

Nivolumab for the treatment of Japanese patients with advanced metastatic non-small cell lung cancer: a review of clinical trial evidence for efficacy and safety

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Abstract: Programmed cell death (PD)-1 immune checkpoint inhibitors have emerged as promising options for the treatment of multiple cancer types. Nivolumab is a fully human immunoglobulin G4 monoclonal antibody, which inhibits the PD-1 receptor and has been approved in the United States, Europe, and Asia for the treatment of advanced NSCLC. This review focuses on nivolumab's efficacy and safety in the treatment of NSCLC patients in Japan.

Keywords: Nivolumab, Non-small cell lung cancer, PD-1 inhibitor, Japanese

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Lung cancer, which currently claims more than 77,000 lives annually, has become the leading cause of cancer-related deaths in Japan.¹ Although molecular targeted therapies have been developed against mutations in epidermal growth factor receptor (*EGFR*), rearrangements in anaplastic lymphoma kinase (*ALK*) and *ROS1*, and the V600E mutation in *BRAF*, cytotoxic chemotherapy remains the mainstay treatment for advanced non-small-cell lung cancer (NSCLC) without driver mutations. Recently developed immune checkpoint inhibitors have revolutionized cancer therapy and are recognized as a novel treatment option for patients with advanced cancer.

Programmed cell death (PD)-1 immune checkpoint inhibitors have emerged as promising options for the treatment of multiple cancer types. These inhibitors bind to the PD-1 receptors expressed on T cells with high affinity and disrupt the inhibitory signaling induced by PD-ligand 1 (PD-L1) and PD-L2 to restore effector T cell function.² Nivolumab is a fully human immunoglobulin G4 monoclonal antibody that inhibits the PD-L1 receptor and has been approved for the treatment of patients with advanced NSCLC in the United States, Europe, and Japan.^{3,4} In two phase III studies, nivolumab monotherapy was

found to provide a statistically superior survival benefit compared with docetaxel,^{5,6} which is a second-line standard therapy in patients with advanced, previously treated NSCLC, although Asian patients were not virtually included in these two studies. Importantly, some of the responses were reported to persist after the discontinuation of treatment for reasons other than disease progression.^{7,8} Numerous studies have demonstrated the efficacy and tolerability of nivolumab in Caucasian patients with advanced NSCLC.^{9,10} This review focuses on the efficacy and safety of nivolumab in Japanese patients with advanced or recurrent NSCLC.

Phase I trials

Yamamoto and colleagues evaluated the safety, efficacy, tolerability, pharmacological activity, and pharmacokinetic profiles of single and multiple doses of nivolumab administered to 17 Japanese patients with malignant solid tumors.¹¹ The study included three, five, six, and three patients treated with 1, 3, 10, and 20 mg/kg nivolumab, respectively, and median age of the cohort was 61.0 (range, 34–74) years. Surgery, radiotherapy, chemotherapy, molecular targeted therapy, immunotherapy, and endocrine therapy were previously

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administered to 70.6%, 29.4%, 94.1%, 52.9%, 29.4%, and 23.5% of the patients, respectively. No dose-limiting toxicities (DLTs) were observed up to the highest nivolumab dose of 20 mg/kg. The most common adverse drug reaction was lymphopenia, which occurred in 10 (58.8%) patients, including 2 (11.8%) with grade 3 or worse adverse events (AEs). Other common adverse drug reactions included eosinophilia, pyrexia, hypoalbuminemia, rash, ventricular extrasystoles, fatigue, and hyperuricemia in eight (47.1%), six (35.3%), five (29.4%), five (29.4%), four (23.5%), four (23.5%), and four (23.5%) patients, respectively. There were no treatment-related deaths from the first nivolumab dose to the end of the follow-up period. Anti-nivolumab antibody titers based on tests conducted at the start and the end of the study were positive in 2 of the 17 patients; however, there were no serious allergic reactions reported in any of the patients. Mean $t_{1/2}$ of serum nivolumab ranged between 13 and 21 days, and the area under the receiving operating characteristic curve (AUC) increased from 1 to 20 mg/kg in a dose-proportional manner. At nivolumab doses of 1–10 mg/kg, C_{max} increased almost dose-proportionally; however, at nivolumab doses of 10–20 mg/kg, this increase was not dose-proportional. Based on the Response Evaluation Criteria in Solid Tumors guidelines (v1.0), complete response was observed in one patient (melanoma) treated with 3 mg/kg nivolumab, and partial response was observed in one patient in each of the 1 mg/kg (colorectal cancer) and 10 mg/kg (medullary thyroid cancer) cohorts.

