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Nivolumab in advanced non-small-cell lung cancer patients who failed prior platinum-based chemotherapy

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ABSTRACT

Objectives: To investigate the efficacy and safety of nivolumab in Korean patients with stage IIIB/IV or recurrent non-small-cell lung cancer (NSCLC) who failed platinum-based chemotherapy.

Materials and methods: In this multicenter, open-label, Phase II study, 100 patients with stage IIIB or IV squamous (n = 44) or non-squamous (n = 56) NSCLC received nivolumab 3 mg/kg every 2 weeks for 6 weeks per treatment cycle. Patients continued treatment until disease progression or intolerable adverse events (AEs), and then entered a follow-up phase. The primary efficacy endpoint was the centrally assessed objective response rate (ORR).

Results: The ORR was 20.0% (95% confidence interval [CI]: 13.3–28.9%) in the total population, 15.9% (7/44 patients; 95% CI: 7.9–29.4%) in patients with squamous NSCLC, and 23.2% (13/56 patients; 95% CI: 14.1–35.8%) in patients with non-squamous NSCLC. Median overall survival was 13.9 (95% CI: 10.8–18.5) months in the total population, 12.3 (95% CI: 8.2–18.5) months in squamous NSCLC, and 16.3 (95% CI: 10.8, −) months in non-squamous NSCLC. Median progression-free survival was 2.8 (95% CI: 1.4–5.7), 2.6 (95% CI: 1.3–5.7), and 5.3 (95% CI: 1.4–7.1) months in the total, squamous, and non-squamous NSCLC populations, respectively. The median duration of response was 11.7 (95% CI: 5.6, −), 12.0 (95% CI: 4.8, −), and 12.1 (95% CI: 3.0, −) months in the total, squamous, and non-squamous NSCLC populations, respectively. The most frequent AEs were decreased appetite, dyspnea, and cough in 43 (43.0%), 32 (32.0%), and 29 (29.0%) patients, respectively. The most common Grade ≥3 AE was pneumonia, occurring in 7.0% of patients. Common treatment-related AEs included decreased appetite (14.0%) and pruritus (6.0%), neither of which was Grade ≥3.

Conclusion: The efficacy and safety of nivolumab in Korean patients with advanced or recurrent squamous or non-squamous NSCLC are consistent with previous reports.

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small-cell lung cancer; OR, objective response; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed death-1; PD-L1, programmed death ligand1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TKI, tyrosine kinase inhibitor

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1. Introduction

Non-small-cell lung cancer (NSCLC) accounts for 85% of all lung cancers, of which around 70% are non-squamous [1,2]. In Korea in 2013, there were 24,027 new cases of lung cancer and 17,399 deaths from lung cancer [3]. Lung cancer was the third most common cancer in men and the fifth most common cancer in women, and the leading cause of death in both sexes [3].

The National Comprehensive Cancer Network Guidelines recommend a platinum agent plus a third-generation anticancer agent as first-line drug treatment for patients with stage IIIB/IV NSCLC negative for epidermal growth factor receptor (*EGFR*) mutation and *EML4–ALK* translocation, and an EGFR tyrosine kinase inhibitor (TKI) or anaplastic lymphoma kinase (ALK) TKI, such as erlotinib or crizotinib, in NSCLC positive for an *EGFR* mutation or *EML4–ALK* translocation [4].

However, survival rates with a platinum agent and a third-generation anticancer agent remain low, with median progression-free survival (PFS) of 4.5–6.2 months and median overall survival (OS) of 10.3–12.3 months [5,6]. Docetaxel has been approved for second-line treatment in patients with disease progression after first-line chemotherapy, but the survival rates are also low in docetaxel-treated patients with resistance to first-line therapies [7,8], with a median OS of 32.6–40.0 weeks [7] and a median PFS of 2.9 months [8]. Newer second-line agents, such as pemetrexed and erlotinib, despite having more favorable side-effect profiles than docetaxel, provide no benefit over docetaxel in terms of overall survival [8,9]. It is clear that new treatment options are urgently needed for patients with refractory NSCLC.

The programmed death 1 (PD-1) receptor is expressed on activated T cells. By binding to its ligands PD-L1 and PD-L2, which are expressed on tumors, it downregulates T-cell activation and promotes the ability of tumors to escape detection by the immune system [10].

Nivolumab, developed by Ono Pharmaceutical Co., Ltd., and Bristol-Myers Squibb, is a fully human IgG4 PD-1 antibody, which blocks PD-1–mediated signaling [11–13] and may help restore the body's anti-tumor immunity. Early trials have shown promising effects of nivolumab on survival in all NSCLC subtypes regardless of PD-L1 expression [11,14].

Two recent trials, CheckMate 017 and 057 [15,16], demonstrated longer OS with nivolumab than with docetaxel among patients with advanced squamous or non-squamous NSCLC that had progressed during or after platinum-based chemotherapy. However, as in most clinical trials of immunotherapy with checkpoint inhibitors, the majority of enrolled patients were Caucasians, and few minorities, particularly Asians, were represented, despite the huge burden of lung cancer in Asia. Specifically, Asians represented only 2–3% of the populations of CheckMate 017 and 057 [15,16]. In this study, we investigated the efficacy and safety of nivolumab in Korean patients with stage IIIB/IV or recurrent squamous or non-squamous NSCLC resistant to platinum-based chemotherapy.

