Prognostic Implication of PD-L1 Expression on Osimertinib Treatment for *EGFR*-mutated Non-small Cell Lung Cancer

TOSHIHIRO SHIOZAWA[1*], TAKESHI NUMATA[2*], TOMOHIRO TAMURA[3], TAKEO ENDO[2],
TAKAYUKI KABURAGI[3], YUSUKE YAMAMOTO[4], HIDEYASU YAMADA[5], NORIHIRO KIKUCHI[6],
KAZUHITO SAITO[7], MASAHARU INAGAKI[7], KOICHI KURISHIMA[8], YASUNORI FUNAYAMA[9],
KUNIHIKO MIYAZAKI[10,] NOBUYUKI KOYAMA[11], KINYA FURUKAWA[12],
HIROYUKI NAKAMURA[12], SHINJI KIKUCHI[13], HIDEO ICHIMURA[13],
YUKIO SATO[13], IKUO SEKINE[14], HIROAKI SATOH[15] and NOBUYUKI HIZAWA[1]

[1]Department of Respiratory Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan;
[2]Division of Respiratory Medicine, Mito Medical Center, Mito, Japan;
[3]Respiratory Center, Ibaraki Prefectural Central Hospital, Kasama, Japan;
[4]Division of Respiratory Medicine, Hitachi General Hospital, Hitachi, Japan;
[5]Division of Respiratory Medicine, Hitachinaka Medical Center, University of Tsukuba, Hitachinaka, Japan;
[6]Division of Respiratory Medicine, Kasumigaura Medical Center, Tsuchiura, Japan;
[7]Divisions of Respiratory Medicine and Thoracic Surgery, Tsuchiura Kyodo General Hospital, Tsuchiura, Japan;
[8]Division of Respiratory Medicine, Tsukuba Medical Center Hospital, Tsukuba, Japan;
[9]Division of Respiratory Medicine, Tsukuba Gakuen Hospital, Tsukuba, Japan;
[10]Division of Respiratory Medicine, Ryugasaki Saiseikai Hospital, Ryugasaki, Japan;
[11]Department of Respiratory Medicine, Saitama Medical Center, Saitama Medical University, Saitama, Japan;
[12]Divisions of Respiratory Medicine and Thoracic Surgery,
Tokyo Medical University, Ibaraki Medical Center, Ami, Japan;
[13]Department of Thoracic Surgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan;
[14]Department of Medical Oncology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan;
[15]Division of Respiratory Medicine, Mito Kyodo General Hospital-Mito Medical Center,
University of Tsukuba, Mito, Japan

Abstract. *Background/Aim: Real-world data on the clinical outcomes of first-line osimertinib treatment for non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations is lacking. This study aimed to reveal the treatment outcomes and prognostic factors of osimertinib as first-line therapy in clinical practice settings. Patients and Methods: We retrospectively evaluated clinical outcomes of patients with EGFR-mutated NSCLC treated with osimertinib as first-line therapy across 12 institutions in Japan between August 2018 and March 2020. Results: Among 158 enrolled patients, the objective response rate (ORR) was 68%, and the estimated median progression-free survival (PFS) was 17.1 months [95% confidence interval (CI)=14.5-19.7]. Subgroup analysis showed that PFS in the group with high programmed death-ligand 1 (PD-L1) expression was significantly shorter than that in groups with low or no PD-L1 expression (10.1 vs. 16.1 vs. 19.0 months; p=0.03). Univariate and multivariate analyses demonstrated that high PD-L1 expression was the only independent adverse prognostic factor of osimertinib outcome related to PFS (hazard ratio=2.71; 95%CI=1.26-5.84; p=0.01). In terms of anti-tumor response, there was no statistically significant correlation between PD-L1 expression and the ORR (67% vs. 76% vs. 65%; p=0.51). No significant correlation was also found between PD-L1 and the incidence of de novo resistance to osimertinib (p=0.39). Conclusion: Although PD-L1 expression was not associated with either*

*These Authors contributed equally to the present study.

Correspondence to: Toshihiro Shiozawa, MD, Department of Respiratory Medicine, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575, Japan. Tel: +81 298533144, Fax: +81 298533144, e-mail: t-shiozawa@md.tsukuba.ac.jp

Key Words: Lung cancer, EGFR mutation, osimertinib, PD-L1.

the ORR or frequency of de novo resistance, high PD-L1 expression could be an independent adverse prognostic factor related to PFS in osimertinib treatment.