Phase II trials

Nonsquamous NSCLC

In a multicenter phase II trial in Japan,¹² patients with advanced or recurrent nonsquamous NSCLC who developed progressive disease after platinum-containing chemotherapy were treated with 3 mg/kg nivolumab, which was administered intravenously every 2 weeks until progressive disease or unacceptable toxicity was observed. Primary endpoint was overall response rate (ORR) assessed by an independent radiology review committee, and secondary endpoints included investigator-assessed ORR, overall survival (OS), progression-free survival (PFS), duration of response, time to response, and safety. Across 19 sites in Japan, a total of 76 patients were enrolled in this study. The IRC-assessed ORR was 22.4% [95% confidence

interval (CI) 14.5–32.9], and the median PFS and OS were 2.8 (95% CI 1.4–3.4) and 17.1 (95% CI 13.3–23.0) months, respectively, and the OS rate at 1 year was 68.0% (95% CI 56.2–77.3). Importantly, the response to treatment in current/former smokers was better than that in nonsmokers (ORR 29.1% versus 4.8%). Patients with wild-type *EGFR* or unknown *EGFR* mutation status ($n = 56$) exhibited higher ORR than those with positive ($n = 20$) *EGFR* mutations (ORR 28.6% versus 5.0%). Additionally, PD-L1 expression was likely associated with higher ORR as well as longer OS and PFS. During the study, 64 patients (84.2%) experienced treatment-related AEs. Briefly, treatment-related AEs reported in $\geq 10\%$ of the patients included malaise ($n = 11$, 14.5%), pyrexia ($n = 11$, 14.5%), rash ($n = 11$, 14.5%), decreased appetite ($n = 11$, 14.5%), fatigue ($n = 9$, 11.8%), nausea ($n = 9$, 11.8%), and pruritus ($n = 8$, 10.5%). Computed tomography showed interstitial shadows in six patients and included interstitial lung disease ($n = 4$, 5.3%)¹³ and lung disorder ($n = 2$, 2.6%). AEs related to treatment and grade ≥ 3 were reported in 17 patients and were resolved with appropriate treatment, including steroid therapy or discontinuation of nivolumab. Therefore, nivolumab was well tolerated and showed clinical efficacy in Japanese patients with nonsquamous NSCLC progressed after platinum-containing chemotherapy, especially in those with a history of smoking, wild-type/unknown *EGFR* mutation status or positive PD-L1 expression.

Squamous NSCLC

A study including 35 patients from 17 sites in Japan evaluated nivolumab in squamous NSCLC.¹⁴ The IRC-assessed and study site-assessed ORR rates were 25.7% (95% CI 14.2–42.1) and 20.0% (95% CI 10.0–35.9), respectively. The median OS, median PFS, and median time to response were 16.3 (95% CI 12.4–25.4), 4.2 (95% CI 1.4–7.1), and 2.7 (range, 1.2–5.5) months, respectively. The IRC-assessed best overall response in 25.7%, 28.6%, and 45.7% of patients was partial response, stable disease, and progressive disease, respectively. Treatment-related AEs were reported in 24 patients (68.6%). Grade 3 treatment-related lymphocytopenia was observed in two patients (5.7%). Serious treatment-related AEs were interstitial lung disease in one patient (2.9%) and atrial fibrillation and pneumonitis in one patient (2.9%).¹⁵ Most of the treatment-related AEs

resolved with appropriate treatment, including discontinuation of nivolumab or steroid therapy. Therefore, nivolumab was effective and well tolerated in Japanese patients with advanced or recurrent squamous NSCLC that progressed following platinum-containing chemotherapy.

