Impact of maintenance therapy following induction immunochemotherapy for untreated advanced non-small cell lung cancer patients

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Abstract

Purpose The primary objective of this study was to identify the potential predictors to assess the impact of maintenance therapy after induction immunochemotherapy in the real-world setting of patients with advanced non-small cell lung cancer (NSCLC).

Methods We retrospectively identified 152 patients with advanced NSCLC who received immunochemotherapy at 8 hospitals in Japan between January 2019 and December 2019. Patients who received at least four cycles of induction immunochemotherapy and one cycle of maintenance therapy with immune checkpoint inhibitors were included. We investigated the biomarkers for progression-free survival (PFS) for maintenance therapy after induction immunochemotherapy.

Results Out of the 92 patients with advanced NSCLC included in the study, 42 received maintenance therapy with cytotoxic agents, whereas 50 received maintenance therapy without cytotoxic agents. Among those who received maintenance therapy without cytotoxic agents, responders to prior immunochemotherapy had significantly longer PFS than non-responders ($p=0.004$), except those with maintenance therapy with cytotoxic agents. In non-responders to prior immunochemotherapy, patients with maintenance therapy with cytotoxic agents had significantly longer PFS than those with maintenance therapy without cytotoxic agents (log-rank $p=0.007$), whereas, among responders to prior immunochemotherapy, there was no significant difference in PFS for different maintenance regimens (log-rank $p=0.31$).

Conclusions This retrospective study showed that response to prior immunochemotherapy was associated with clinical outcomes among patients with advanced NSCLC who received maintenance therapy.

Keywords Non-small cell lung cancer · Immunochemotherapy · Maintenance therapy · Pemetrexed · Immune checkpoint inhibitor
Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide (Bray et al. 2018). Novel combination therapies, such as immune checkpoint inhibitors (ICIs) plus chemotherapy or dual-immunotherapy with or without chemotherapy have recently been introduced as standard treatments for patients with advanced non-small cell lung cancer (NSCLC) (Ettinger et al. 2018; Planchard et al. 2018; Akamatsu et al. 2019; Hellmann et al. 2019; Paz-Ares et al. 2021). Furthermore, follow-up maintenance therapy has been the standard treatment for patients with advanced NSCLC who responded positively to previous immunochemotherapy (Paz-Ares et al. 2018; Gandhi et al. 2018; West et al. 2019; Socinski et al. 2018).

In the KEYNOTE-189 trial, the addition of pembrolizumab to platinum-based chemotherapy followed by pemetrexed plus pembrolizumab maintenance had demonstrated higher overall survival (OS) and progression-free survival (PFS), compared to platinum-based chemotherapy followed by pemetrexed among patients with previously untreated metastatic nonsquamous NSCLC (Gandhi et al. 2018). Contrastingly, the phase III PARAMOUNT trial provided evidence for better results with pemetrexed continuation maintenance therapy as compared with placebo (Paz-Ares et al. 2013). This evidence suggests that pemetrexed maintenance therapy could be a useful therapeutic strategy for patients with advanced NSCLC who responded positively to previous immunochemotherapy, irrespective of the induction immunochemotherapy.

However, a previous prospective cohort study demonstrated that pemetrexed maintenance therapy induced acute kidney injury in approximately 30% of patients with advanced NSCLC and promoted treatment discontinuation among 20% of them (Visser et al. 2018). Another retrospective cohort study disclosed that NSCLC patients on pemetrexed-based long-term treatment were at risk of developing renal impairment, despite renal function remaining stable following pemetrexed treatment induction. This suggested that a long duration of pemetrexed-based chemotherapy exposure might be harmful (de Rouw et al. 2020). Therefore, the decision to continue cytotoxic agents with maintenance following induction immunochemotherapy in patients with advanced NSCLC remains unclear.

Thus, the primary objective of this study was to identify the potential predictors to assess the impact of chemotherapy containing maintenance therapy after induction immunochemotherapy in the real-world setting of patients with advanced NSCLC.

We present the following article in accordance with the STROBE reporting checklist.

