Efficacy of anti-PD-1 antibodies in NSCLC patients with an EGFR mutation and high PD-L1 expression

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Abstract

Introduction Several studies have demonstrated that non-small cell lung cancer patients (NSCLCs) harboring epidermal growth factor receptor (EGFR) mutations have poor clinical outcomes in response to treatment with programmed death-1 (PD-1) inhibitors. However, it remains unclear whether EGFR-mutated NSCLCs with a high programmed death-ligand-1 (PD-L1) expression (tumor proportion score ≥ 50%) respond to PD-1 inhibitors.

Methods We retrospectively investigated the NSCLCs who had received PD-1 inhibitors between January 2016 and December 2018 to assess the efficacy of PD-1 inhibitors in patients with an EGFR mutation and high PD-L1 expression.

Results There were 153 patients with a high PD-L1 expression level, and the median progression-free survival (mPFS) was 5.3 months [95% confidence interval (CI) 1.3–12.4 months] in the patients with EGFR mutations (n = 17) and 8.3 months (95% CI 6.0–11.7 months) in those with wild-type EGFR (n = 136; hazard ratio (HR) 1.62; 95% CI 0.83–2.87). Among the 110 patients in the low PD-L1 expression group, the mPFS was 1.6 months (95% CI 1.3–5.9 months) in the patients with EGFR mutations (n = 18) and 3.8 months (95% CI 2.5–5.9 months) in those with wild-type EGFR (n = 92; HR 2.59; 95% CI 1.48–4.31). The HR for PFS in the group with EGFR mutations and high PD-L1 expression was 0.97 (95% CI 0.56–1.59) compared to the group with wild-type EGFR and low PD-L1 expression.

Conclusions PD-1 inhibitors can serve as one of the treatment options for NSCLCs with an EGFR mutation and high PD-L1 expression.

Keywords Non-small cell lung cancer · Programmed death-ligand-1 · Epidermal growth factor receptor · Immune checkpoint inhibitor

Introduction

Immune checkpoint inhibitors (ICIs), particularly inhibitors of the programmed death-1 (PD-1) axis, have revolutionized the treatment of non-small cell lung cancer (NSCLC). Treatment with ICIs has been shown to result in a significant tumor response and overall survival (OS) benefit in advanced NSCLC (Borghaei et al. 2015; Brahmer et al. 2015; Mok et al. 2019; Reck et al. 2016). Pembrolizumab monotherapy has become a standard first-line treatment for advanced NSCLC in patients with a PD-L1 tumor proportion score (TPS) of at least 50%, based on the results of the KEYNOTE-024 phase III trial (Reck et al. 2016). Several studies have also shown a relationship between high PD-L1 expression and a higher objective response rate (ORR) and better survival in NSCLC patients treated with PD-1 inhibitors, including nivolumab and pembrolizumab (Aguiar et al. 2017). However, most clinical studies have excluded specific patients, for example, patients with epidermal growth factor receptor (EGFR) mutations.

Several studies have reported disappointing clinical outcomes with lower response rates and shorter survival in patients with EGFR-mutated NSCLC treated with PD-1...
inhibitors than in patients with EGFR-wild NSCLC (Bylik-icki et al. 2017; Gainor et al. 2016; Lee et al. 2018; Santambrogio and Rammensee 2019). EGFR tyrosine kinase inhibitors (EGFR-TKIs) are standard first-line treatment for EGFR-mutated NSCLC. Lisberg et al. reported a phase II trial of pembrolizumab in TKI-naive patients with advanced EGFR-mutated, PD-L1-positive NSCLC and concluded that pembrolizumab is not appropriate as a first-line treatment for EGFR-mutated NSCLC before EGFR-TKI therapy (Lisberg et al. 2018). However, it remained unclear whether EGFR-mutated NSCLC with high PD-L1 expression (TPS ≥ 50%) responds to ICIs, because the sample size in their trial was too small. We retrospectively investigated the relationship between PD-L1 expression and the efficacy of PD-1 inhibitors in NSCLC patients to assess the efficacy of PD-1 inhibitors in patients with an EGFR mutation and high PD-L1 expression.

Materials and methods

Study design

This study was a retrospective, single-center, observational study conducted at the National Cancer Center Hospital in Japan. The study was approved by the Institutional Review Board of the National Cancer Center Hospital (No. 2015-355).