2. Methods

2.1. Patient selection

Eligible patients had histologically or cytologically confirmed stage IIIB or IV NSCLC that was unsuited to radical radiotherapy according to the Union for International Cancer Control-TNM classification (7th edition), or recurrent NSCLC. Patients had at least one measurable lesion and a history of prior treatment with any of the following systemic anticancer agents:

- Platinum-based chemotherapy and up to one prior treatment regimen for patients negative for or with unknown *EGFR* activation mutations or *ALK* gene translocation.
- Platinum-based chemotherapy and an EGFR TKI, and up to two prior treatment regimens, for patients with *EGFR* activation mutations.
- Platinum-based chemotherapy and an ALK inhibitor, and up to two prior treatment regimens, for patients with *ALK* gene translocation.

All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Patients with metastases to the brain or meninges were included in the study if the metastatic lesions were asymptomatic and did not require treatment.

Patients with active autoimmune disease, history of chronic or recurring autoimmune disease, current or prior interstitial lung disease, or pulmonary fibrosis were excluded. Immunosuppressants, anticancer agents (e.g., chemotherapy, molecular targeted therapy, or immunotherapy), surgery for cancer, radiotherapy, radiopharmaceuticals, transplant therapy, and any other investigational product were prohibited for the duration of the trial. Conditional administration of corticosteroids was allowed for adverse event (AE) management.

2.2. Study design and treatment

The open-label, prospective, single-arm Phase II study was performed in 10 centers in Korea (Trial registration: ClinicalTrial.gov, identifier NCT02175017).

In each treatment cycle, patients received an intravenous infusion of nivolumab at a dose of 3 mg/kg every 2 weeks for 6 weeks. Changes in dose were not allowed. Radiological assessments (computed tomography/magnetic resonance imaging) were conducted every 6 weeks. Patients entered subsequent treatment cycles unless they met discontinuation criteria, including disease progression, unacceptable AEs, and consent withdrawal. Patients who were discontinued for any of these reasons entered the follow-up phase.

Nivolumab could be continued in patients with progressive disease with agreement from the sponsor if there was no worsening of clinical symptoms attributable to disease progression, continued treatment was expected to provide a clinical benefit, nivolumab could continue to be safely administered, and the patient and investigator agreed to continue treatment.

Based on previous trials [15–20], repeated intravenous treatment with 3 mg/kg nivolumab with a 2-week dosing interval was selected as the recommended clinical dosage for NSCLC.

Follow-up to determine survival status was performed every 6 months after the first day of treatment of the last patient enrolled in the study.

2.3. Endpoints

The primary efficacy endpoint was the centrally assessed objective response rate (ORR), which was calculated as (Number of patients whose confirmed best objective response is complete response [CR] or partial response [PR]/Total number of patients) × 100.

The secondary efficacy endpoints were the investigator-assessed ORR, OS, centrally assessed and investigator-assessed PFS, duration of response, best objective response, and percent change in tumor diameter.

Objective responses were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST criteria, Version 1.1) [21].

Safety was assessed in terms of AEs and treatment-related AEs, which were graded in severity from 1 to 5 based on the Common Terminology Criteria for Adverse Events (Version 4.0) [22].

Anti-nivolumab antibodies were assessed to determine immunogenicity of nivolumab which could potentially lead to loss of efficacy and safety concerns. Using the electrochemiluminescence immunosorbent assay method, anti-nivolumab antibodies were detected up to 1 year after the start of investigational product administration (up to Cycle 9). Assays for anti-nivolumab antibodies were performed at an arbitrary time between 6 and 12 weeks after the final investigational

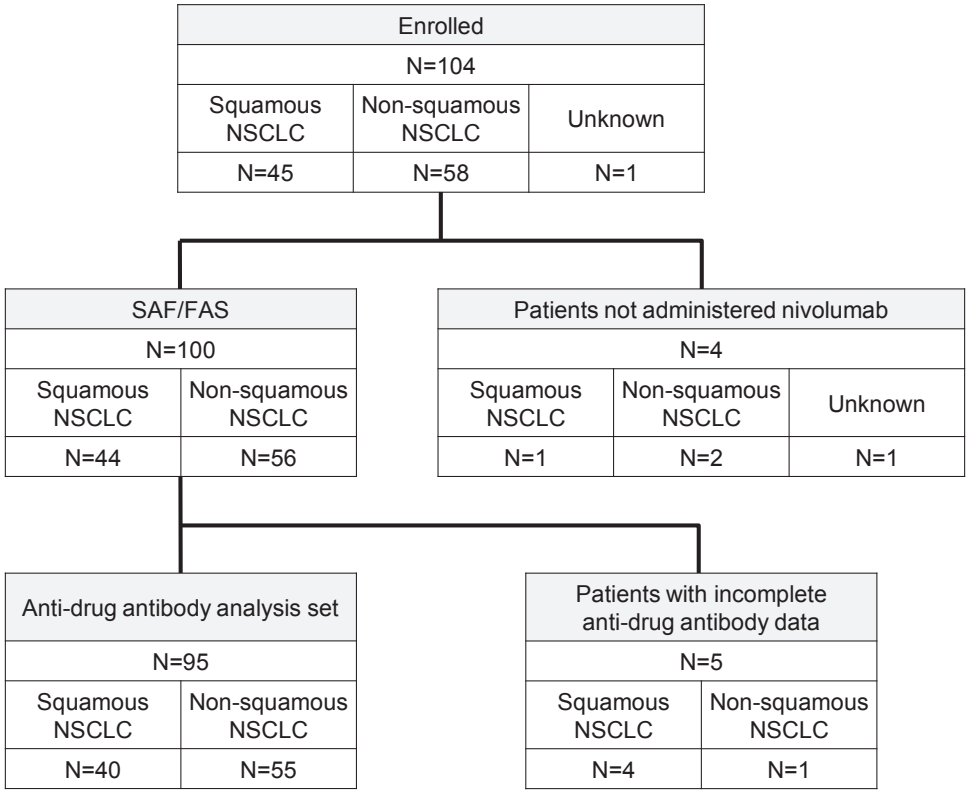

Fig. 1. Patient disposition.
FAS, full analysis set; NSCLC, non-small cell lung cancer; SAF, safety analysis set.