Materials and methods

Patients

In this study, 152 patients with advanced NSCLC on combination therapy of immunochemotherapy and chemotherapy at 8 institutions in Japan (University Hospital Kyoto Prefectural University of Medicine, Japanese Red Cross Kyoto Daiichi Hospital, Japanese Red Cross Kyoto Daini Hospital, Uji-Tokushukai Medical Center, Otsu City Hospital, Matsushita Memorial Hospital, Fukuoka University Hospital, and Fujita Health University Hospital) between January and December 2019 were retrospectively identified. Patients who received at least four cycles of induction therapy and one cycle of maintenance therapy were included. The medical records of each patient were reviewed to collect the following data: age at the start of induction therapy; sex; smoking status; treatment regimens; body mass index (BMI) at the start of induction therapy; laboratory findings at the start of maintenance therapy; Eastern Cooperative Oncology Group Performance Status (ECOG-PS) at the start of induction therapy; disease staging classified using the TNM stage classification system version 8; histological subtypes; epidermal growth factor receptor (EGFR) mutation status; anaplastic lymphoma kinase (ALK) fusion status; programmed death ligand 1 (PD-L1) expression level in tumors measured using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Santa Clara, CA, USA); best overall response (BOR) without confirmation evaluated by each attending physician according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; and PFS of maintenance therapy.

Ethical consideration

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committees of the Kyoto Prefectural University of Medicine (approval no. ERB-C-1803) and each participating hospital. Informed consent was not required due to the retrospective nature of the study, and used the official website as an opt-out method, which was also approved by the ethics committee of each hospital.

Statistical analysis

We retrospectively collected data on September 30, 2020. Patients who were alive and progression-free were censored at the date of the last follow-up update. Student’s t test was used to compare the means of continuous variables (such as age). To compare the proportions of categorical variables (such as sex) between the groups, Fisher’s exact test was employed. Survival curves were calculated with
the Kaplan–Meier method, and differences were compared using the log-rank test. PFS of maintenance therapy was calculated from the date of initiation of maintenance therapy to the date of disease progression or death from any cause. Cox proportional hazards models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs). The variables with \( p < 0.10 \) in univariate analysis were included in the multivariate analysis. Patients whose laboratory data was missing or whose BOR was not evaluable (NE) were excluded from the analysis. PFS cutoff point for patients without chemotherapy for maintenance therapy was set at 90 days, based on PFS of the control arm in the PARA-MOUNT trial (Paz-Ares et al. 2012). Responders were defined as patients who achieved complete response (CR) and partial response (PR), and non-responders were defined as patients who had stable disease (SD). Maintenance immunotherapy with cytotoxic chemotherapy (ICI maint with chemo) was defined as maintenance therapy with pemetrexed and ICIs, and maintenance immunotherapy without cytotoxic chemotherapy (ICI maint without chemo) was defined as maintenance therapy with ICIs alone or in combination with anti-VEGF antibody bevacizumab. Neutrophil-to-lymphocyte ratio (NLR) was defined as the absolute neutrophil count divided by the absolute lymphocyte count. The cutoff value of NLR was set at five, based on a previous study (Diem et al. 2017). Statistical analyses were performed using EZR statistical software (version 1.42. Division of Hematology, Saitama Medical Center, Jichi Medical University, Japan) (Kanda 2013). All statistical tests were two-tailed, and a \( p \) value less than 0.05 was considered significant.

**Results**

**Patient characteristics**

A total of 152 patients with advanced NSCLC on a combination of immunotherapy plus chemotherapy at 8 hospitals in Japan from January to December 2019 were identified. Ninety-three of the identified patients who had received at least 4 cycles of induction therapy and 1 cycle of maintenance therapy were included in this study. Fifty patients received ICI maint without chemo and 43 patients received ICI maint with chemo. One patient receiving ICI maint with chemo was excluded from analysis due to missing laboratory data (Fig. 1). The median follow-up time after initiation of maintenance therapy was 9.8 months.