Molecularly targeted therapies have contributed to an improvement in the survival of patients with recurrent or advanced non-small cell lung cancer (NSCLC) harboring driver oncogenes. Mutations in the epidermal growth factor receptor (*EGFR*), which is a driver oncogene in NSCLC, lead to tumorigenesis and tumor growth *via* the activated *EGFR* signaling pathway (1). Previous phase III studies demonstrated that *EGFR* tyrosine kinase inhibitors (EGFR-TKIs) as first-line therapy for *EGFR*-mutated NSCLC had better outcomes than a platinum-based regimen in terms of both progression-free survival (PFS) and objective response rate (ORR) (2-4). EGFR-TKIs are thus the current standard first-line agents for treating patients with *EGFR*-mutated advanced NSCLC.

First- to third-generation EGFR-TKIs are available in clinical practice. Of these, osimertinib, categorized as a third-generation EGFR-TKI, has irreversible anti-tumor activity against both *EGFR*-sensitizing and *EGFR*-resistant T790M mutations. In the global phase III FLAURA trial involving patients with untreated *EGFR*-mutated recurrent or advanced NSCLC, osimertinib prolonged PFS and overall survival (OS) compared with the standard of care achieved by first-generation EGFR-TKIs (5, 6). Thus, osimertinib is regarded as the most recommended first-line agent in these patients (7).

In clinical practice, osimertinib is indicated for a heterogeneous population, including patients with decreased performance status, symptomatic brain or leptomeningeal metastases, and uncommon mutations. However, as per the criteria of FLAURA trials, these patient groups are ineligible for osimertinib treatment. This discrepancy in recommendations suggests that there is a data gap regarding treatment outcomes between the results of the FLAURA trial and those noted in current clinical practice. Therefore, in addition to pivotal clinical trial data, it is important to collect and analyze post-marketing clinical data. Although the use of osimertinib as a first-line agent has increased since its approval, data regarding outcomes and prognostic factors with this treatment in clinical practice are still lacking.

To bridge this knowledge gap, we conducted this multi-institutional, retrospective, observational study to evaluate the treatment outcomes and prognostic factors of first-line osimertinib for treatment of patients with recurrent or advanced *EGFR*-mutated NSCLC.

Patients and Methods

Data collection. Twelve institutions in Ibaraki Prefecture, Japan participated in this study. We enrolled patients with recurrent or advanced NSCLC with *EGFR* mutations who received osimertinib as a first-line agent between August 2018 and March 2020. The data cut-off was May 31, 2020.

The following clinical data were collected: age, sex, smoking status (current, former, or never), Eastern Cooperative Oncology Group performance status (PS), stage at diagnosis according to the TNM Classification of Malignant Tumors (eighth edition), histology, type of *EGFR* mutation, presence of central nervous system (CNS) metastasis, and programmed death-ligand 1 (PD-L1) expression status using immunohistochemistry. Based on previous studies, PD-L1 expression was classified as none, low, and high if the tumor percentage score (TPS) of PD-L1 was <1%, 1%-49%, and > 50%, respectively (8, 9).

Statistical analysis. The endpoints in this study were the efficacy outcomes. The radiological anti-tumor response was evaluated based on the Response Evaluation Criteria in Solid Tumors (version 1.0.10). The ORR was defined as the proportion of patients who achieved anti-tumor response with complete response (CR) or partial response (PR). The disease control rate (DCR) was defined as the ORR plus the proportion of patients achieving stable disease (SD).

The definition of *de novo* resistance was based on a previous report as those whose best overall response was PD or whose PFS was less than 6 months (10). PFS was defined as the duration from the initiation of osimertinib treatment to disease progression or death from any cause. OS was defined as the duration from the initiation of osimertinib treatment to death from any cause. If death did not occur at the cut-off date, patients were censored. If patients were lost during the observation period, they were censored on the last day of confirmed survival. Clinical evaluations of PFS and OS were conducted using the Kaplan–Meier method. The log-rank test was used to compare two different survival curves. A Cox regression model was applied to examine prognostic factors related to survival. Univariate and multivariate hazard ratios (HRs) were reported with 95% confidence intervals (CIs). Statistical analysis was performed using IBM SPSS Statistics for Windows (version 24.0; IBM Corp., Armonk, NY, USA). All tests were two-sided and judged statistically significant if the calculated *p*-values were <0.05.