product dose, if feasible. Patients with two or more samples collected at consecutive time points after the first dose of the investigational product and testing positive for anti-nivolumab antibodies with a minimum interval of 16 weeks between the first and last positive samples were considered to be persistently positive for anti-nivolumab antibodies.

A post-hoc analysis was conducted to evaluate ORR in subgroups of patients, including those with ECOG status 0 versus 1; with versus without central nervous system metastases; with versus without an *EGFR* mutation; and in current/former smokers versus never smokers.

2.4. Ethics and study oversight

The institutional review board of each participating center approved the study, and all patients provided informed consent. The study was conducted in line with the ethical principles that have their origin in the Declaration of Helsinki.

2.5. Statistical methods

The sample size was set based on an assumption of a threshold response rate of 8.8% with docetaxel [8] and an expected response rate of 23.1% and 21.4% for patients with squamous NSCLC and patients with non-squamous NSCLC, respectively, with nivolumab. Therefore, 41 patients with squamous NSCLC and 52 patients with non-squamous NSCLC were expected to provide a statistical power of ≥80% in a binomial test (normal approximation) with a one-sided significance level of 2.5% (two-sided significance level of 5.0%).

The centrally assessed ORR and its 95% confidence interval (CI) (Wilson's method) were calculated, and the results were summarized for the total population and in patients stratified by NSCLC type (squamous versus non-squamous).

The investigator-assessed ORR and its 95% CI (Wilson's method) were also calculated.

OS and PFS were plotted using Kaplan–Meier curves, which were used to determine the median OS and PFS with 95% CIs. The OS rate at 6 and 12 months and PFS rates at 3, 6, and 12 months with 95% CIs were determined using the Kaplan–Meier method. The OS and PFS rates with 95% CIs at 18 months were assessed as part of a post-hoc analysis.

The median and its 95% CI for the duration of response were estimated by the Kaplan–Meier method.

Subgroup analyses (according to anti-nivolumab antibody status and presence/absence of brain metastases) were predefined for the analysis of ORR, and were performed post hoc for the analyses of PFS and OS.

The results of all analyses are presented for the total population and for patients with squamous NSCLC and non-squamous NSCLC separately.

Statistics were performed using SAS/STAT (SAS Inc., Cary, NC, USA).

The statistical analysis plan was refined as follows before the database was locked. The definition of the enrolled set was added to the statistical analysis plan. The diameter of target lesions was originally intended to be analyzed as a baseline characteristic, but was instead evaluated as part of the efficacy analysis.

3. Results

3.1. Patients and treatment

Patients were enrolled from July 7, 2014, to December 1, 2014. The database cut-off date was June 1, 2016.

Of 123 patients who gave informed consent, three patients withdrew their consent, and 16 failed the screening test (one voluntarily discontinued and 15 either did not meet inclusion criteria, or met an exclusion criterion). Of the 104 enrolled patients, four were excluded because of failure to meet eligibility criteria (n = 2) or continuation was deemed unsuitable by an investigator (n = 2). Therefore, 100

Table 1
Baseline characteristics of patients.

	Total $N = 100$	Squamous NSCLC $N = 44$	Non-squamous NSCLC $N = 56$
Age (years)			
Median (range)	66.5 (29–80)	69.5 (40–80)	63.5 (29–77)
≥75, *n* (%)	15 (15.0)	9 (20.5)	6 (10.7)
Sex, *n* (%)			
Male	78 (78.0)	44 (100.0)	34 (60.7)
Female	22 (22.0)	0	22 (39.3)
Non-squamous subtype, *n* (%)			
Adenocarcinoma	50 (50.0)	0	50 (89.3)
Large cell carcinoma	1 (1.0)	0	1 (1.8)
Other	5 (5.0)	0	5 (8.9)
Disease stage, *n* (%)			
IIIB	6 (6.0)	5 (11.4)	1 (1.8)
IV	91 (91.0)	37 (84.1)	54 (96.4)
Recurrent	3 (3.0)	2 (4.5)	1 (1.8)
Prior treatment for NSCLC, *n* (%)			
Surgery	18 (18.0)	9 (20.5)	9 (16.1)
Radiotherapy	24 (24.0)	11 (25.0)	13 (23.2)
Medication	100 (100.0)	44 (100.0)	56 (100.0)
Platinum-based chemotherapy	100 (100.0)	44 (100.0)	56 (100.0)
EGFR-TKI	8 (8.0)	1 (2.3)	7 (12.5)
Number of treatment regimens for NSCLC, *n* (%)			
1	91 (91.0)	42 (95.5)	49 (87.5)
2	9 (9.0)	2 (4.5)	7 (12.5)
Smoking history, *n* (%)			
Never smoker	22 (22.0)	1 (2.3)	21 (37.5)
Current/former smoker	78 (78.0)	43 (97.7)	35 (62.5)
ECOG PS, *n* (%)			
0	14 (14.0)	6 (13.6)	8 (14.3)
1	86 (86.0)	38 (86.4)	48 (85.7)
Brain metastasis, *n* (%)			
No	74 (74.0)	34 (77.3)	40 (71.4)
Yes	26 (26.0)	10 (22.7)	16 (28.6)
EGFR status, *n* (%)			
Positive	8 (8.0)	1 (2.3)	7 (12.5)
Negative	56 (56.0)	13 (29.5)	43 (76.8)
Unknown	36 (36.0)	30 (68.2)	6 (10.7)

NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PS performance status; CNS, central nervous system.

patients received nivolumab and were included in the safety and full analysis sets (FAS) (Fig. 1). Their demographic and baseline characteristics are shown in Table 1. The patients were aged 29–80 years (median 66.5 years). There were 44 patients with squamous NSCLC and 56 with non-squamous NSCLC. Most patients (86.0%) had an ECOG performance status of 1, and all had previously received platinum-based chemotherapy (most commonly cisplatin), while the most commonly used concurrent non-platinum chemotherapy was gemcitabine, in 41 patients (41.0%). Eight (8.0%) patients (1 with squamous and 7 with non-squamous disease) had a known *EGFR* mutation and had previously received an EGFR TKI.

The median (range) duration of treatment was 2.50 (0.03–22.47) months. The median (range) number of doses was 6 (1–47). At 18 months' follow-up, 87 patients had discontinued treatment, most commonly because of disease progression (n = 58). Thirteen patients had treatment beyond progression. Subsequent chemotherapies included docetaxel/paclitaxel (n = 14), gemcitabine + carboplatin/cisplatin (n = 12), pemetrexed (n = 8), paclitaxel + carboplatin (n = 3), pemetrexed + cisplatin (n = 2), vinorelbine (n = 2), and gefitinib (n = 2).

3.2. Efficacy

3.2.1. Objective response rate

The centrally assessed ORR was 20.0% (95% CI: 13.3–28.9%) in the total population, 15.9% (7/44 patients; 95% CI: 7.9–29.4%) in patients with squamous NSCLC, and 23.2% (13/56 patients; 95% CI: 14.1–35.8%) in patients with non-squamous NSCLC (Table 2). The investigator-assessed ORRs were similar to the centrally assessed ORRs (Table 2).

3.2.2. OS and PFS

Fig. 2A–D show the Kaplan–Meier curves for OS and PFS, according to the histological subtype of NSCLC. Median follow-up was 8.9 and 12.3 months in patients with squamous and non-squamous NSCLC, respectively.

The OS rate at 6 months was 75.6% in the total population, 71.3% in patients with squamous NSCLC, and 78.7% in patients with non-squamous NSCLC (Table 2). The corresponding values were 58.3%, 50.4%, and 63.9% at 12 months and 40.8%, 34.7%, and 45.1% at 18 months.

The median OS was 13.9 (95% CI: 10.8–18.5) months in the total population, 12.3 (95% CI: 8.2–18.5) months in patients with squamous NSCLC, and 16.3 (95% CI: 10.8, −) months in patients with non-squamous NSCLC.

The centrally assessed median PFS was 2.8 (95% CI: 1.4–5.7) months, 2.6 (95% CI: 1.3–5.7) months, and 5.3 (95% CI: 1.4–7.1) months in the total population, in patients with squamous NSCLC, and in patients with non-squamous NSCLC, respectively.

The centrally assessed PFS rates in the total population, and in patients with squamous and non-squamous NSCLC at 3, 6, 12, and 18 months are shown in Table 2.

3.2.3. Other efficacy parameters

The median time to response was 2.8 (95% CI: 1.4–3.0), 2.8 (95% CI: 1.2–3.0), and 2.8 (95% CI: 1.4–3.9) months in the total population,

Table 2
Efficacy outcomes.

	Total $N = 100$	Squamous NSCLC $N = 44$	Non-squamous NSCLC $N = 56$
Best OR, *n* (%) (centrally assessed)			
CR	2 (2.0)	1 (2.3)	1 (1.8)
PR	18 (18.0)	6 (13.6)	12 (21.4)
SD	29 (29.0)	12 (27.3)	17 (30.4)
PD	36 (36.0)	18 (40.9)	18 (32.1)
NE	14 (14.0)	7 (15.9)	7 (12.5)
No target lesion	1 (1.0)	0	1 (1.8)
ORR, *n* (%) (95% CI[a])	20 (20.0) (13.3–28.9)	7 (15.9) (7.9–29.4)	13 (23.2) (14.1–35.8)
Time to response (centrally assessed), months (median, 95% CI)	N = 20 2.8 (1.4–3.0)	N = 7 2.8 (1.2–3.0)	N = 13 2.8 (1.4–3.9)
Duration of response (centrally assessed), months (median, 95% CI)	N = 20 11.7 (5.6, −)	N = 7 11.7 (4.8, −)	N = 13 12.1 (3.0, −)
Best OR, *n* (%) (investigator-assessed)			
CR	2 (2.0)	1 (2.3)	1 (1.8)
PR	19 (19.0)	7 (15.9)	12 (21.4)
SD	43 (43.0)	19 (43.2)	24 (42.9)
PD	25 (25.0)	12 (27.3)	13 (23.2)
NE	11 (11.0)	5 (11.4)	6 (10.7)
ORR, *n* (%) (95% CI[a])	21 (21.0) (14.2–30.0)	8 (18.2) (9.5–32.0)	13 (23.2) (14.1–35.8)
OS rate, % (95% CI[b])			
6 months	75.6 (65.3–83.2)	71.3 (54.2–83.0)	78.7 (64.9–87.6)
12 months	58.3 (47.0–68.0)	50.4 (33.1–65.5)	63.9 (48.8–75.6)
18 months	40.8 (29.9–51.3)	34.7 (19.3–50.5)	45.1 (30.3–58.8)
PFS rate (centrally assessed), % (95% CI[b])			
3 months	48.8 (38.1–58.6)	40.5 (25.0–55.4)	54.9 (40.3–67.3)
6 months	36.7 (26.5–47.0)	30.6 (16.4–46.0)	41.2 (27.2–54.6)
12 months	20.1 (11.8–30.0)	13.6 (4.5–27.8)	25.1 (13.2–38.9)
18 months	12.4 (5.9–21.3)	6.8 (1.2–19.3)	16.7 (7.1–29.9)

