Efficacy and safety of nivolumab in Japanese patients with advanced or recurrent squamous non-small cell lung cancer

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Limited treatment options are available for stage IIIIB/IV non-small cell lung cancer (NSCLC). Nivolumab, a programmed cell death-1 immune checkpoint inhibitor antibody, has been shown to be effective for the treatment of NSCLC. The present study investigated the effectiveness and safety of nivolumab in Japanese patients with advanced or recurrent squamous NSCLC that progressed after platinum-containing chemotherapy. In this multicenter phase II study, patients were treated with nivolumab (3 mg/kg, i.v.) every 2 weeks until progressive disease or unacceptable toxicity was seen. Primary endpoint was overall response rate (ORR) assessed by independent radiology review committee (IRC) and secondary endpoints included a study site-assessed ORR, overall survival (OS), progression-free survival (PFS), duration of response, time to response, best overall response (BOR), and safety. The study included 35 patients from 17 sites in Japan. Patients had IRC-assessed ORR of 25.7% (95% CI 14.2, 42.1) and the study site-assessed ORR was 20.0% (95% CI 10.0, 35.9). Median OS, median time to response and median PFS were 16.3 (95% CI 12.4–25.4), 2.7 (range 1.2–5.5) and 4.2 (95% CI 1.4–7.1) months, respectively. The IRC-assessed BOR was partial response, stable disease, and progressive disease for 25.7%, 28.6%, and 45.7% of patients, respectively. Treatment-related adverse events were reported in 24 patients (68.6%), most of which resolved with appropriate treatment including steroid therapy or discontinuation of nivolumab. Nivolumab was effective and well tolerated in Japanese patients with advanced or recurrent squamous NSCLC that progressed after platinum-containing chemotherapy. Clinical trial registration number: JapicCTI-132072

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It has been shown that combination chemotherapy as second-line treatment in NSCLC improves the overall response rate (ORR) and PFS compared with single-agent chemotherapy. However, combination chemotherapies have failed to improve overall survival (OS) in these patients and have been associated with more adverse events (AE) than single-agent therapy. Therefore, there is an unmet need for newer agents with better efficacy and safety.

Programmed cell death-1 (PD-1) is a receptor present on cytotoxic T cells which binds to its natural ligands PD ligand-1 (PD-L1) and PD ligand-2 (PD-L2) and is activated in response to inflammation or infection. Binding of PD-L1 to its receptor causes deactivation of T cells leading to immunosuppression. Expression of PD-L1 in NSCLC generates an immunosuppressive tumor microenvironment and promotes

Lung cancer is one of the leading causes of cancer-related death worldwide. Non-small cell lung cancer (NSCLC) accounts for up to 85% of lung cancers and is classified based on histology as either squamous or non-squamous cell carcinoma. Squamous NSCLC accounts for approximately 30% of NSCLC cases. Guidelines recommend using combination therapy for the first-line treatment of patients with stage IIIIB/IV squamous NSCLC unsuited to radical radiotherapy, consisting of a platinum agent plus a third-generation agent such as carboplatin/paclitaxel or cisplatin/gemcitabine. As for second-line therapy, docetaxel has been a standard treatment in patients with squamous NSCLC for more than a decade, with a median progression-free survival (PFS) of 2.7 months and median overall survival of 7.4 months. It has been shown that combination chemotherapy as second-line treatment in NSCLC improves the overall response rate (ORR) and PFS compared with single-agent chemotherapy. However, combination chemotherapies have failed to improve overall survival (OS) in these patients and have been associated with more adverse events (AE) than single-agent therapy. Therefore, there is an unmet need for newer agents with better efficacy and safety.