Subjects

Patients with advanced NSCLC who had been treated with an anti-PD-1 antibody between March 2017 and December 2018 at the National Cancer Center Hospital in Japan were identified from the database. Patients with no PD-L1 expression data were excluded. We reviewed the medical records and abstracted the following patient characteristics: age, gender, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), histology, disease status, EGFR mutation status, details of treatment, and survival. PD-L1 expression was evaluated using the PD-L1 22C3 pharmDx (Dako, Carpinteria, CA, USA) and EGFR mutations were identified using the Cobas® EGFR Mutation Test v2 (Cobas; Roche Diagnostics, Basel, Switzerland). The patients who were adopted as subjects of our study were divided into four groups according to PD-L1 expression level and EGFR mutation status. In our study, low PD-L1 expression was defined as the presence of < 50% positive-staining tumor cells, whereas ≥ 50% positive staining was considered high PD-L1 expression. The efficacy of treatment with the PD-1 inhibitors in the four groups was assessed by evaluating progression-free survival (PFS).

Treatment and assessment

In the safety analysis, we evaluated adverse events associated with ICIs or EGFR-TKIs according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Objective tumor response in patients with target lesions was evaluated based on the Response Evaluation Criteria in Solid Tumors version 1.1 and assessment by computed tomography every 6–8 weeks after the start of treatment.

Statistical analysis

Differences between groups were analyzed using Fisher’s exact test for categorical variables. PFS was defined as the time between the start of PD-1 inhibitor treatment and progression or death from any cause; PFS was censored at a date when the patient was confirmed to be progression free. Patients whose treatment was discontinued due to toxicity in the absence of disease progression were censored at the start of the next treatment. Overall survival (OS) was measured until death or censored at the latest follow-up examination of surviving patients. Survival rates were estimated by the Kaplan–Meier method and compared using the log-rank test. All statistical analyses were performed using the JMP version 14.0 software program (SAS Institute, Cary, NC, USA). All P values were two sided, and p < 0.05 was considered evidence of a statistically significant difference.

Results

Patient characteristics

In this study, the 414 NSCLC patients treated with nivolumab or pembrolizumab at the National Cancer Center Hospital between March 2017 and December 2018 were identified as candidates for inclusion, and 263 of them were ultimately adopted as subjects of our study. We excluded 151 patients for the following reasons: absence of PD-L1 data (n = 125), participation in a clinical trial of pembrolizumab or nivolumab (n = 22), and NSCLC with ALK rearrangement (n = 4) (Fig. 1). The median age of the subjects was 62 years (range 33–87 years). High PD-L1 expression was found in 153 patients (58.2%). Thirty-five (7.5%) patients had EGFR mutations, and 29 (82.9%) of these 35 patients had an exon 19 deletion or exon 21 L858R mutation (Table 1).
Efficacy

The median follow-up time was 11.3 months [95% confidence interval (CI) 9.0–14.7 months]. Table 2 summarizes the efficacy of the PD-1 inhibitors. Kaplan–Meier curves for PFS according to PD-L1 expression level and EGFR mutation status are shown in Fig. 2. In the high PD-L1 expression group, the ORR was 29.4% (95% CI 1.3–53.1%) in the EGFR mutation subgroup (n = 17) and 43.4% (95% CI 35.4–51.8%) in the wild-type EGFR subgroup (n = 136). Median PFS was 5.3 months (95% CI 1.3–12.4 months) in the EGFR mutation subgroup and 8.3 months (95% CI 6.0–11.7 months) in the wild-type EGFR subgroup [hazard ratio (HR) 1.62; 95% CI 0.83–2.87; p = 0.125]. In the low PD-L1 expression group, the ORR was 0% in the EGFR mutation subgroup (n = 18) and 16.3% (95% CI 10.1–25.2%) in the wild-type EGFR subgroup (n = 92). Median PFS was 1.6 months (95% CI 1.3–2.5 months) in the EGFR mutation subgroup and 3.8 months (95% CI 2.5–5.9 months) in the wild-type EGFR subgroup (HR 0.39; 95% CI 0.23–0.66; p < 0.001). The PFS of the group with EGFR mutations and high PD-L1 expression was similar to the PFS in the group with wild-type EGFR and low PD-L1 expression (HR 0.97; 95% CI 0.56–1.59; p = 0.909). In the EGFR mutation group, median OS was 26.4 months (95% CI, 6.7 to not evaluated) in the high PD-L1 expression subgroup and 12.7 months (95% CI 2.6 to not evaluated) in the low PD-L1 expression subgroup. In the wild-type EGFR group, median OS was 36.2 months (95% CI 21.0–36.2 months) in the high PD-L1 expression subgroup and 13.0 months (95% CI 9.9–29.7 months) in the low PD-L1 expression subgroup. Regarding the patterns of progression after PD-1 inhibitors, there was no significant difference between the EGFR mutation group and the wild-type EGFR group.