ORR (%) = (Number of patients whose confirmed best overall response is CR or PR/Total number of patients) × 100.
OS (days) = (The date of death due to any cause) − (The first dose date of nivolumab) + 1.
PFS (days) = (The earlier date of the first documented PD or death due to any cause) − (The first dose date of nivolumab) + 1.
NSCLC, non-small cell lung cancer; ORR objective response rate; CI, confidence interval; OS, overall survival; PFS, progression-free survival; OR objective response; CR, complete response; PR, partial response, SD, stable disease; PD, progressive disease; NE, not evaluable.
[a] 95% CI calculated using Wilson's method.
[b] 95% CI calculated using the Kaplan–Meier method.

patients with squamous NSCLC, and patients with non-squamous NSCLC, respectively. The respective values for median centrally assessed duration of response were 11.7 (95% CI: 5.6, −), 11.7 (95% CI: 4.8, −), and 12.1 (95% CI: 3.0, −) months (Table 2 and Fig. 3).

The centrally assessed best objective response in the total population and in the squamous and non-squamous populations is shown in Table 2. In the total population, 2.0% of patients had a CR, 18.0% had a PR, and 29.0% had stable disease. The corresponding values in the squamous and non-squamous populations were 1 (2.3%), 6 (13.6%), and 12 (27.3%), and 1 (1.8%), 12 (21.4%), and 17 (30.4%).

The best percent change and the percent change in tumor diameter are shown in Figs. S1A and S1B, respectively.

3.3. Safety

AEs and treatment-related AEs in ≥10% of patients are shown in Table 3. Treatment-related AEs occurring in ≥10% of patients were decreased appetite (14.0%) and pruritus (6.0%) in the total population, decreased appetite (15.9%) in patients with squamous NSCLC, and decreased appetite (12.5%) and pruritus (10.7%) in patients with non-squamous NSCLC. None of these AEs were Grade ≥3. The most common Grade ≥3 AE was pneumonia, which occurred in 7.0% of patients. AEs leading to discontinuation were observed in 15 patients (major events were pneumonia (n = 3) and pneumonitis (n = 2)). Of the AEs leading to death, five cases were lung-related, namely three cases of pneumonia, one of lung infection and one of pneumonitis. Only the death caused by pneumonitis was considered related to nivolumab.

Serious AEs, including deaths, occurred in 40 patients (40.0%), and those related to nivolumab were pneumonitis (3.0%), pneumonia (1.0%), pulmonary embolism (1.0%), neoplasm progression (1.0%), myalgia (1.0%), drug eruption (1.0%), alanine aminotransferase (ALT) increased (1.0%), and aspartate aminotransferase (AST) increased (1.0%). All of these serious treatment-related AEs occurred in one patient each, except for pneumonitis, which occurred in three patients.

The incidences of treatment-related select AEs (i.e., those AEs with a potential immunologic cause or of interest in the present study, summarized by category [Endocrine, Gastrointestinal, Hepatic, Pulmonary, Renal, Skin and Hypersensitivity/Infusion Reactions] and preferred term) are shown in Table S1. Select AEs with an incidence of ≥3% were pruritus (19, 19.0%), rash (9, 9.0%), diarrhea (8, 8.0%), ALT increased (8, 8.0%), AST increased (7, 7.0%), pneumonitis (3, 3.0%), urticaria (3, 3.0%), and hypothyroidism (3, 3.0%).

Of the 95 patients included in the anti-nivolumab antibody analysis set, 13 (13.7%) were positive for anti-nivolumab antibodies, including one (1.1%) who was persistently positive. Treatment-related AEs occurring in anti-nivolumab antibody-positive patients were herpes zoster infection, pain, and palmar-plantar erythrodysesthesia syndrome, all of which were Grade ≤2.