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Table 1. Demographic and baseline characteristics of patients included in the present study

| Characteristic                      | N = 35 |
|-------------------------------------|--------|
| Age, years                          | 65.0   |
| Range                               | 31–85  |
| <65, n (%)                          | 15 (42.9)|
| ≥65, n (%)                          | 20 (57.1)|
| Gender, n (%)                       | 32 (91.4)|
| Male                                | 3 (8.6) |
| ECOG performance status, n (%)      | 18 (51.4)|
| 0                                   | 17 (48.6)|
| Disease stage, n (%)                | 6 (17.1)|
| IIB                                 | 24 (68.6)|
| IV                                  | 5 (14.3)|
| Recurrent                           | 3 (8.6) |
| Brain metastasis, n (%)             | 32 (91.4)|
| Yes                                 | 33 (94.3)|
| No                                  | 2 (5.7) |
| Smoking status, n (%)               | 1 (2.9) |
| Never smoked                        | 29 (82.9)|
| Former smoker                       | 5 (14.3)|
| Prior systemic regimens, n (%)      | 35 (100.0)|
| Platinum-based therapy              | 17 (48.6)|
| Carboplatin                         | 16 (45.7)|
| Cisplatin                           | 2 (5.7) |
| Nedaplatin                          | 2 (5.7) |
| EGFR-TKI                            | 2 (5.7) |
| Erlotinib                           | 2 (5.7) |

ECOG, Eastern Cooperative Oncology Group; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.

tumor immune escape, thus leading to poor prognosis of the disease.11

Nivolumab is a fully human immunoglobulin G4 monoclonal antibody, which inhibits the PD-1 receptor and has been approved in the USA, EU and Japan for the treatment of advanced NSCLC.12,13 Studies have demonstrated the efficacy and tolerability of nivolumab in Caucasian patients with advanced NSCLC.14-16 The aim of the present study was to investigate the efficacy and safety of nivolumab in Japanese patients with advanced or recurrent squamous NSCLC that progressed after platinum-containing chemotherapy.

Materials and Methods

Study design. This was a multicenter, open-label phase II study (Fig. S1a). The study protocol was reviewed and approved by the institutional review board of each study site before the study and the study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. The data cut-off date was 17 December 2015. Clinical trial registration number: JapicCTI-132072.

Patients enrolled in this study were aged ≥20 years, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and had histologically or cytologically confirmed squamous NSCLC, stage IIIIB/IV disease (according to UICC-TNM classification [7th edition])17 or recurrent NSCLC after surgical resection. Further inclusion criteria included: (i) ≥1 measurable lesion by RECIST guideline (version 1.1); (ii) a history of prior treatment of at least one regimen of platinum-containing chemotherapy; (iii) percutaneous oxygen saturation (SpO2) ≥94%; and (iv) adequate organ function. Patients were excluded if they had hypersensitivity to antibody products, a history of autoimmune disease and interstitial lung disease or pulmonary fibrosis, were treated with any systemic corticosteroid or immune suppressant in the last 28 days, or had active diverticulitis or symptomatic gastrointestinal ulcerative disease.

Nivolumab 3 mg/kg was given i.v. every 2 weeks in each 6-week cycle until progressive disease (PD) or unacceptable toxicity was observed. At the end of each cycle, patients underwent diagnostic imaging and patients who met the criteria for the start of the next cycle continued the treatment. Criteria for the start of the next cycle were: (i) no ≥grade 3 AE; (ii) no ≥grade 2 increase in aspartate aminotransferase, alanine aminotransferase, or total bilirubin from baseline (for which a causal relationship with nivolumab cannot be ruled out); and (iii) no occurrence of an autoimmune disease, as indicated by signs/symptoms or general laboratory test data. Patients who met at least one of the criteria for discontinuation discontinued treatment and moved to the follow-up period; criteria for discontinuation included: tumor response of PD according to the RECIST guideline (version 1.1); aggravation of clinical symptoms caused by disease progression; ≥grade 2 interstitial lung disease; ≥grade 2 eye pain or reduced visual acuity which did not resolve to ≥grade 1 with local treatment for which a causal relationship with nivolumab could not be ruled out; or ≥grade 3 bronchospasm, hypersensitivity reaction, injection reaction, or uveitis, for which a causal relationship with nivolumab could not be ruled out. Patients were allowed to continue