Toxicity

An immune-related adverse event (irAE) developed in 5 (29.4%) of the 17 patients with EGFR-mutated NSCLC and high PD-L1 expression. The most frequent adverse events in this study were diarrhea (n = 2) and hypothyroidism (n = 2). Grade 3 alanine and aspartate aminotransferase elevation was observed in one patient. Grade 4 small intestinal perforation occurred in one patient treated with nivolumab, and nivolumab was discontinued; however, PD-1 inhibitor therapy was continued after the irAE in the other patients. There were no grade 5 adverse events related to the PD-1 inhibitors.

Discussion

The results of our study showed that PD-L1 expression was associated with the efficacy of PD-1 inhibitors in patients with EGFR mutations. The ORR and median PFS in the high PD-L1 expression group were 29.4% (95% CI 1.3–53.1%) and 5.3 months (95% CI 1.3–12.4 months), respectively, compared with 0% and 1.6 months (95% CI 1.3–2.5 months), respectively, in the low PD-L1 expression group. In the group of patients with an EGFR mutation, the efficacy of the PD-1 inhibitors was greater in the subgroup of patients with high PD-L1 expression than in the subgroup with low PD-L1 expression. Moreover, PFS in the group with EGFR mutations and high PD-L1 expression was similar to PFS in the group with wild-type EGFR and low PD-L1 expression (HR 0.97; 95% CI 0.56–1.59; p = 0.909).

Berghoff et al. recently reviewed ICI treatment in patients with oncogene-addicted NSCLC (Berghoff et al. 2019). They evaluated the efficacy of ICIs in NSCLC patients with wild-type EGFR and in patients with EGFR-mutated NSCLC in five clinical trials: CheckMate 057 (Borghaei et al. 2015), KEYNOTE-010 (Herbst et al. 2016), OAK (Rittmeyer et al. 2017), POPLAR (Fehrenbacher et al. 2016), and IMpower150 (Socinski et al. 2018), and found that the survival benefits of treatment with an ICI tended to
be lower in patients with EGFR mutations than in patients with wild-type EGFR. Lee et al. performed a meta-analysis study that assessed the role of ICIs as second-line therapy in advanced EGFR-mutated NSCLC (Lee et al. 2018). Their analysis of the data from three clinical trials (CheckMate 057 (Borghaei et al. 2015), KEYNOTE-010 (Herbst et al. 2016), and KEYNOTE-189 (Herbst et al. 2018)) revealed that the objective response rate (ORR) and median progression-free survival (mPFS) were significantly higher in patients with EGFR mutations compared to those with wild-type EGFR. The details of the patient characteristics and the efficacy of PD-1 inhibitors are presented in Tables 1 and 2, respectively.