Ethical approval. This study was initiated after the study protocol was approved by the institutional review board of all institutions (approval number in Tsukuba University Hospital: R01-385). This retrospective observational study was conducted in compliance with the Helsinki Declaration. Individual patient data were anonymized prior to enrollment.

Informed consent was waived because the present study was a retrospective, observational research. Opt-out was done on the website of each institution.

Results

Patient characteristics. Among 161 patients initially enrolled, three were excluded from the analysis owing to the lack of data, resulting in a total of 158 eligible patients for the current study. Table I shows the patient characteristics. The median age was 73 years (range=39-93 years). Females accounted for 58% of the sample population, and adenocarcinoma was present in 95% of all cases. The proportions of *EGFR* mutation subtypes were 52% exon19 deletion, 43% exon21 L858R point mutation, and 5% uncommon mutation. Forty-five patients (28%) had CNS metastases at the time of diagnosis. The TPS of PD-L1 was none, low, and high in 60

Table I. *Patient characteristics.*

	N=158
Age (years)	73 (39-93)
Sex	
Male	66
Female	92
Smoking status	
Never	83
Former or current	74
Unknown	1
PS	
0/1/2/3/4/unknown	50/79/18/7/2/2
Clinical stage	
3/4/recurrent/other	15/120/22/1
Histology	
Adenocarcinoma	150
Squamous cell carcinoma	5
Other	3
EGFR mutation	
Exon 19 del	82
L858R	68
Uncommon	8
CNS metastasis	
Yes	45
No	113
PD-L1 expression	
None	60
Low	41
High	27
Unknown	30

PS: Performance status; EGFR: epidermal growth factor receptor; CNS: central nervous system; PD-L1: programmed death-ligand 1.

(38%), 41 (26%), and 27 (17%) patients, respectively. The remaining 30 patients (19%) had unknown TPS.

Survival. The median follow-up period of the present study was 12.5 months. The estimated median PFS was 17.1 months (95%CI=14.5-19.7). OS did not reach the median.

We examined the outcomes of osimertinib therapy according to patient subgroups of age, sex, smoking status, PS, stage, mutation subtype, CNS metastases, and TPS. No significant difference in PFS was observed with respect to age (<70 *vs.* ≥70 years, Figure 1A), sex (male *vs.* female, Figure 1B), smoking status (never *vs.* current or former, Figure 1C), PS (0-1 *vs.* 2-4, Figure 1D), stage (III or recurrent *vs.* IV, Figure 1E), mutation subtype (Exon 19 del *vs.* L858R *vs.* uncommon, Figure 1F), and CNS metastasis (present *vs.* absent Figure 1G). However, the high TPS group had a significantly poorer PFS of 10.1 months compared with the low and no TPS groups that had a PFS of 16.1 and 19.0 months, respectively (log-rank p=0.03, Figure 1H).

Next, we performed univariate and multivariate analyses to evaluate prognostic factors associated with PFS. Among

collected patient characteristics, we selected the eight factors mentioned above. As shown in Table II, only high TPS was found to be a statistically significant adverse prognostic factor related to PFS (HR=2.71; 95%CI=1.26-5.84; p=0.01).

Anti-tumor response. At the cut-off date, a response assessment was obtained for 140 patients. The best overall responses to osimertinib in the overall population included a CR of 3% (n=6), PR of 65% (n=102), SD of 14% (n=22), and PD of 6% (n=10), with an ORR of 68% and a DCR of 82%. We further compared best overall responses to osimertinib focusing on PD-L1 expression (Figure 2). There was no statistically significant difference in the ORR among the high, low, and no TPS groups (67%, 76%, and 65%, respectively; p=0.51, Figure 2A). DCR was also similar among the high, low, and no TPS groups (81%, 88%, and 80%, respectively; p=0.57, Figure 2B).

De novo resistance to osimertinib. We further evaluated the relationship between PD-L1 expression and the incidence of *de novo* resistance. We excluded cases whose best overall response was not evaluable and whose information regarding PD-L1 expression was not obtained; as a result, 114 cases were included. As shown in Table III, there was no statistically significant correlation between PD-L1 expression and the incidence of *de novo* resistance to osimertinib (p=0.39).