Table 2. Tumor response and survival in patients with advanced squamous NSCLC treated with nivolumab

| Study site assessed | Best overall response | Overall survival | Time to response |
|---------------------|-----------------------|------------------|-----------------|
| IRC assessed        | n (%)                 | ORR (CR + PR), % (95% CI) | Rate at 1 year, % (95% CI) | Rate at 1 year, % (95% CI) | Median, months (95% CI) |
|                     |                       |                  |                 |                         |                          |
| Nivolumab 3 mg/kg   | 22.9                  | 25.7 (14.2, 42.1) | 71.4 (53.4, 83.5) | 4.2 (1.4, 7.1) | 24.5 (10.7, 41.3) |
| IV                  | 29.3                  | 16.3 (12.4, 25.4) | 94%             | 1.7–29.3†          | NR (3.0–22.9)†          |
|                   |                       |                  |                  |                          |                          |
| Study site          |                       |                  |                  |                          |                          |
|                     | Complete response     | 0 (0.0)          | 0 (0.0)          | 0.6–25.5†            |                          |
|                     | Partial response      | 9 (25.7)         | 7 (20.0)         | 1.7–29.3†          |                          |
|                     | Stable disease        | 10 (28.6)        | 10 (28.6)        | 1.7–29.3†          |                          |
|                     | Progressive disease   | 16 (45.7)        | 18 (51.4)        | 1.7–29.3†          |                          |
|                     | ORR (CR + PR), % (95% CI) | 25.7 (14.2, 42.1) | 20.0 (10.0, 35.9) | 4.2 (1.4, 7.1) | 24.5 (10.7, 41.3) |

†Censored value.

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treatment after initial disease progression if they had gained clinical benefit from the treatment without any unacceptable treatment-related AE, as reported by the investigator. Treatment-related AE were followed up every 2 weeks until these events resolved, were resolving, or had stabilized. Laboratory tests and diagnostic imaging were repeated as necessary to ensure patient safety.

**Efficacy assessments.** The primary efficacy endpoint was independent radiology review committee (IRC)-assessed confirmed ORR, evaluated based on tumor response assessed according to RECIST guidelines (version 1.1). Secondary endpoints included study site-assessed confirmed ORR, OS, PFS, duration of response (DOR), time to response, best overall response (BOR), and change in tumor size. ORR was calculated as the proportion of patients with a BOR of complete response (CR) or partial response (PR).

**Safety assessments.** Adverse events were evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Select AE (those with a potential immunological cause) were grouped according to pre-specified categories.

**Subgroup analysis.** A pre-specified subgroup analysis for ORR and a post-hoc subgroup analysis for OS and PFS were carried out to determine the association between these efficacy variables and the patient age, gender, ECOG performance status, brain metastasis, disease stage and smoking status.

**Biomarker analysis.** Tumor PD-L1 expression was assessed retrospectively in pretreatment (archival or recent) tumor-biopsy specimens using a validated, automated immunohistochemical assay (Dako North America Santa Clara, CA, USA) that used a rabbit anti-human PD-L1 antibody (clone 28-8; Epitomics Cambridge, MA, USA). Tumor PD-L1 expression was confirmed when the tumor-cell membranes were stained (at any intensity) at predetermined expression levels of ≥1%, ≥5%, and ≥10% in a section that included at least 100 tumor cells that could be evaluated.

**Statistical analysis.** The expected response rate for nivolumab was set at 26%. Assuming a threshold response rate of 9% for nivolumab, 30 patients were needed in order to ensure a power of ≥80% at a one-sided significance level of 0.025 in binominal tests (normal approximation). If a tumor response is achieved in at least six of 30 patients, the null hypothesis is rejected. To allow for several non-evaluable patients, 35 patients were planned to be enrolled in the study.