Patient characteristics classified by maintenance regimens are shown in Table 1. The median age of the patients with ICI maint with chemo and those with ICI maint without chemo was 69 years (range 45–79) and 68 years (range 39–79), respectively. About 95.2\% (\( n = 40 \)) of the patients received ICI maint with chemo of platinum with pemetrexed plus pembrolizumab while the remaining received carboplatin with pemetrexed plus atezolizumab. The regimens in the patients with ICI maint without chemo were carboplatin with paclitaxel, atezolizumab, and bevacizumab (26.0\%, \( n = 13 \)), carboplatin with paclitaxel or nab-paclitaxel plus pembrolizumab (72.0\%, \( n = 36 \)), and carboplatin with nab-paclitaxel plus atezolizumab (2.0\%, \( n = 1 \)). All patients receiving ICI maint with chemo suffered from adenocarcinoma. The patients with ICI maint without chemo showed a higher proportion of squamous cell carcinoma (52.0\%, \( n = 26 \)).

**Association of clinical outcomes of maintenance therapy to induction immunochemotherapy**

The results of univariate and multivariate analyses for PFS of maintenance therapy using Cox proportional hazards models are presented in Table 2. Multivariate analysis elaborated that CR plus PR for induction immunochemotherapy and serum albumin \( \geq 3.5 \) g/dL were significantly associated with prolonged PFS in patients with ICI maint without chemo (HR 0.31, 95% CI 0.14–0.68, \( p = 0.004 \); HR 0.20, 95% CI 0.064–0.64, \( p = 0.007 \)). In contrast, in patients with ICI maint with chemo, multivariate analysis was not performed because the \( p \) values for all variables were above 0.10 in univariate analysis.
Table 1  Patient characteristics classified according to maintenance regimens