Combination therapy

Kanda and colleagues conducted a phase Ib study of combination therapy with nivolumab and standard chemotherapy in patients with advanced NSCLC.¹⁵ The study objectives were assessment of tolerability, safety, antitumor activity, and pharmacokinetics of combination therapy including nivolumab in patients with advanced NSCLC. The treatment arms were nivolumab (10 mg/kg) + gemcitabine/cisplatin (arm A), pemetrexed/cisplatin (arm B), paclitaxel/carboplatin/bevacizumab (arm C), and docetaxel (arm D). The regimens in arms A, B, and D were repeated every 3 weeks for up to four cycles, and the regimen in arm C was repeated for up to six cycles. In addition, nivolumab, either alone (arm A) or with pemetrexed (arm B), bevacizumab (arm C), or docetaxel (arm D), was administered every 3 weeks as maintenance therapy until unacceptable toxicity or disease progression. DLTs were evaluated during the first treatment cycle. The study enrolled six patients in each of the four arms for a total of 24 patients between April 2013 and March 2014. DLTs were observed in only one patient in arm A as an increase in alanine aminotransferase level. Therefore, all four treatment arms were regarded as tolerable. The increase in alanine aminotransferase that met the definition of a DLT resolved with discontinuation of the protocol treatment and did not require systemic corticosteroid therapy. The rates of hematological AEs of grade ≥ 3 were 16.7%, 16.7%, 100%, and 100% in arms A, B, C, and D, respectively. Conversely, the rates of non-hematological AEs of grade ≥ 3 were 66.7%, 66.7%, 0%, and 50% in arms A, B, C, and D, respectively. There were no treatment-related deaths. The rates of AEs leading to the discontinuation of nivolumab were 33.3%, 50%, 0%, and 50%, and those leading to the discontinuation of chemotherapy were 16.7%, 50%, 33.3%, and 50% in arms A, B, C, and D, respectively. The ORR rates were 50% in arm A, 50% in arm B, 100% in arm C, and 16.7% in arm D. The median PFS rates were 6.28, 9.63, and 3.15 in arms A, B, and D,

respectively, whereas it was not reached in arm C. Finally, the median times to response were 2.10, 2.17, 2.14, and 2.04 months in arms A, B, C, and D, respectively. In the study, 10 mg/kg nivolumab administered every 3 weeks plus standard chemotherapy was well tolerated in patients with advanced NSCLC. Additionally, other AEs observed during the study were acceptable. Although AEs specific to immune checkpoint inhibitors, such as toxicities of the skin, liver, gastrointestinal system, lungs, endocrine system, and kidneys, as well as infusion reaction, were observed in some patients, most of these events were grade 1 or 2. Therefore, this study provided evidence for the safety and potential antitumor activity of the combination therapy in Japanese patients with advanced NSCLC.

Approval of nivolumab in Japan

On December 17, 2015, nivolumab was approved for advanced squamous and nonsquamous NSCLC after chemotherapy. According to the Japan Lung Cancer Society guidelines, nivolumab is the preferred agent for the treatment of advanced NSCLC without sensitizing *EGFR* mutations or *ALK* rearrangements in patients with an Eastern Cooperative Oncology Group performance status of 0–2 whose disease progressed after first-line chemotherapy. Nivolumab was approved for treatment irrespective of PD-L1 expression.

In conclusion, nivolumab has superior efficacy compared with docetaxel, and responses to nivolumab appeared long-lasting, even beyond treatment cessation. Compared with cytotoxic chemotherapy, nivolumab-associated toxicities were generally more acceptable and manageable. With additional clinical trials under way, it is expected that nivolumab will become increasingly important in the treatment of NSCLC patients.

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Conflict of interest statement

The author declares that there is no conflict of interest.

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