Baseline characteristics of patients enrolled in the study were summarized using frequency distributions and summary statistics. Primary efficacy and safety analyses were conducted in all patients who received at least one dose of nivolumab.
Table 3. Incidence of treatment-related adverse events (AE) reported in ≥5% of study patients and treatment-related select AE (N = 35)

| Treatment-related adverse events, n (%) | All grades | Grade 3 or higher |
|----------------------------------------|------------|-------------------|
| Total                                  | 24 (68.6)  | 2 (5.7)           |
| Malaise                                | 5 (14.3)   | 0 (0.0)           |
| Pyrexia                                | 5 (14.3)   | 0 (0.0)           |
| Rash                                   | 5 (14.3)   | 0 (0.0)           |
| Decreased appetite                     | 5 (14.3)   | 0 (0.0)           |
| Diarrhea                               | 3 (8.6)    | 0 (0.0)           |
| Lymphocyte count decreased             | 3 (8.6)    | 2 (5.7)           |
| Nausea                                 | 3 (8.6)    | 0 (0.0)           |
| Anemia                                 | 2 (5.7)    | 0 (0.0)           |
| Arthralgia                             | 2 (5.7)    | 0 (0.0)           |
| Aspartate aminotransferase increased   | 2 (5.7)    | 0 (0.0)           |
| Blood creatine phosphokinase increased | 2 (5.7)    | 0 (0.0)           |
| Dermatitis acneiform                   | 2 (5.7)    | 0 (0.0)           |
| Erythema                               | 2 (5.7)    | 0 (0.0)           |
| Hypersensitivity                       | 2 (5.7)    | 0 (0.0)           |
| Hypoalbuninemia                        | 2 (5.7)    | 0 (0.0)           |
| Edema peripheral                       | 2 (5.7)    | 0 (0.0)           |
| Peripheral sensory neuropathy          | 2 (5.7)    | 0 (0.0)           |
| Pulmonary hemorrhage                   | 2 (5.7)    | 0 (0.0)           |
| Rash maculopapular                     | 2 (5.7)    | 0 (0.0)           |
| Autoimmune thyroiditis                 | 2 (5.7)    | 0 (0.0)           |

Table 4. Subset analysis for independent radiology review committee-assessed overall response rate by baseline characteristics of patients

| Baseline characteristics | No. responders (n/N) | ORR (%) | 95% CI | Odds ratio† | 95% CI |
|-------------------------|----------------------|---------|--------|-------------|--------|
| Age, years              |                      |         |        |             |        |
| <65                     | 2/15                 | 13.3    | 3.7, 37.9 | 0.29 0.05, 1.64 |
| ≥65                     | 7/20                 | 35.0    | 18.1, 56.7 |
| Gender                  |                      |         |        |             |        |
| Male                    | 9/32                 | 28.1    | 15.6, 45.4 | NA NA NA |
| Female                  | 0/3                  | 0       | 0.0, 56.1 | NA NA NA |
| ECOG performance status |                      |         |        |             |        |
| 0                       | 6/18                 | 33.3    | 16.3, 56.3 | 2.33 0.48, 11.40 |
| 1                       | 3/17                 | 17.6    | 6.2, 41.0 |
| Brain metastasis        |                      |         |        |             |        |
| Yes                     | 0/3                  | 0       | 0.0, 56.1 | 0.0 NA NA |
| No                      | 9/32                 | 28.1    | 15.6, 45.4 |
| Disease stage           |                      |         |        |             |        |
| III B                   | 0/6                  | 0       | 0.0, 39.0 | - - - |
| IV                      | 6/24                 | 25.0    | 12.0, 44.9 |
| Recurrent               | 3/5                  | 60.0    | 23.1, 88.2 |
| Smoking status†         |                      |         |        |             |        |
| Yes                     | 8/34                 | 23.5    | 12.4, 40.0 |
| No                      | 1/1                  | 100     | 20.7, 100.0 | 0.0 NA NA |

AE and grade observed since the start of the first dose of nivolumab and 28 days after the last dose or the start of subsequent anti-cancer therapy after the last dose, whichever comes first, are tabulated.