| Characteristics                  | Total (%) | ICI maint with chemo (%) | ICI maint without chemo (%) | p value |
|----------------------------------|-----------|---------------------------|----------------------------|---------|
| Number                           | 92        | 42                        | 50                         |         |
| Age                              |           |                           |                            |         |
| Median (range)                   |           |                           |                            |         |
| Sex                              |           |                           |                            |         |
| Male                             | 68 (73.9) | 27 (64.3)                 | 41 (82.0)                  | 0.061   |
| Female                           | 24 (26.1) | 15 (35.7)                 | 9 (18.0)                   |         |
| ECOG-performance status          |           |                           |                            |         |
| 0                                | 45 (48.9) | 25 (59.5)                 | 20 (40.0)                  | 1.0†    |
| 1                                | 44 (47.8) | 16 (38.1)                 | 28 (56.0)                  |         |
| 2/3                              | 3 (3.3)   | 1 (2.4)                   | 2 (4.0)                    |         |
| Stage                            |           |                           |                            |         |
| III/IV                           | 72 (78.3) | 29 (69.0)                 | 43 (86.0)                  | 0.075   |
| Recurrent                        | 20 (21.7) | 13 (31.0)                 | 7 (14.0)                   |         |
| Smoking status                   |           |                           |                            |         |
| Current/former                   | 72 (78.3) | 30 (71.4)                 | 42 (86.0)                  | 0.21    |
| Never                            | 20 (21.7) | 12 (28.6)                 | 8 (16.0)                   |         |
| Histology                        |           |                           |                            |         |
| Adenocarcinoma                   | 57 (62.0) | 42 (100)                  | 15 (30.0)                  | <0.001  |
| Squamous cell carcinoma          | 26 (28.2) | 0 (0.0)                   | 26 (52.0)                  |         |
| Other                            | 9 (9.8)   | 0 (0.0)                   | 9 (18.0)                   |         |
| Oncogenic driver                 |           |                           |                            |         |
| EGFR mutation positive           | 5 (5.4)   | 1 (2.4)                   | 4 (8.0)                    | 0.37‡   |
| ALK rearrangement positive       | 0 (0.0)   | 0 (0.0)                   | 0 (0.0)                    |         |
| EGFR and ALK wild type           | 67 (72.8) | 41 (97.6)                 | 26 (52.0)                  |         |
| Not investigated                 | 20 (21.7) | 0 (0.0)                   | 20 (40.0)                  |         |
| PD-L1 TPS                        |           |                           |                            |         |
| ≥ 50%                            | 30 (32.6) | 11 (26.2)                 | 19 (38.0)                  | 0.27§   |
| 1–49%                            | 30 (32.6) | 14 (33.3)                 | 16 (32.0)                  |         |
| < 1%                             | 21 (22.8) | 12 (28.6)                 | 9 (18.0)                   |         |
| Not investigated                 | 11 (11.6) | 5 (11.9)                  | 6 (12.0)                   |         |
| Induction regimen                |           |                           |                            |         |
| Platinum + pemetrexed+pembrolizum | 40 (43.5) | 40 (95.2)                 | 0 (0.0)                    |         |
| Carboplatin + pemetrexed + atezolizumab | 2 (2.2)  | 2 (4.8)                   | 0 (0.0)                    |         |
| Carboplatin + paclitaxel + bevacizumab + atezolizumab | 13 (14.1) | 0 (0.0)                   | 13 (26.0)                  |         |
| Carboplatin + paclitaxel + nab-paclitaxel + pembrolizumab | 36 (39.1) | 0 (0.0)                   | 36 (72.0)                  |         |
| Carboplatin + nab-paclitaxel + atezolizumab | 1 (1.1)   | 0 (0.0)                   | 1 (2.0)                    |         |
| Maintenance regimen              |           |                           |                            |         |
| Pemetrexed + pembrolizum         | 40 (43.5) | 40 (95.2)                 | 0 (0.0)                    |         |
| Pemetrexed + atezolizumab        | 2 (2.2)   | 2 (4.8)                   | 0 (0.0)                    |         |
| Pembrolizum                      | 36 (39.1) | 0 (0.0)                   | 36 (72.0)                  |         |
| Atezolizumab                     | 1 (1.1)   | 0 (0.0)                   | 1 (2.0)                    |         |
| Atezolizumab + bevacizumab       | 13 (14.1) | 0 (0.0)                   | 13 (26.0)                  |         |
| Renal function at the start of maintenance therapy | eGFR ≥ 60 mL/min/1.73 m² | 70 (76.1) | 32 (76.2) | 38 (76.0) | 1.0 |
|                                  | eGFR < 60 mL/min/1.73 m² | 22 (23.9) | 10 (23.8) | 12 (24.0) |     |
| Body mass index at the start of induction therapy | BMI ≥ 18.5 | 85 (92.4) | 40 (95.2) | 45 (90.0) | 0.45 |
|                                  | BMI < 18.5 | 7 (7.6) | 2 (4.8) | 5 (10.0) |     |
Kaplan–Meier curves illustrated that responders of induction immunochemotherapy had significantly longer PFS of ICI maint without chemo than non-responders (HR 0.31, 95% CI 0.14–0.67; log-rank \( p = 0.002 \)) (Fig. 2A). Contrastingly, there was no significant difference in PFS associated with ICI maint with chemo among responders and non-responders of induction therapy (HR 0.89, 95% CI 0.35–2.29; log-rank \( p = 0.82 \)) (Fig. 2B). Similarly, the Kaplan–Meier curves for PFS in patients with ICI maint with chemo and ICI maint without chemo were evaluated according to the responsiveness to prior immunochemotherapy. Among non-responders, the patients receiving ICI maint with chemo had significantly longer PFS than those with ICI maint without chemo (HR 0.28, 95% CI 0.10–0.74; log-rank \( p = 0.007 \)) (Fig. 2C). In contrast, among responders to prior immunochemotherapy, there was no significant difference in PFS between the two groups (HR 0.69, 95% CI 0.34–1.42; log-rank \( p = 0.31 \)) (Fig. 2D).