Discussion

The present study investigated the clinical outcomes and prognostic factors of osimertinib as a first-line treatment for advanced or recurrent NSCLC harboring *EGFR* mutations in a clinical practice setting. The results showed that the efficacy of osimertinib in the overall population was favorable, similar to that in the FLAURA trial. Although there was no statistically significant difference in the ORR and the incidence of *de novo* resistance among the high, low, and no TPS groups, the PFS of osimertinib in the high TPS group was inferior to that in the low or no TPS groups. Furthermore, univariate and multivariate analyses showed that high PD-L1 expression was an independent adverse prognostic factor associated with PFS in osimertinib treatment.

Compared to the FLAURA study, there were several differences in baseline patient characteristics in the present study. Specifically, in our study, there were more elderly patients and a higher frequency of decreased PS and presence of CNS metastases, while there was a lower frequency of never smokers. Racial differences were also observed. Some clinical factors, such as decreased PS and the presence of CNS metastasis, are poor prognostic factors for advanced NSCLC. Therefore, we conducted a subgroup analysis to evaluate whether these clinical factors affected the efficacy of osimertinib. The results showed that factors
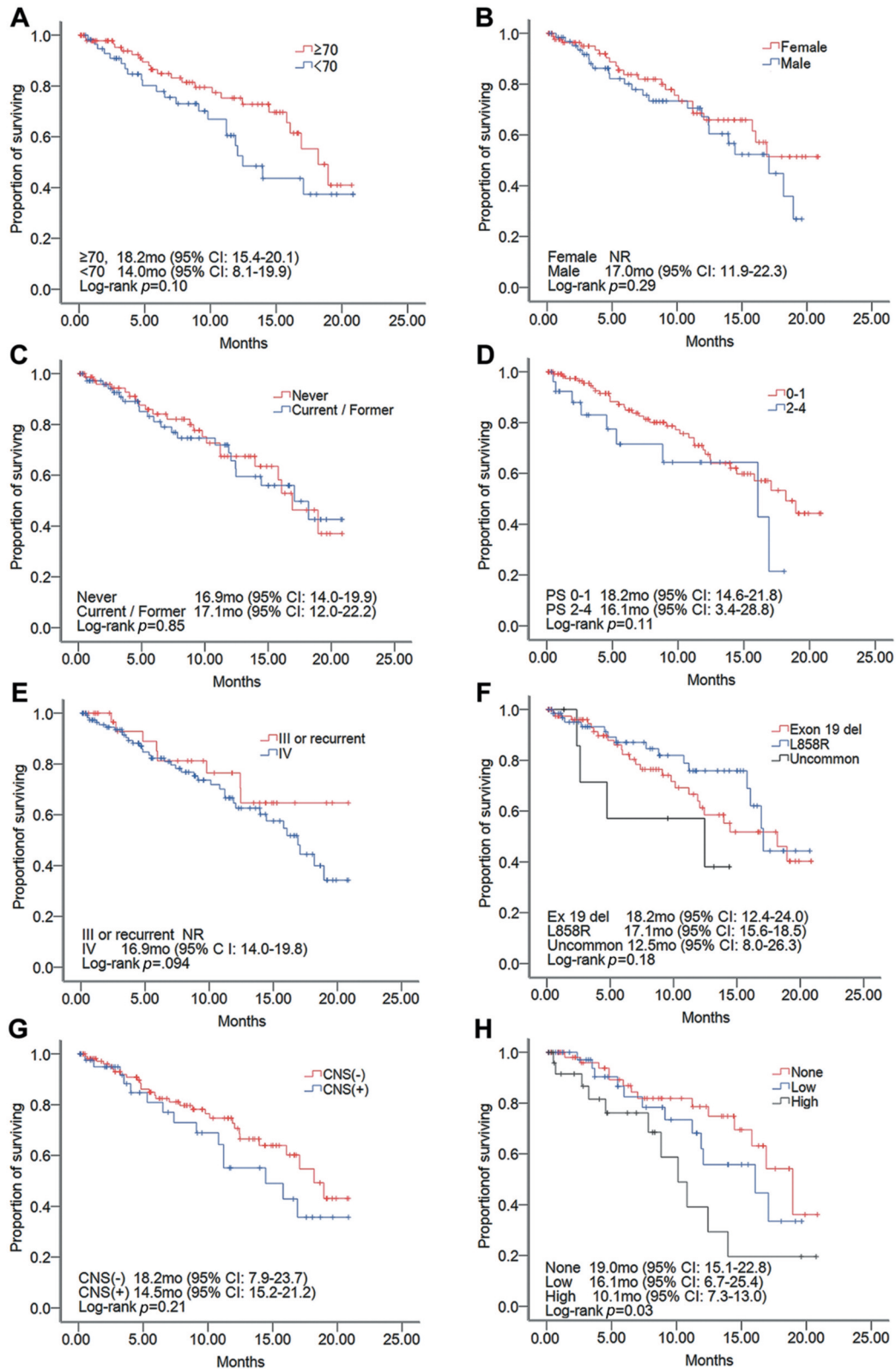
Figure 1. *Progression-free survival according to age (A), sex (B), smoking status (C), PS (D), stage (E), mutation subtype (F), CNS metastasis (G), and PD-L1 expression levels (H). PS: Performance status; CNS: central nervous system; PD-L1: programmed death-ligand 1; CI: confidence interval; NR: not reached.*