Results

The study enrolled 35 patients from 17 sites in Japan (Fig. 1b). The majority of patients were male (91.4%), had no brain metastasis (91.4%), had undergone one prior systemic regimen (94.3%) and were current/former smokers (97.1%; Table 1). During the study, a median of eight doses of nivolumab were given (range 2-62) and 11 patients received >12 doses. The median duration of therapy was 3.6 months (range 0.5-29.3) and the median overall survival was 16.3 months (range 1.7-29.3). After discontinuation of treatment, 68.6% of the patients received subsequent systemic cancer therapy. 48.6% of the patients received subsequent docetaxel (Table S1).

Efficacy. Nine patients had IRC-assessed response to treatment, resulting in an ORR of 25.7% (95% CI 14.2, 42.1) and seven patients had study site-assessed response to treatment with an ORR of 20.0% (95% CI 10.0, 35.9; Table 2). IRC-assessed BOR was PR for nine patients (25.7%), SD for 10 patients (28.6%), and PD for 16 patients (45.7%; Table 2, Fig. 1c). Study site-assessed BOR was PR for seven patients (20.0%), SD for 10 patients (28.6%), and PD for 18 patients (51.4%).

The lower limit of the 95% CI of the ORR with nivolumab exceeded the threshold response rate of 9% which was based on the ORR (8.8%) for docetaxel.(18) Kaplan-Meier plots for OS and PFS are shown in Figure 1a and b. The median OS with nivolumab treatment was 16.3 months (95% CI 12.4, 25.4) and the OS rate at 1 year was 71.4% (95% CI 53.4, 83.5). The median IRC-assessed PFS was 4.2 months (95% CI 1.4, 7.1) and the median site-assessed PFS was 2.7 months (95% CI 1.5, 5.6). The median DOR has not been reached (range 3.0-22.9). The median time to response was 2.7 months (range 1.2-5.5) in the nine patients who responded to study treatment. A change in tumor size (tumor shrinkage) was seen in more than half of the study population and the antitumor effect of nivolumab was sustained for a long period of time in these patients (Fig. 1d).

Safety. Treatment-related AE were reported in 24 patients (68.6%). The incidence of treatment-related AE of all grades and ≥Grade 3 reported in ≥5% of patients is shown in Table 3. Grade 3 treatment-related AE included decreased lymphocyte count (2 patients, 5.7%), and no ≥Grade 3 treatment-related select AE were reported. Serious treatment-related AE occurred in two patients (5.7%); one patient experienced both atrial fibrillation and pneumonitis (2.9%) and one patient experienced interstitial lung disease (2.9%) (Table S2). An article discussing clinical findings and imaging characteristics of pneumonitis and interstitial lung disease cases reported in the present study has been published.(19)
Treatment-related AE led to treatment interruption in six patients (17.1%), of which three patients (8.6%) discontinued treatment as a result of secondary adrenocortical insufficiency, hypersensitivity, and interstitial lung disease (n = 1; 2.9% each) (Table S3). There were no deaths as a result of AE during the study. However, one patient died of respiratory failure which occurred 31 days after the last dose of nivolumab without resolution of pneumonitis, after docetaxel treatment was initiated following nivolumab discontinuation. This event was not included in the analysis as it occurred beyond 28 days after the last dose or shortly after starting post-study treatment after the last dose.

**Subgroup analysis.** The post-hoc subgroup analysis indicated an association between ORR, OS, and PFS and patient age, gender, ECOG performance status, brain metastasis, disease stage and smoking status (Table 4; Table S4). The correlation between response and OS was also examined. The OS at 24 months was 74.1% in the PR (n = 9) group, 15.0% in the SD (n = 10) group and 31.3% in the PD (n = 16) group (Fig. S2). Median OS of patients with CR/PR, SD and PD with nivolumab treatment was 27.5 months, 15.3 months and 12.8 months, respectively. Patients who responded to nivolumab treatment (n = 9) included those aged ≥70 years (n = 4), with an ECOG performance status of 1 (n = 3) and never smoked (n = 1) (Table S5).

**Biomarker analysis.** Of the 35 patients included in the study, 19 (54.3%) had a tumor tissue specimen collected at baseline, all of which had quantifiable PD-L1 levels. Of these 19 patients, 78.9%, 68.4% and 57.9% of patients were positive for PD-L1 expression of 1%, 5% and 10%, respectively. Although the subgroup analysis showed that the ORR and PFS outcomes were greater for PD-L1-positive patients, no significant association between the PD-L1 expression levels and the efficacy outcomes was determined (Table 5).