Furthermore, we analyzed the characteristics of prior immunochemotherapy responders and non-responders who received ICI maint without chemo. It was found that non-responders were more likely to have positive oncogenic driver mutations with NLR ≥ 5 (20.0% vs 2.9%, \( p = 0.007 \); 20.0% vs 2.9%, \( p = 0.075 \), respectively) (Table 3). On assessing the association between responsiveness to prior immunochemotherapy and PFS duration with ICI maint without chemo, it was found that patients with PFS > 90 days of ICI maint without chemo had a significantly higher response rate to prior immunotherapy than did those with PFS ≤ 90 days (89.2% vs 45.4%, \( p = 0.001 \)) (Fig. 3). These findings suggest that response to induction therapy might serve as a predictor for outcomes to maintenance immunotherapy without cytotoxic chemotherapy in NSCLC patients.

### Discussion

Existing literature suggests that immunotherapy regimens, including those comprising ICIs, contribute to long-term survival among advanced NSCLC patients (Garon et al. 2019; Gadgeel et al. 2020). Therefore, maintenance therapy following induction treatment plays a critical role in controlling the disease progression and enhancing patient survival. However, the impact of maintenance therapy among patients with advanced NSCLC has not been fully understood.

In this study, we identified a population of patients with advanced NSCLC who demonstrated good outcomes following administration of maintenance therapy after induction immunochemotherapy. Among non-responders to prior immunochemotherapy, it was noted that treatment with ICI maint with chemo significantly prolonged PFS compared to those receiving ICI maint without chemo. In contrast, there was no significant difference in PFS between responders receiving ICI maint with chemo or ICI maint without chemo. This is the first study to demonstrate the significance of response to prior immunochemotherapy as a potential predictor for the success of maintenance therapy after induction immunochemotherapy in patients with advanced NSCLC.

A previous meta-analysis demonstrated that response to ICIs monotherapy was associated with good clinical outcomes, including long PFS for patients with advanced NSCLC. It also suggested that non-responders to induction therapy might not be a suitable population for ICI maint without chemo (Ye et al. 2020).

This study found no difference in PFS for ICI maint with chemo between non-responders and responders to prior immunochemotherapy. Previous studies indicate that intervention by cytotoxic chemotherapy elicited antitumor

| Characteristics | Total (%) | ICI maint with chemo (%) | ICI maint without chemo (%) | \( p \) value |
|-----------------|-----------|--------------------------|-----------------------------|--------------|
| Complete response | 5 (5.4) | 3 (7.2) | 2 (4.0) | 0.38¶ |
| Partial response  | 55 (59.8) | 22 (52.4) | 33 (66.0) | 
| Stable disease    | 29 (31.5) | 14 (33.3) | 15 (30.0) | 
| Not evaluable     | 3 (3.3) | 3 (7.1) | 0 (0.0) | 

ICI immune checkpoint inhibitor, maint maintenance, chemo chemotherapy, ECOG Eastern Cooperative Oncology Group, EGFR epidermal growth factor receptor, ALK anaplastic lymphoma kinase, PD-L1 TPS programmed death ligand 1 tumor proportion score, eGFR estimated glomerular filtration rate

¶ ECOG-performance status 0/1 versus 2/3
‡ EGFR mutation positive versus all others
§ PD-L1 TPS ≥ 50% versus all others
¶ Complete response + partial response versus all others

Table 1 (continued)
Table 2  Cox proportional hazards models for progression-free survival of types of maintenance therapy

