Analysis of Pleiotropic Effects of Nivolumab in Pretreated Advanced or Recurrent Non-small Cell Lung Cancer Cases

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Abstract. Background/Aim: Nivolumab is an immune checkpoint inhibitor for advanced non-small cell lung cancer (NSCLC). We investigated the safety and efficacy of nivolumab by analyzing the response factor, adverse effects (AE), and the post-treatment condition of pretreated advanced or recurrent NSCLC patients. Patients and Methods: Nivolumab (3 mg/kg) was administered to 79 pre-treated NSCLC patients from December 2015 to January 2018. Nivolumab efficacy and AE were assessed using the Response Evaluation Criteria in Solid Tumors and the Common Terminology Criteria, respectively. Results: Progression-free survival (PFS) was significantly prolonged in cases where the therapeutic effect of the pretreatment was a partial response (p=0.0004). Five cases (6.3%) experienced grade 3-4 AEs. PFS was significantly prolonged in the skin rash group versus the non-skin rash group, and in patients where nivolumab treatment was discontinued. Conclusions: Long-term survival was observed in patients with skin rash. Therapeutic effect of nivolumab immediately following its administration appears to be favorable for survival.

Nivolumab is the first immune checkpoint inhibitor developed in Japan for advanced non-small cell lung cancer (NSCLC) (1). It is an antibody against programmed cell death 1 (PD-1), which blocks the binding of PD-1 to PD-ligand 1 (PD-L1) and PD-L2 receptors and suppresses tumor proliferation by activating cancer antigen-specific T-cells and increasing their cytotoxic activity (2). While chemotherapy is generally used as a first-line treatment for NSCLC (3), Carbone et al. reported a better safety profile for Nivolumab when used as a first line treatment (4). The CheckMate 017 trial on squamous cancer (5) and the CheckMate 057 trial on non-squamous cancer (6) found a significant increase in the overall survival (OS) period in the group treated with nivolumab compared to the docetaxel group. These results have also been validated in the Japanese Phase II trial ONO-4538-05 for squamous cancer (7) and the ONO-4538-06 trial for non-squamous cancer (8), with response rates of 25.7% and 19.7%, respectively. New insights on the predictive effects of immune-related adverse events (irAE) of therapy with immune checkpoint inhibitors are emerging from large-scale clinical trials (9) and the important role of nivolumab as a chemotherapeutic agent for NSCLC (10).

One feature of nivolumab is that it offers a clinical paradigm shift in the treatment of lung cancer, largely because of its efficacy in squamous cancer of smokers for whom treatment choices have hitherto been limited (11). This study aimed to corroborate previous findings and further elucidate the safety and efficacy of nivolumab in clinical settings.

Patients and Methods

This study was approved by the Institutional Ethics Review Board of Hyogo College of Medicine, Japan and complies with the 2013 Helsinki Declaration. The requirement for informed consent was waived for this retrospective study.

Patients. Intravenous Nivolumab (3 mg/kg) was administered to 79 patients (58 males and 21 females) with pretreated advanced or recurrent NSCLC every 2 weeks over a 6-week cycle, until radiographic disease progression, unacceptable toxicity, or withdrawal was confirmed. Safety
Terminology Criteria for Adverse Events, version 4.0 (13) was used to rate the AE during the study.

Assessment of safety. The National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 4.0 (13) was used to rate the AE during the study.

Assessment of efficacy. Tumor response was assessed according to the RECIST guidelines, version 1.1 (12). The primary endpoint was the confirmed overall response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and disease control rate.

Statistical analysis. Data are presented as proportions (%) or mean±standard deviation unless otherwise stated. Fisher’s exact test or the chi-square test were used for data comparisons. The survival time of patients who were known to be alive at the time of the data update was censored at the date of the last follow-up. The Kaplan-Meier method was used to calculate OS. Kaplan-Meier curves between the groups were compared using a generalized Wilcoxon test, with the level of statistical significance set at 5% (2-tailed). All statistical analyses were performed using the SPSS version 22.0 for Windows (IBM Japan, Ltd., Tokyo, Japan).