### Table 1 Patient characteristics

|                      | All patients N | PD-L1 high EGFR + N | PD-L1 high EGFR − N | PD-L1 low EGFR + N | PD-L1 low EGFR − N |
|----------------------|----------------|---------------------|---------------------|--------------------|--------------------|
| Total N              | 263            | 17                  | 136                 | 18                 | 92                 |
| Median age, years (range) | 62 (33–87)    | 62 (47–85)          | 62 (33–87)          | 64.5 (37–83)       | 62 (33–83)         |
| Sex                  |                |                     |                     |                    |                    |
| Female               | 83             | 7                   | 36                  | 15                 | 25                 |
| Male                 | 180            | 10                  | 100                 | 3                  | 67                 |
| ECOG-PS              |                |                     |                     |                    |                    |
| 0, 1                 | 236            | 14                  | 125                 | 16                 | 81                 |
| 2                    | 27             | 3                   | 11                  | 2                  | 11                 |
| Smoking history      |                |                     |                     |                    |                    |
| Never smoker         | 53             | 7                   | 21                  | 12                 | 13                 |
| Smoker               | 210            | 10                  | 115                 | 6                  | 79                 |
| Histologic classification |            |                     |                     |                    |                    |
| Adenocarcinoma       | 203            | 16                  | 107                 | 18                 | 62                 |
| Squamous             | 52             | 0                   | 24                  | 0                  | 28                 |
| Others               | 8              | 1                   | 5                   | 0                  | 2                  |
| Disease status       |                |                     |                     |                    |                    |
| Stage IV             | 140            | 9                   | 75                  | 12                 | 44                 |
| Stage III            | 53             | 3                   | 30                  | 2                  | 18                 |
| Recurrence           | 70             | 5                   | 31                  | 4                  | 30                 |
| EGFR mutation status |                |                     |                     |                    |                    |
| Ex19del              | 21             | 8                   | 0                   | 13                 | 0                  |
| L858R                | 8              | 6                   | 0                   | 2                  | 0                  |
| Others               | 6              | 3                   | 0                   | 3                  | 0                  |
| Negative             | 0              | 0                   | 136                 | 0                  | 92                 |
| ICIs status          |                |                     |                     |                    |                    |
| Pembrolizumab        | 141            | 11                  | 105                 | 4                  | 21                 |
| Nivolumab            | 122            | 6                   | 31                  | 14                 | 71                 |
| Line of ICI          |                |                     |                     |                    |                    |
| First-line           | 92             | 2                   | 85                  | 0                  | 5                  |
| Second-line          | 111            | 3                   | 42                  | 2                  | 64                 |
| Third-line or more   | 60             | 12                  | 9                   | 16                 | 23                 |

ECOG-PS Eastern Cooperative Oncology Group Performance Status, EGFR epidermal growth factor receptor, ICI immune checkpoint inhibitors, PD-L1 programmed death-ligand 1

### Table 2 Summary of the efficacy of PD-1 inhibitors

|                      | ORR (%) 95% CI | mPFS (month) 95% CI | HR of mPFS 95% CI |
|----------------------|---------------|---------------------|------------------|
| PD-L1 high EGFR − N=136 | 43.4          | 8.3                 | 0.56             |
|                      | 35.4–51.8     | 6.0–11.7            | 0.40–0.78        |
| PD-L1 high EGFR + N=17 | 29.4          | 5.3                 | 0.97             |
|                      | 1.3–53.1      | 1.3–12.4            | 0.56–1.59        |
| PD-L1 low EGFR − N=92 | 16.3          | 3.8                 | Reference        |
|                      | 10.1–25.2     | 2.5 to 5.9          |                  |
| PD-L1 low EGFR − N=18 | 0             | 1.6                 | 2.59             |
|                      |               | 1.3–2.5             | 1.48–4.31        |

CI confidence interval, EGFR epidermal growth factor receptor, HR hazard ratio, mPFS median progression-free survival, ORR objective response rate, PD-L1 programmed death-ligand 1
and POPLAR (Fehrenbacher et al. 2016)) showed that ICIs did not improve OS compared with docetaxel therapy. Both meta-analyses also evaluated the results of ICI therapy in PD-L1-positive NSCLC, but there have been no reports on the efficacy of ICIs in patients with EGFR-mutated NSCLC and high PD-L1 expression. Our own data showed that PD-1 inhibitors were beneficial as second-line or later treatment of patients with EGFR-mutated NSCLC and high PD-L1 expression.