**Discussion**

The present study demonstrated that nivolumab was effective and safe in Japanese patients with advanced or recurrent squamous NSCLC. In the present study, nivolumab was associated with an ORR of 25.7%, a median OS of 16.3 months, and a median PFS of 4.2 months. The IRC-assessed BOR was PR for nine patients (25.7%), SD for 10 patients (28.6%), and PD for 16 patients (45.7%). The results of present study are consistent with those observed in the phase III randomized controlled CheckMate 017 trial that compared the efficacy of nivolumab with docetaxel in a Caucasian population with advanced squamous NSCLC. The ORR of nivolumab was 20% (27/135 patients) [95% CI 14, 28] and the median PFS was 3.5 months (95% CI 2.1, 4.9). Median OS was 9.2 months (95% CI 7.3, 13.3) with nivolumab compared with 6.0 months (95% CI 5.1, 7.3) with docetaxel, indicating superiority of nivolumab over docetaxel. Furthermore, nivolumab also reduced the risk of death by 41% compared with docetaxel (hazard ratio 0.59, 95% CI 0.44, 0.79). Other studies of nivolumab have also shown similar ORR and PFS in previously treated patients with advanced squamous NSCLC. In summary, the present study highlights the effectiveness of nivolumab in the treatment of Japanese patients with advanced or recurrent squamous NSCLC that progressed after platinum-containing chemotherapy.

Nivolumab was well tolerated in this study; treatment-related AE were reported in 68.6% of patients. The most common treatment-related AE were malaise, pyrexia, rash, decreased appetite, diarrhea, lymphocyte count decreased, and nausea. Serious treatment-relates AE were atrial fibrillation (n = 1, 2.9%), interstitial lung disease (n = 1, 2.9%), and pneumonitis (n = 1, 2.9%). Atrial fibrillation resolved with appropriate treatment and interstitial lung disease resolved with steroid pulse therapy. The AE reported in this study were consistent with those observed in previous trials of nivolumab in patients with advanced NSCLC. The PD-L1 expression is considered as a potential predictive biomarker in patients with NSCLC. In the CheckMate 017 trial, a PD-L1 subgroup analysis indicated that tissue PD-L1 expression is neither a prognostic nor predictive factor for nivolumab in squamous NSCLC. The OS was significantly longer with nivolumab than with docetaxel regardless of PD-L1 status. In addition, there was no clear association between OS and ORR stratified by PD-L1 expression at different cut-off levels (1%, 5% and 10%). The efficacy profile of nivolumab stratified by PD-L1 expression status in our study coincided with the CheckMate 017 study, with no clear association between the efficacy of nivolumab with PD-L1 expression status.

There are a few limitations to the present study, including the relatively small sample size and the absence of a comparator group. Also, the lack of heterogeneity in the characteristics of the patients (mostly male, relatively older population) may influence the results of this study.

The results of the present study are in line with the outcomes of the CheckMate 017 study and demonstrate that...
nivolumab is associated with clinical efficacy and manageable tolerability in Japanese patients with advanced or recurrent squamous NSCLC progressed after platinum-containing chemotherapy, which is expected to be clinically useful. Early diagnosis and treatment of treatment-related AE can ensure safety during treatment.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Subsequent cancer therapy

Table S2. Treatment-related serious adverse events reported in patients treated with nivolumab (N = 35)

Table S3. Treatment-related adverse events leading to discontinuation of nivolumab (N = 35)

Table S4. Subset analysis for (a) independent radiology review committee-assessed progression-free survival and (b) overall survival by baseline characteristics of patients

Table S5. Baseline characteristics of patients who responded to nivolumab treatment

Fig. S1. (a) Overall study design and (b) patient disposition during the study.

Fig. S2. (a) Progression-free survival and (b) overall survival in patients with nivolumab treatment based on best overall response (BOR).