Results

Patient background characteristics. The background characteristics of the 79 patients are displayed in Table I. The median age was 70 years (range, 41-86 years). There were 67 smokers and 12 non-smokers. In terms of ECOG PS, 67

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**Table I. Demographics and baseline characteristics of patients included in the present study.**

| Baseline characteristics | N       | %       |
|--------------------------|---------|---------|
| Age, years               |         |         |
| Median                   | 70      |         |
| Range                    | 41-86   |         |
| <75                      | 57      | 72.2    |
| ≥75                      | 22      | 27.8    |
| Gender                   |         |         |
| Male                     | 58      | 73.4    |
| Female                   | 21      | 26.6    |
| Smoking status           |         |         |
| Never                    | 12      | 15.2    |
| Former/Current           | 67      | 84.8    |
| ECOG PS                  |         |         |
| 0                        | 15      | 19      |
| 1                        | 47      | 59.5    |
| 2                        | 15      | 19      |
| 3                        | 2       | 2.5     |
| Histology                |         |         |
| Adenocarcinoma           | 43      | 54.4    |
| Squamous cell carcinoma  | 32      | 40.5    |
| Adenosquamous            | 1       | 1.3     |
| NOS                      | 1       | 1.3     |
| Pleomorphic carcinoma    | 2       | 2.5     |
| Stage                    |         |         |
| IIA                      | 1       | 1.3     |
| IIIA                     | 11      | 13.9    |
| IIIB                     | 13      | 15.5    |
| IV                       | 39      | 49.4    |
| Recurrence               | 15      | 19      |
| Response to Prior chemotherapy |   |         |
| PR                       | 34      | 43      |
| SD                       | 30      | 38      |
| PD                       | 15      | 19      |
| Driver mutation          |         |         |
| EGFR mutation            |         |         |
| Positive                 | 7       | 8.9     |
| Wild type or unknown     | 72      | 91.1    |

ECOG PS, Eastern cooperative oncology group performance status; EGFR, epidermal growth factor receptor; PD, progressive disease; PR, partial response; SD, stable disease.

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Subgroup analysis. A prespecified subgroup analysis for ORR and a post hoc subgroup analysis for PFS and OS were performed to determine the association between the efficacy variables and patients’ sex, age, histological subtype, treatment regimen, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking status, the therapeutic effect of the pretreatment, and possible mutations in the epidermal growth factor receptor (EGFR) gene.

PD-L1 analysis. Tumor PD-L1 expression was evaluated in pretreated (old or recent) tumor-biopsy specimens using a validated, automated immunohistochemical assay (Dako North America, Inc., Carpenteria, CA, USA) using a rabbit anti-human PD-L1 antibody (clone 22C3, Dako). Immunohistochemical staining was conducted on 1-μm thick sections of formalin-fixed paraffin embedded (FFPE) tumor blocks according to manufacturer’s protocol on Ventana Benchmark Ultra (Ventana Medical Systems, Inc. Tucson, AZ, USA) (14).

Biopsies with at least 100 tumor cells in each section were analyzed and were grouped into three categories: i) <1%, ii) 1-49%, and iii) ≥50% of tumor PD-L1 expression.

Statistical analysis. Data are presented as proportions (%) or mean±standard deviation unless otherwise stated. Fisher’s exact test or the chi-square test were used for data comparisons. The survival time of patients who were known to be alive at the time of the data update was censored at the date of the last follow-up. The Kaplan-Meier method was used to calculate OS. Kaplan-Meier curves between the groups were compared using a generalized Wilcoxon test, with the level of statistical significance set at 5% (2-tailed). All statistical analyses were performed using the SPSS version 22.0 for Windows (IBM Japan, Ltd., Tokyo, Japan).
cases were rated at 0-1 (PS0, 15; PS1, 47), and 17 cases were rated at ≥2 (PS2, 15; PS3, 2). Histological types included 43 cases of adenocarcinoma, 32 cases of squamous cell carcinoma, and 4 cases of other cancer types. 

The median PFS period across all 79 cases was 7.8 months, and the median OS classification was Not Reached (NR) (Figure 1). No significant differences in median PFS period were observed between the groups with respect to age, gender, or histological classification (Figure 2a, b, and c). In addition, 7 (8.9%) cases were tested positive for the EGFR gene mutation and 72 (91.1%) cases were classified as wild-type or unknown. The presence or absence of EGFR mutation had no significant difference in the median PFS period (Figure 2d). Regarding the smoking history and PS, smokers exhibited a significantly longer median PFS compared to non-smokers (p=0.0031: smokers: 8.5 months; non-smokers: 2.5 months) (Figure 3a). In addition, cases of PS0-1 exhibited a significantly longer median PFS compared to cases of PS 2 (p=0.0025: PS0-1: 8.9 months; PS2: 2.4 months) (Figure 3b). 