Data regarding the relative risk of toxicity with ICIs and EGFR-TKIs in NSCLC patients in several studies have revealed more severe irAEs when EGFR-TKIs were used in combination with ICIs or used after ICIs. Ahn et al. reported that a phase Ib clinical trial of concurrent durvalumab (anti-EGFR-TKI agent) plus osimertinib was halted due to a high rate of interstitial lung disease (Ahn et al. 2016). Schoenfeld et al. found that treatment with an ICI followed by osimertinib was associated with severe irAEs (Schoenfeld et al. 2019), but no irAEs were observed in their study when osimertinib preceded ICI therapy or when treatment with an ICI was followed by other EGFR-TKIs. A case reported by Kaira et al. showed that EGFR-TKI re-challenge immediately after nivolumab therapy may be tolerable and effective in patients with EGFR-TKI resistance (Kaira and Kagamu 2019). Whether irAEs are more severe when EGFR-TKIs are used in combination with ICIs or after ICIs remains a matter of controversy. If future investigations elucidate the mechanisms of toxicity and clinical situations in which toxicity develops, it might be possible to provide better treatment options and clinical benefits to patients with EGFR-mutated NSCLC and high PD-L1 expression.

This study had several limitations. First, this study was retrospective and conducted in a single center. The follow-up periods were not identical; however, all patients were regularly followed up every 1–2 months as outpatients, and evaluations were performed every 3–6 months for 1 year. In addition, their condition was subsequently checked every 6 months by X-ray, computed tomography (CT), magnetic resonance imaging, or positron emission tomography CT. Second, patient characteristics were not uniform across the groups, and that may have led to selection bias.

**Conclusions**

In conclusion, our study showed that patients with EGFR-mutated NSCLC and higher PD-L1 expression received a greater benefit of treatment with PD-1 inhibitors in terms of ORR and PFS than patients with low PD-L1 expression did. In addition, the ORR and PFS in the group of NSCLC patients with an EGFR mutation and high PD-L1 expression were similar to the ORR and PFS in the group with wild-type EGFR and low PD-L1 expression. The findings in our study suggest that even in NSCLC patients with an EGFR mutation evaluation of PD-L1 expression can help predict the efficacy of PD-1 inhibitors, and that PD-1 inhibitors can serve as one of the treatment options for patients with an EGFR mutation and high PD-L1 expression.
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Author contributions  KM and HH made contributions to the conception and design, acquisition of data, and data analysis. KM drafted the manuscript. HH made substantial contributions to the study design and revision of the manuscript. KM analyzed and interpreted data and edited the manuscript. All authors critically reviewed the manuscript, and all approved the final version submitted for publication.

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Data availability  The datasets generated during the current study are not publicly available due to ethical restrictions, but are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest  Dr. Ohe reports grants and personal fees from Ono Pharmaceutical, grants and personal fees from Bristol-Myers Squibb, grants and personal fees from MSD, grants from AstraZeneca, during the conduct of the study; grants and personal fees from Boehringer Ingelheim, personal fees from Otsuka, grants and personal fees from Ono Pharmaceutical, personal fees from Astellas, personal fees from MSD, grants from AstraZeneca, personal fees from Taiho, personal fees from Guardant Health, grants and personal fees from Chugai, grants and personal fees from Eli Lilly, grants and personal fees from Taiho, personal fees from Takeda, grants and personal fees from Ono, grants from Chugai, grants and personal fees from Daiichi Sankyo, grants and personal fees from Bristol-Myers Squibb, grants and personal fees from Taiho, personal fees from DSM, grants and personal fees from MSD, grants and personal fees from Novartis, grants and personal fees from Daiichi Sankyo, grants and personal fees from Bristol-Myers Squibb, grants and personal fees from Eli Lilly, personal fees from Taiho, personal fees from AstraZeneca, grants and personal fees from Ono, personal fees from Astellas, grants from MSD, personal fees from Ono Pharmaceutical, personal fees from Daiichi Sankyo, grants and personal fees from Novartis, personal fees from Takeda, grants and personal fees from MSD, grants and personal fees from AstraZeneca, grants and personal fees from Taiho, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Novartis, grants and personal fees from Astellas, grants and personal fees from Daiichi Sankyo, grants and personal fees from Bristol-Myers Squibb, grants and personal fees from Taiho, grants and personal fees from MSD, personal fees from Ono, grants and personal fees from Astellas, grants and personal fees from Merck Serono, grants from Genomic Health, grants and personal fees from Lilly, grants and personal fees from Ono. The remaining authors declare no conflict of interest.

Ethics approval and consent to participate  The study was approved by the Institutional Review Board of the National Cancer Center Hospital (No. 2015–355).

Consent for publication  This manuscript contains no individual person’s data.

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