the University Hospital Medical Information Network, Japan (protocol identification no. UMIN000028561).

Discussion and Conclusion

Several rechallenge studies with ICIs have shown clinically meaningful efficacy without enhancing toxicity.[8] In NSCLC, a retrospective study reported that in 12 cases of pembrolizumab monotherapy after progression of nivolumab, there was 1 (8.3%) partial response.[9] As the study included both responders and non-responders to initial nivolumab therapy, the ORR of pembrolizumab is relatively modest. In patients with melanoma who relapsed after completion of 2 years of pemblolizumab treatment, rechallenge demonstrated ORR of 50% (4 of 8 patients).[10] This suggests that patients who responded to initial ICIs are likely to respond to ICI rechallenge, but there is still no solid evidence. Thus, prospective assessment of readministration with ICIs in patients who responded to prior PD-1/PD-L1 inhibitors will answer an important clinical question.

As described above, some patients may benefit from rechallenge with ICIs. Thus, exploration of the biomarker for patient enrichment is clinically meaningful. Tissue and blood samples obtained at the time of registration will provide useful information about predictive biomarkers. The dynamics of PD-L1 status during treatment in this population can be clarified by monitoring of CTC samples.

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Disclosure

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