3.4. Efficacy in subgroups of patients

In post-hoc analyses, the ORRs assessed after stratification of patients by various factors were somewhat higher in patients with ECOG status 0 compared with those with ECOG status 1, and in patients without central nervous system metastases compared with those with them (Table S2). Of 13 (13.7%) patients positive for anti-nivolumab

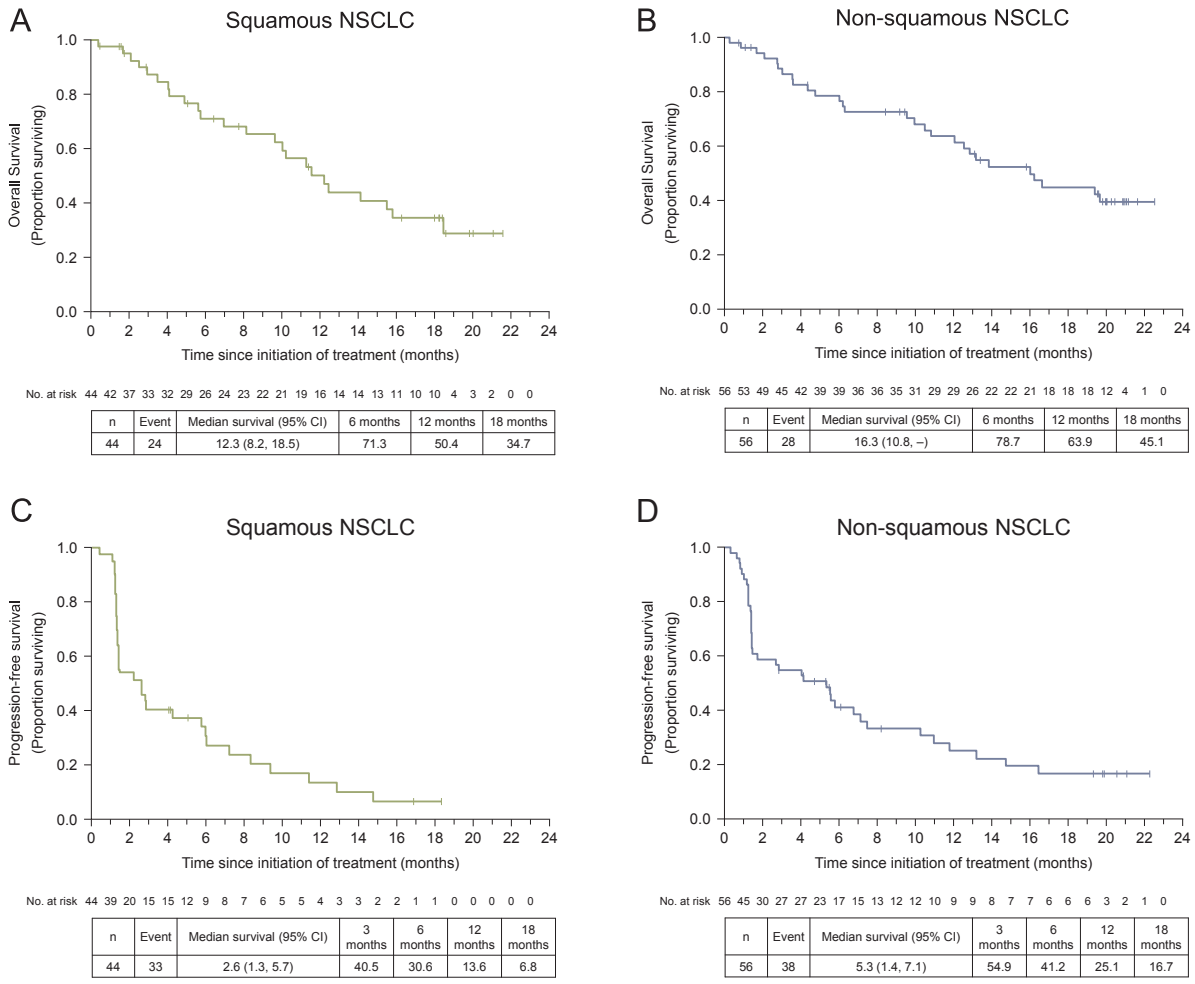

Fig. 2. Kaplan–Meier plots of overall survival (A, B) and progression-free survival (C, D) according to histologic subtype.

antibodies, one (with squamous NSCLC) was persistently positive and had a PR.

4. Discussion

In this study of nivolumab in Korean patients with advanced platinum-refractory squamous NSCLC or non-squamous NSCLC, the ORR was 20.0%. At 6, 12, and 18 months, the OS rate was 75.6%, 58.3%, and 40.8%, and the PFS rate was 36.7%, 20.1%, and 12.4%, respectively. The ORR, OS, and PFS were slightly greater in patients with non-squamous NSCLC than in patients with squamous NSCLC.

These results are consistent with those of the international CheckMate 017 and 057 studies [15,16], which enrolled platinum-refractory patients with squamous and non-squamous NSCLC, respectively. The 1-year survival rate in patients with squamous NSCLC treated with nivolumab was 42% in CheckMate 017 [15] compared with 50.4% in our study. Meanwhile, the 1-year survival in patients with non-squamous NSCLC treated with nivolumab was 51% in CheckMate 057 [16] compared with 63.9% in our study. Among patients with squamous NSCLC treated with nivolumab, the 12-month PFS was 21% in CheckMate 017 [15] compared with 13.6% in our study. Among patients with non-squamous NSCLC treated with nivolumab, the PFS at 12 months was 25.1% in our study compared with 19% in CheckMate 057 [16]. While there are some differences in the results between patients with squamous and non-squamous NSCLC, within our study and between our study and the CheckMate studies, the results indicate that nivolumab achieves an early and durable tumor response in Korean patients with NSCLC similar to that in non-Korean patients, regardless of the histological subtype of NSCLC.