| Items                                      | ICI maint with chemo PFS (univariate analysis) | ICI maint without chemo PFS (univariate analysis) |
|--------------------------------------------|------------------------------------------------|--------------------------------------------------|
|                                            | HR (95% CI) | p value | HR (95% CI) | p value |
| (A)                                        |             |         |             |         |
| Age                                        |             |         |             |         |
| < 75                                       | Reference   | –       | Reference   | –       |
| ≥ 75                                       | 1.13 (0.25–5.04) | 0.87 | 1.79 (0.69–4.67) | 0.24 |
| Sex                                        |             |         |             |         |
| Female                                     | Reference   | –       | Reference   | –       |
| Male                                       | 0.58 (0.24–1.40) | 0.23 | 0.45 (0.21–0.98) | 0.044 |
| ECOG-PS                                    |             |         |             |         |
| 0                                          | Reference   | –       | Reference   | –       |
| ≥ 1                                        | 1.17 (0.48–2.82) | 0.73 | 1.06 (0.52–2.15) | 0.87 |
| Postoperative recurrence                   |             |         |             |         |
| No                                         | Reference   | –       | Reference   | –       |
| Yes                                        | 1.43 (0.57–3.60) | 0.44 | 0.84 (0.29–2.40) | 0.74 |
| Smoking status                             |             |         |             |         |
| Never                                      | Reference   | –       | Reference   | –       |
| Current/former                            | 1.25 (0.45–3.49) | 0.67 | 0.47 (0.21–1.06) | 0.069 |
| Histology                                  |             |         |             |         |
| Non-squamous                               | Reference   | –       | Reference   | –       |
| Squamous                                   | 1.18 (0.59–2.38) | 0.64 | –           |         |
| PD-L1                                      |             |         |             |         |
| < 50%                                      | Reference   | –       | Reference   | –       |
| ≥ 50%                                      | 0.48 (0.16–1.47) | 0.20 | 0.80 (0.39–1.64) | 0.54 |
| Bevacizumab regimen                        |             |         |             |         |
| No                                         | Reference   | –       | Reference   | –       |
| Yes                                        | 1.25 (0.58–2.69) | 0.58 | –           |         |
| eGFR                                       |             |         |             |         |
| < 60 mL/min/1.73 m²                        | Reference   | –       | Reference   | –       |
| ≥ 60 mL/min/1.73 m²                        | 0.68 (0.26–1.78) | 0.43 | 1.21 (0.52–2.79) | 0.66 |
| BMI                                        |             |         |             |         |
| < 18.5                                     | Reference   | –       | Reference   | –       |
| ≥ 18.5                                     | 1.32 (0.18–9.92) | 0.79 | 5.02 (0.68–37.02) | 0.11 |
| Best overall response                      |             |         |             |         |
| SD                                         | Reference   | –       | Reference   | –       |
| CR + PR†                                   | 0.89 (0.35–2.29) | 0.82 | 0.31 (0.14–0.67) | 0.0027 |
| Serum albumin                              |             |         |             |         |
| < 3.5 g/dL                                 | Reference   | –       | Reference   | –       |
| ≥ 3.5 g/dL                                 | 0.99 (0.23–4.27) | 0.99 | 0.27 (0.090–0.80) | 0.018 |
| NLR                                        |             |         |             |         |
| < 5                                        | Reference   | –       | Reference   | –       |
| ≥ 5                                        | 1.58 (0.36–6.85) | 0.54 | 1.82 (0.55–6.00) | 0.32 |
| Items                                      | ICI maint without chemo PFS (multivariate analysis) |        |
|                                            | HR (95% CI) | p value |             |         |
| (B)                                        |             |         |             |         |
| Male sex                                   | 0.53 (0.16–1.78) | 0.31 | –           |         |
| Current/former smoker                      | 0.73 (0.20–2.66) | 0.63 | –           |         |
| CR + PR                                    | 0.31 (0.14–0.68) | 0.0036 | –           |         |
| Serum albumin ≥ 3.5 g/dL                   | 0.20 (0.064–0.64) | 0.0068 | –           |         |

Univariate analysis (A) and multivariate analysis (B)