**Adverse events**. The AEs observed in the 79 subjects participating in this study are described in Table II. Regarding grade 1-2 AEs, skin rash was observed in 14 (17.7%) cases. The skin rash (+) group exhibited significantly longer PFS (p=0.0016) and OS (p=0.0036) periods than the skin rash (−) group (Figure 4a and b). The more clinically relevant grade 3-4 AEs developed in 5/79 (6.3%) of all cases, and although there were no cases of hematological toxicities, other types of toxicities occurred. These included 2 (2.5%) cases that presented with diarrhea, 2 (2.5%) cases with interstitial lung disease, and 1 (1.3%) case with liver dysfunction. No cases of febrile neutropenia or treatment-related mortality were recorded. Nivolumab was discontinued in 61 cases either due to AE or primary disease deterioration. Such large number of discontinued cases could have resulted due to administration of nivolumab as a 3rd or a later-line treatment. Out of the total cases (n=61) in which the administration of nivolumab was discontinued, those that were due to AEs (10/61; 16.4%) exhibited a significantly prolonged PFS compared to those that were due to a primary disease deterioration (51/61; 83.6%)
PFS in the primary disease deterioration vs. the AE-related discontinued treatment group; \( p = 0.0025 \). PFS in the primary disease deterioration-related discontinued treatment group was 3.3 months. Regarding OS, no significant difference was observed between these two groups \( (p = 0.3447) \). OS for the primary disease deterioration-related discontinued treatment group was 16.5 months (Figure 5a and b).

**Treatment results.** The results of treatment for each of the 79 subjects are described in Table III. Regarding the tumor shrinkage response, response rate (RR) was obtained in 23/79 (29.1%) cases, and disease control rate (DCR) was obtained in 58/79 (73.4%) cases. Similar or better outcomes emerged from the treatment with nivolumab in our study as compared to ONO-4538-05, ONO-4538-06, CheckMate 017 and CheckMate 057 trials (Table IV) (5-8). In addition, patients who were smokers and had squamous cell carcinoma exhibited a higher response rate. (RR: Smokers vs. Non-smokers: 32.8% vs. 8.3%; RR: All vs. Squamous cell carcinoma: 29.1% vs. 40.6%)

The antitumoral effect of each treatment during the course was evaluated as i) the response rate (2nd, 38.3%; 3rd, 23.1%; 4th and greater, 10.5%), ii) the disease control rate (2nd, 70.2%; 3rd, 84.6%; 4th and greater, 84.2%), and iii) the median PFS period (2nd, 7.1 months; 3rd, 10.1 months; 4th and greater, 7.8 months) (Table V). No significant differences were observed between the different treatment lines, suggesting that good anti-tumor efficacy can be obtained even at the 3rd, 4th line of treatment or at later ones, if favorable parameters, like PS, show improvement.

Additionally, the breakdown of the pre-treatment responses prior to the administration of nivolumab across all 79 patients was as follows: i) partial remission (PR), 34/79 (43%); ii) stable disease (SD), 30/79 (38%); and iii) progressive disease (PD), 15/79 (19%).

The median PFS periods per pre-treatment response classification were: i) 18.4 for PR, ii) 7.1 for SD, and iii) 3.2 months for PD. Moreover, patients in the pre-treatment PR group exhibited significantly longer PFS periods compared to SD and PD groups (hazard ratio, 0.2691; 95% confidence interval, 0.06545-0.4009; \( p = 0.0001 \) (Figure 6).

**PD-L1 subgroup analysis.** Although the level of PD-L1 protein expression was confirmed in 18 subjects, no significant differences in OS and PFS were observed between the groups with the three levels of expression. (PFS: ≥50%/1-49%/ <1% = 2.1/6.2/2.5 (months); OS: ≥50%/1-49%/ <1% = Not reached (NR)/8.5/19.4 (months)).

**Discussion**

In this study, we determined the safety and efficacy of nivolumab in a clinical setting. Our results showed similar or better rates of efficacy and safety of nivolumab compared to previously reported results in large-scale clinical trials (6, 13). We considered the possibility that a favorable PS as well as the smoking history of patients (0-1/≥2, 62/17 cases; Y/N, 67/12 cases, respectively) could serve as predictive response factors. Compared to previous reports these factors posed significant differences in PFS or OS. Age (75-years-old or
younger), histological type, PD-L1 staining, or EGFR mutation status did not significantly affect the treatment outcome. PFS increased in skin rash (+) group compared to skin rash (−) group.