Unlike CheckMate 017 and 057 [15,16], which demonstrated a superior clinical benefit of nivolumab to that of docetaxel, our study did not include a comparator drug. However, the ORR in our study (20.0%) was numerically greater than that of a phase III study that included a docetaxel group (8.8%) [8].

The efficacy of nivolumab in our study was comparable to that reported for pembrolizumab and atezolizumab as second-line treatment in NSCLC. The median OS in our study was 13.9 (95% CI: 10.8, 18.5) months. This was similar to the median OS of 10.4 (95% CI: 9.4, 11.9) months with 2 mg/kg pembrolizumab and 12.7 (95% CI: 10.0, 17.3) months with 10 mg/kg pembrolizumab reported for patients with PD-L1 tumor proportion score of ≥1% in the KEYNOTE 010 study [23] and 13.8 (95% CI: 11.8, 15.7) months reported with atezolizumab in the OAK study [24].

The safety profile of nivolumab in Korean patients was similar to that in the non-Korean patients in CheckMate 017 and 057 [15,16]. No previously unknown safety concerns were identified. Treatment-related AEs occurring in ≥10% of patients with squamous or non-squamous NSCLC were decreased appetite and pruritus in our study; fatigue, nausea, decreased appetite, and asthenia in CheckMate 057 [16]; and fatigue, decreased appetite, and asthenia in CheckMate 017 [15]. There were no significant differences in the profiles of AEs between the anti-nivolumab antibody-negative and -positive patients. Of select AEs, the incidences of diarrhea, hypothyroidism, pneumonitis, and rash were similar in our study to those in the previously published squamous [15] and non-squamous [16] NSCLC populations. Pneumonia is a frequent AE in patients with lung cancer, and the episodes of pneumonia in this

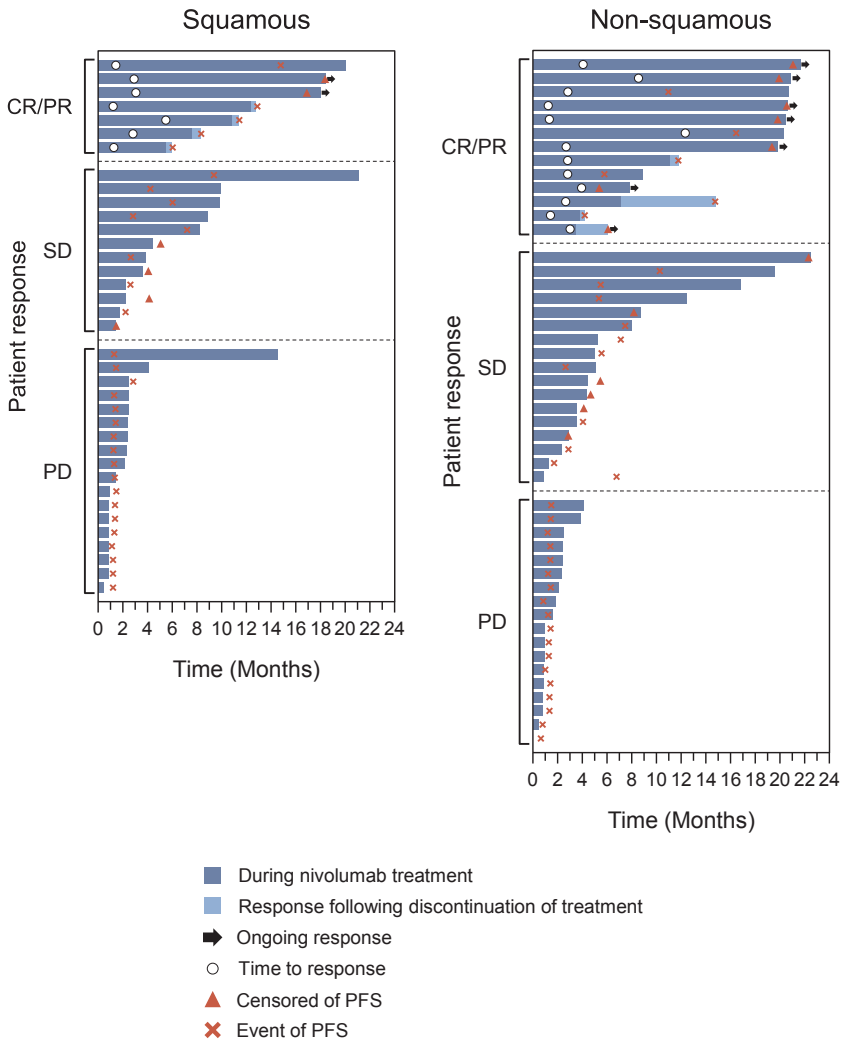

Fig. 3. Duration of response in patients with squamous and non-squamous NSCLC. CR, complete response; PD, progressive disease; PFS, progression free survival; PR, partial response; SD, stable disease.

study were manageable.

The ORRs with nivolumab were assessed in various subgroups of patients in post-hoc analyses. The ORRs were comparable among the subgroup of patients divided by age, sex, disease stage, and prior treatment, but were higher in patients with ECOG status 0 versus 1 (35.7% versus 17.4%) and in those without versus with central nervous system metastases (23.0% versus 11.5%). The trends revealed by subanalyses of the data by *EGFR* mutation and smoking status in our study were different from those in previous studies, which showed a favorable effect of nivolumab regardless of smoking status and *EGFR* mutation status. However, our sample size was limited so further research is needed to verify this.