ICI immune checkpoint inhibitor, maint maintenance, chemo chemotherapy, PFS progression-free survival, HR hazard ratio, CI confidence interval, ECOG Eastern Cooperative Oncology Group, PD-L1 TPS programmed death ligand 1 tumor proportion score, eGFR estimated glomerular filtration rate.
immune systems through several mechanisms, including eliciting immunogenic tumor cell death, increasing the ratio between effector T and regulatory T cells (Tregs) in the peripheral blood, and reducing myeloid-derived suppressor cells in tumor tissues (Bracci et al. 2014; Wang et al. 2017; Roselli et al. 2013). Therefore, in the case of ineffective induction immunochemotherapy, multidisciplinary maintenance, including chemotherapy, might be needed to enhance the effects of maintenance therapy. Although the pemetrexed containing maintenance enhanced the efficacy of maintenance immunotherapy, there is a possibility of increased frequency of adverse effects, such as kidney injury, during long periods of maintenance therapy, leading to discontinuation of effective maintenance treatment (Visser et al. 2018; Dumoulin et al. 2020). Therefore, reduction of overmedication remains essential to drug tolerability along with long-term survival and economic viability. Future long-term follow-up studies are needed to support these findings.

Fig. 2 Kaplan–Meier curves for PFS of maintenance therapy in patients under ICI maint without chemo (A) and those with ICI maint with chemo (B) according to responsiveness to prior immunochemo therapy. Kaplan–Meier curves for PFS of maintenance therapy in non-responders (C) and responders (D) to prior immunochemo therapy according to maintenance regimens. ICI immune checkpoint inhibitor, maint maintenance, chemo chemotherapy, PFS progression-free survival

Table 2 (continued) filtration rate, BMI body mass index, SD stable disease, CR complete response, PR partial response, NE not evaluable, NLR neutrophil-to-lymphocyte ratio

† Analysis except for NE
### Table 3 Characteristics of the patients under ICI maint without chemo classified by responsiveness of prior immunochemotherapy

| Characteristics                                      | Responders | Non-responders | p value |
|------------------------------------------------------|------------|----------------|---------|
| **Number**                                           | 35         | 15             |         |
| **Age**                                               |            |                |         |
| Median (range)                                       | 69 (39–79) | 67 (54–77)     | 0.74    |
| **Sex**                                               |            |                |         |
| Male                                                 | 29 (82.9)  | 12 (80.0)      | 1.0     |
| Female                                               | 6 (17.1)   | 3 (20.0)       |         |
| **ECOG-performance status**                          |            |                |         |
| 0                                                    | 14 (40.0)  | 6 (40.0)       | 1.0     |
| 1                                                    | 19 (54.3)  | 9 (60.0)       |         |
| 2/3                                                  | 2 (5.7)    | 0 (0.0)        |         |
| **Stage**                                            |            |                |         |
| III/IV                                               | 31 (88.6)  | 12 (80.0)      | 0.42    |
| Recurrent                                            | 4 (11.4)   | 3 (20.0)       |         |
| **Smoking status**                                   |            |                |         |
| Current/former                                       | 30 (85.7)  | 12 (80.0)      | 0.68    |
| Never                                                | 5 (14.3)   | 3 (20.0)       |         |
| **Histology**                                        |            |                |         |
| Adenocarcinoma                                       | 9 (25.7)   | 6 (40.0)       | 1.0     |
| Squamous cell carcinoma                              | 18 (51.4)  | 8 (53.3)       |         |
| Other                                                | 8 (22.9)   | 1 (6.7)        |         |
| **Oncogenic driver**                                 |            |                |         |
| EGFR mutation positive                               | 1 (2.9)    | 3 (20.0)       | 0.075   |
| EGFR wild type                                       | 21 (60.0)  | 5 (33.3)       |         |
| Not investigated                                      | 13 (37.1)  | 7 (46.7)       |         |
| **PD-L1 TPS**                                        |            |                |         |
| ≥ 50%                                                | 16 (45.7)  | 3 (20.0)       | 0.12    |
| 1–49%                                                | 11 (31.4)  | 5 (33.3)       |         |
| < 1%                                                 | 5 (14.3)   | 4 (26.7)       |         |
| Not investigated                                      | 3 (8.6)    | 3 (20.0)       |         |
| **Regimen**                                          |            |                |         |
| Carboplatin + nab-paclitaxel + bevacizumab + atezolizumab | 8 (22.9)  | 5 (33.3)       | 0.49    |
| Carboplatin + paclitaxel / nab-paclitaxel + pembrolizumab | 26 (74.3) | 10 (66.7)      |         |
| Carboplatin + nab-paclitaxel + atezolizumab          | 1 (2.9)    | 0 (0.0)        |         |
| **Renal function at the start of maintenance therapy** |            |                |         |
| eGFR ≥ 60 mL/min/1.73 m²                              | 27 (77.1)  | 11 (73.3)      | 1.0     |
| eGFR < 60 mL/min/1.73 m²                              | 8 (22.9)   | 4 (26.7)       |         |
| **BMI at the start of induction therapy**            |            |                |         |
| ≥ 18.5                                               | 30 (85.7)  | 15 (100)       | 0.31    |
| < 18.5                                               | 5 (14.3)   | 0 (0.0)        |         |
| **Serum albumin at the start of maintenance therapy** |            |                |         |
| ≥ 3.5 g/dL                                           | 32 (91.4)  | 14 (93.3)      | 1.0     |
| < 3.5 g/dL                                           | 3 (8.6)    | 1 (6.7)        |         |
| **NLR at the start of maintenance therapy**          |            |                |         |
| ≥ 5                                                  | 1 (2.9)    | 3 (20.0)       | 0.075   |
| < 5                                                  | 34 (97.1)  | 12 (80.0)      |         |