Although 40% or more of the total number of cases analyzed in the study used nivolumab as a 3rd or a later line treatment, the 1-year survival rate was comparable to that reported by Freeman-Keller et al. using nivolumab alone or in combination with a peptide vaccine (16). In addition, the presence of irAEs has been suggested as a risk factor for predicting the therapeutic effect of ipilimumab or nivolumab in cases of melanoma (16). In the current study, only 5 subjects with NSCLC presented with AEs of grade 3-4 and PFS was significantly prolonged in the skin rash group versus the non-skin rash group. Our findings are in line with previous reports of increased survival of NSCLC patients experiencing irAEs after immunotherapy (17, 18).

Regarding chemotherapy, Schvartsman et al. have reported a better ORR for chemotherapy immediately after the administration of nivolumab as compared to historical data before the development of immunotherapy (19). Nakahama et al. have showed a better disease control post nivolumab treatment if pre-nivolumab chemotherapy showed a good clinical response (20). Thus, nivolumab might serve as chemotherapy for prolonging the survival of NSCLC patients.

This study included many cases "unfit for clinical trials," such as patients with poor PS, complicated interstitial pneumonia, organ dysfunction, as well as patients with...
Table IV. **Nivolumab trials.**

| Trial Control Arm | Objective                  | Present study  | ONO-4538-05   | ONO-4538-06   | CheckMate017 | CheckMate057 |
|-------------------|----------------------------|----------------|---------------|---------------|--------------|--------------|
| Control Arm       | Retrospective              | Phase II       | Phase II      | Phase III     | Phase III    |
| Objective         | advanced or                | advanced or    | advanced or   | Docetaxel     | Docetaxel    |
|                   | recurrent NSCLC            | recurrent Sq   | recurrent non-Sq | advanced or     | advanced or     |
| Cases             | 79                         | 35             | 76            | 272           | 582          |
| Dose              | 3mg/kg/2W                  | 3mg/kg/2W      | 3mg/kg/2W     | 3mg/kg/2W     | 3mg/kg/2W    |
| Primary Endpoints | Retrospective              | ORR            | ORR           | OS            | OS           |
|                   |                            | 29.1%          | 25.7%         | 22.4%         | 20% vs. 9%   |
|                   |                            | 7.8 months     | 4.2 months    | 2.8 months    | 2.8 months   |
|                   |                            | NR             | 16.3 months   | 17.1 months   | 9.2 months vs. 2.3 months vs. 4.2 months |
|                   |                            | 1-year survival| 40.5%         | 71.4%         | 42% vs. 24% |
|                   |                            | G3/4 (%)       | 6.3%          | 5.7%          | 7% vs. 55%   |

NSCLC, Non-small cell lung cancer; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Sq, squamous; W, weeks.
multiple cancers. All these elements are difficult to incorporate into generalized clinical trials. Thus, evidence obtained through clinical trials cannot be applied without consideration of such elements when treating patients in the clinical practice.

There are certain limitations inherent to this study. First, the lack of PD-L1 evaluation in post-treatment samples could be problematic. Second, the lack of available follow-up data may have introduced a degree of bias in our analyses. Both these limitations are due to the retrospective nature of the study and restrict our interpretations. In addition, we were unable to ascertain multiple AEs in certain patients. Further retrospective studies, as well as carefully planned prospective studies, will be useful to validate our findings in clinical practice.

In conclusion, long-term survival may be possible for NSCLC patients with skin rash. Furthermore, the therapeutic effect of nivolumab immediately following its administration appeared to be favorable for the survival of these patients. These clinical practice-based insights should be taken into consideration when choosing nivolumab to control tumor growth and achieve long-term survival for NSCLC patients.

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Conflict of Interest

The Authors have no conflicts of interest to declare regarding the contents of this article.

Table V. Baseline characteristics with prior treatment (N=79).

| Tumor response to nivolumab used as differing lines of therapy | 2nd line (N) | 3rd line (N) | ≥4th line (N) |
|---------------------------------------------------------------|------------|------------|-------------|
| PR                                                            | 18         | 3          | 2           |
| SD                                                            | 15         | 8          | 12          |
| PD                                                            | 12         | 2          | 4           |
| NE                                                            | 2          | 0          | 1           |
| Total (N/%)                                                   | 47 (59.5)  | 13 (16.5)  | 19 (24.0)   |
| ORR (%)                                                       | 38.3       | 23.1       | 10.5        |
| DCR (%)                                                       | 70.2       | 84.6       | 84.2        |
| PFS (Months)                                                  | 7.1        | 10.1       | 7.8         |

PR, Partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, overall response rate; DCR, Disease Control Rate; PFS, progression-free survival.

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