In our study, testing for PD-L1 expression was not mandatory, so tumor samples were collected from only 17 patients (11 with squamous NSCLC and 6 with non-squamous NSCLC). Therefore, the effect of PD-L1 expression on the response to nivolumab could not be assessed in our study. It is reported that PD-L1 expression can be heterogeneous, even within the same tumor [25]. However, in the OAK study [24], the PD-L1 inhibitor atezolizumab improved OS compared with docetaxel in previously treated NSCLC patients, regardless of their PD-L1 status.

Nivolumab's ability to produce a response in squamous NSCLC makes it a promising treatment for this particular subtype of NSCLC. Possible future treatments of NSCLC could include nivolumab either alone or in combination with other new therapies such as ipilimumab or platinum-based chemotherapy in both first-line (NCT02477826) and second-line (NCT02864251) settings in stage IV or recurrent NSCLC.

This study has some limitations. It was uncontrolled, so any comparisons to other more standard treatments such as docetaxel must be extrapolated from other studies. The number of patients assessed was relatively small. In the present study, patients were not selected by PD-L1 expression status, so its effect, if any, could not be assessed in this study of Korean patients. Future trials should include assessment of PD-L1 expression status in Korean patients to further determine the efficacy of nivolumab.

5. Conclusions

This study showed that the efficacy and safety of nivolumab in Korean patients with advanced or metastatic squamous or non-squamous NSCLC are consistent with those observed in previous studies in Caucasian patients.

Conflicts of interest

All authors report receiving grants from Ono Pharmaceutical Co., Ltd. and Bristol-Myers Squibb Company during the conduct of the study. Dr. Byoung Chul Cho also reports receiving research funding from Novartis, Bayer, AstraZeneca, the MOGAM Institute, and Dong-A ST, and performing consulting roles for Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, Yuhan, Pfizer, and Eli Lilly. Dr. Jin

Table 3
Incidence of adverse events and treatment-related adverse events in ≥10% of patients (any grade and grade ≥3).[a]

	Total $N = 100$ n (%)		Squamous NSCLC $N = 44$ n (%)		Non-squamous NSCLC $N = 56$ n (%)	
Any AE	97 (97.0)		44 (100.0)		53 (94.6)	
Grade ≥3 AE	44 (44.0)		22 (50.0)		22 (39.3)	
Serious AE	40 (40.0)		20 (45.5)		20 (35.7)	
AE leading to discontinuation	15 (15.0)		5 (11.4)		10 (17.9)	
AE leading to death[b]	5 (5.0)		1 (2.3)		4 (7.1)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AEs						
Decreased appetite	43 (43.0)	2 (2.0)	21 (47.7)	1 (2.3)	22 (39.3)	1 (1.8)
Dyspnea	32 (32.0)	6 (6.0)	14 (31.8)	2 (4.5)	18 (32.1)	4 (7.1)
Cough	29 (29.0)	0	14 (31.8)	0	15 (26.8)	0
Constipation	21 (21.0)	0	10 (22.7)	0	11 (19.6)	0
Fatigue	18 (18.0)	1 (1.0)	7 (15.9)	1 (2.3)	11 (19.6)	0
Productive cough	19 (19.0)	0	10 (22.7)	0	9 (16.1)	0
Pruritus	19 (19.0)	0	7 (15.9)	0	12 (21.4)	0
Pyrexia	17 (17.0)	1 (1.0)	9 (20.5)	1 (2.3)	8 (14.3)	0
Nausea	13 (13.0)	0	7 (15.9)	0	6 (10.7)	0
Pneumonia	12 (12.0)	7 (7.0)	7 (15.9)	5 (11.4)	5 (8.9)	2 (3.6)
Chest pain	12 (12.0)	0	7 (15.9)	0	5 (8.9)	0
Myalgia	11 (11.0)	1 (1.0)	5 (11.4)	1 (2.3)	6 (10.7)	1 (1.8)
Asthenia	11 (11.0)	0	5 (11.4)	0	6 (10.7)	0
Dizziness	11 (11.0)	1 (1.0)	4 (9.1)	0	7 (12.5)	1 (1.8)
Dyspepsia	10 (10.0)	0	5 (11.4)	0	5 (8.9)	0
Insomnia	10 (10.0)	0	4 (9.1)	0	6 (10.7)	0
Rhinorrhea	10 (10.0)	0	3 (6.8)	0	7 (12.5)	0
Rash	9 (9.0)	0	2 (4.5)	0	7 (12.5)	0
Diarrhea	8 (8.0)	1 (1.0)	6 (13.6)	1 (2.3)	2 (3.6)	0
Pain	8 (8.0)	0	5 (11.4)	0	3 (5.4)	0
ALT increased	8 (8.0)	3 (3.0)	2 (4.5)	0	6 (10.7)	3. (5.4)
Headache	8 (8.0)	0	2 (4.5)	0	6 (10.7)	0
Back pain	8 (8.0)	1 (1.0)	1 (2.3)	0	7 (12.5)	0
Treatment-related AEs						
Decreased appetite	14 (14.0)	0	7 (15.9)	0	7 (12.5)	0
Pruritus	6 (6.0)	0	0	0	6 (10.7)	0

NSCLC, non-small cell lung cancer; AE, adverse event; ALT, alanine aminotransferase.
[a] All of the AEs that occurred in ≥10% of patients had a maximum grade of 4.
[b] Only one AE leading to death was reported as being treatment related. This treatment-related AE occurred in a non-squamous NSCLC patient.

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Role of the funding source

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.lungcan.2018.05.023.

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