

# Nivolumab Maintenance as Monotherapy after Carboplatin Plus Nab-Paclitaxel for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer: Study Protocol for Feasibility

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## Abstract

The aim of this study is to determine the feasibility of nivolumab as maintenance therapy after first-line chemotherapy with carboplatin plus nab-paclitaxel in non-small-cell lung cancer. Since we cannot change the dose of nivolumab, we will investigate the recommended doses and cycles of pretreatment chemotherapy with carboplatin plus nab-paclitaxel that affect maintenance therapy. The primary endpoint is incidence of any grade  $\geq 3$  adverse events during the first 12 weeks of nivolumab treatment. Twelve patients are required in this study.

**Keywords:** Maintenance therapy; Nivolumab; Non-small-cell lung cancer; Study protocol

## Introduction

Nivolumab, a fully Immunoglobulin G4 (IgG4) programmed death-1 antibody, has demonstrated activity and tolerability in previously treated advanced non-small-cell lung cancer (NSCLC) [1]. A significant improvement in overall survival (OS) with nivolumab was observed in squamous NSCLC patients in the CheckMate 017 trial (nivolumab versus docetaxel) and in non-squamous NSCLC patients in the CheckMate 057 trial (nivolumab versus docetaxel) [2,3]. Nivolumab was also associated with longer progression-free survival (PFS) compared with docetaxel in the CheckMate 017 trial. In the study of nivolumab in combination with platinum-based doublet chemotherapy in NSCLC, it has been reported that the safe profile of nivolumab and platinum-based chemotherapy was consistent with what would be expected for individual drugs [4]. However, treatment-related adverse events led to discontinuation in 21% of patients, and discontinuation of treatment associated with adverse events was higher with combination therapy [4].

The safety and efficacy of pemetrexed and bevacizumab have been proven as maintenance therapy for non-squamous NSCLC. Continued maintenance therapy with pemetrexed after induction therapy with cisplatin plus pemetrexed significantly improved PFS and OS compared with placebo therapy for non-squamous NSCLC, and switching to maintenance therapy with pemetrexed after platinum-based doublet chemotherapy also improved PFS and OS [5,6]. Continued maintenance therapy with bevacizumab after carboplatin plus paclitaxel had a significant survival benefit compared with carboplatin plus paclitaxel alone therapy [7]. Nab-paclitaxel as maintenance therapy after carboplatin plus nab-paclitaxel in squamous NSCLC is under clinical trial [8]. Maintenance therapy after first-line chemotherapy is being established as a common treatment for both non-squamous and squamous NSCLC.

Based on these considerations, we conducted a feasibility study of nivolumab as maintenance therapy after first-line chemotherapy with carboplatin plus nab-paclitaxel for NSCLC.

## Protocol of the Study

### Objective

The study is a feasibility study that is designed to demonstrate the safety and efficacy of maintenance nivolumab monotherapy administered to patients with advanced NSCLC who showed clinical benefit from first-line chemotherapy with carboplatin plus nab-paclitaxel.

### Endpoints

The primary endpoint is determination of the optimal doses and cycles of first-line chemotherapy with carboplatin plus nab-paclitaxel in accordance with the incidence of any grade  $\geq 3$  events during the first 12 weeks of nivolumab treatment. The secondary endpoints are response rate, disease control rate, PFS, and OS.

## Eligibility Criteria

### Inclusion criteria

- The inclusion criteria are:
- Histologically or cytologically confirmed NSCLC
  - No prior treatment
  - Stage IIIB, IV and unsuitable for thoracic radiotherapy
  - Tested negative for epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) translocation
  - Tumor programmed death ligands 1 (PD-L1) expression levels of 1–49%

One or more measurable disease

Eastern Cooperative Oncology Group-performance status of 0 to 1

Aged 20–79 yrs at the time of registration

Adequate function of vital organs, as evaluated within 7 days before registration

Hematopoietic function

White blood cells  $\geq 3000/\text{mm}^3$

Neutrophils  $\geq 1500/\text{mm}^3$

Platelets  $\geq 100,000/\text{mm}^3$

Hemoglobin  $\geq 9.0 \text{ g/dL}$

Liver function

Total bilirubin  $\leq 1.5 \text{ mg/dL}$

Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT)  $\leq 2$  times the normal upper limit

Renal function

Creatinine clearance  $\geq 60 \text{ ml/min}$

Life expectancy of at least 3 months

Able to provide written informed consent before registration

### Exclusion criteria

The exclusion criteria are:

Interstitial pneumonia or pulmonary fibrosis on chest X-ray

Patients who have received chest radiation therapy

Auto-immune disease patients

Patients who have received systemic steroid therapy

Symptomatic brain metastasis

Active hepatic disease

Serious complications (heart failure, renal failure, severe liver dysfunction, gastric ulcer with bleeding, ileus, bowel obstruction, uncontrolled diabetes)

Uncontrolled ascites, pleural effusion, and cardiac effusion

History of multiple malignancies within 3 years

Planning of surgery during the trial

Pregnant or nursing women with the possibility (intention) of the pregnancy

Serious mental disorders

Previous drug allergy

Patients are judged to be unsuitable by the attending physician

### Registration

An eligible report form will be sent to the registration center at the Clinical Research Institute of Kyushu Medical Center. Information on necessary follow-up tests will then be sent from the registration center.

### Study Design

This study is being conducted in accordance with the Declaration of Helsinki and is registered with the University Hospital Medical Information Network in Japan, number UMIN000027985. The research protocol was approved by the ethics committee of Kyushu Medical Center (registration number 17A105).

### Treatment plan and evaluation

According to the study of nivolumab in combination with platinum-based chemotherapy, it has been reported that 45% of patients had grade 3 or 4 treatment-related adverse events [4]. Therefore, we stipulated that induction chemotherapy is unacceptable if nivolumab maintenance monotherapy has an incidence of more than 45% for grade 3 or 4 adverse events. If three or more of the first six patients who had been originally allocated to level 1 experience nivolumab-induced grade 3–4 toxicity, an additional six patients will be enrolled to level 0. (Level 1, carboplatin at an area under the concentration time curve (AUC) 6 mg/ml/min on day 1+nab-paclitaxel 100 mg/m<sup>2</sup> on days 1, 8, and 15 with treatment cycles repeated every 3 weeks for a planned maximum of four cycles; Level 0, carboplatin AUC 5 mg/ml/min on day 1+nab-paclitaxel 100 mg/m<sup>2</sup> on days 1, 8, and 15 with treatment cycles repeated every 3 weeks for a planned maximum of three cycles). If two or less of the first six patients in level 1 experience nivolumab-induced grade 3–4 toxicity, an additional six patients will be enrolled to level 1. We will evaluate optimal doses and cycles of first-line chemotherapy with carboplatin plus nab-paclitaxel for a phase II study. The investigator will evaluate the grade of any adverse events before, during (until first 12 weeks), and after nivolumab monotherapy. In addition, the decision to administer nivolumab monotherapy will be made within 3–5 weeks after the end of first-line chemotherapy with carboplatin plus nab-paclitaxel. Evaluations of toxicity are based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE v4.0). Tumor response is also evaluated every month by Response Evaluation Criteria in Solid Tumors (RECIST) version. 1.1 criteria against the target lesion.

### Confidentiality

Clinical data is used for research purposes only. Results are kept anonymous and safe.

### Conflict of Interest

There is no conflict of interest to report for the researchers concerning this study.

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