ICI immune checkpoint inhibitor, maint maintenance, chemo chemotherapy, ECOG Eastern Cooperative Oncology Group, EGFR epidermal growth factor receptor, PD-L1 TPS programmed death ligand 1 tumor proportion score, eGFR estimated glomerular filtration rate, BMI body mass index, NLR neutrophil-to-lymphocyte ratio

aBevacizumab versus all others
bPD-L1 TPS ≥ 50% versus all others
cECOG-performance status 0/1 versus 2/3
dSquamous versus all others
eEGFR mutation positive versus all others
Despite our best efforts, certain limitations of this study must be acknowledged. First, the distribution of histological subtypes was different between groups receiving ICI maint with chemo and ICI maint without chemo. Although there was no difference between histological subtypes and PFS for ICI maint without chemo, the histological subtypes could potentially affect the comparison between maintenance therapies. Second, we could not evaluate adverse effects associated with maintenance therapy which remains one of the most important factors to select therapeutic strategy in NSCLC patients. Third, a single experienced attending physician determined the timing of tumor imaging and judged the tumor response, which might introduce measurement bias.

In conclusion, this study retrospectively analyzed patient data to identify potential predictors for maintenance therapy after induction immunochemotherapy in patients with advanced NSCLC. It found that response to induction immunochemotherapy was one of the most important factors to select a therapeutic strategy for maintenance therapy in patients with advanced NSCLC. Future prospective large-cohort studies are warranted to confirm our findings.

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Author contributions RN and TY contributed to the study conception and design. RN, KM, AN, YG, YO, TT, CT, KO, YC, RT, TY, OH, and ST obtained the clinical data. Data were interpreted by RN, TY, YM, MI, ST, YK, JU, and KT. The manuscript was prepared by RN and TY. The final version of the manuscript was read and approved by all the authors.

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Availability of data and material The datasets generated during the current study are not publicly available due to ethical constraints, but are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest Tadaaki Yamada received commercial research grants from Pfizer, Ono Pharmaceutical, Janssen Pharmaceutical K.K., and Takeda Pharmaceutical Company Limited. Koichi Takayama received research grants from Chugai-Roche and Ono Pharmaceutical, and personal fees from AstraZeneca, Chugai-Roche, MSD-Merk, Eli Lilly, Boehringer-Ingelheim, and Daiichi-Sankyo. The other authors have no conflicts of interest to declare.

Ethical approval The study protocol was approved by the Ethics Committee of Kyoto Prefectural University of Medicine and was conducted in accordance with the regulations on the handling of patients’ personal information (Ethics Committee registration number: ERB309 C-1803).

Consent to participate Since this was a retrospective study, informed consent was waived and the official website was used as an opt-out method, which was approved by the Ethics Committee of each individual hospital.

Consent for publication Not applicable.

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