Table II. *Univariate and multivariate analyses of factors related to PFS.*

	Univariate		Multivariate	
Variables	HR 95%CI	*p*-Value	HR 95%CI	*p*-Value
Age				
<70 years	ref		ref	
≥70 years	0.73 (0.37-1.44)	0.36	1.00 (0.47-2.11)	0.99
Sex				
Male	ref		ref	
Female	1.56 (0.79-3.50)	0.20	1.58 (0.064-3.84)	0.32
Smoking				
Never	ref		ref	
Current/former	1.06 (0.54-2.07)	0.87	0.98 (0.39-2.45)	0.96
Ps				
0-1	ref		ref	
2-4	1.48 (0.57-3.85)	0.41	1.67 (0.60-4.63)	0.32
Stage				
III or recurrent	ref		ref	
IV	0.66 (0.33-1.32)	0.24	0.40 (0.13-1.21)	0.10
Mutation type				
Exon 19 del	ref		ref	
L858r	1.41 (0.62-3.11)	0.42	1.97 (0.86-4.50)	0.10
CNS metastasis				
Absent	ref		ref	
Present	1.18 (0.57-2.43)	0.65	1.20 (0.53-2.68)	0.66
TPS				
None or low	ref		ref	
High	2.37 (1.16-4.83)	0.02	2.71 (1.26-5.84)	0.01

PFS: Progression-free survival; HR: hazard ratio; CI: confidence interval; PS: performance status; CNS: central nervous system TPS: tumor proportion score; ref: reference.

other than TPS did not affect the outcome (PFS) of osimertinib treatment. A previous phase II trial showed that osimertinib treatment provides a clinical benefit for patients with *EGFR* T790M-mutated NSCLC whose PS score has declined to 2-4 (11). In the FLAURA study, osimertinib resulted in significantly longer survival than the standard of care with first-generation EGFR-TKIs, even in patients who had CNS metastases at diagnosis (12). Together with these previous reports, the present study indicates that osimertinib could be administered to such patients in clinical practice.

In the present study, the estimated median PFS of osimertinib in the high TPS group was 10.1 months (95%CI=7.3-13.0), which was significantly shorter than that in the low or no TPS groups. Additionally, the present study showed that high TPS was an independent adverse factor associated with the PFS of osimertinib treatment. The subset analysis from the FLAURA trial examined the clinical outcomes of osimertinib, focusing on PD-L1 expression (13). Although the PFS of osimertinib was comparable in both PD-L1 positive and negative groups, the threshold for PD-L1 expression in the tumor cells (TCs) was set at 1%. Additionally, evaluation for TC≥50% of the population was lacking in a few cases (n=7). A recent study with 71 patients who received first-line osimertinib revealed that patients with high PD-L1 expression had poorer PFS than those with low or negative PD-L1 (median PFS, 5.0 *vs*. 17.4 months, *p*<0.001) (14). The present study demonstrated results similar to that study in a larger sample size.

The present study suggested that the patients with high TPS had a higher risk of acquired resistance to osimertinib, because there was no statistically significant difference in the incidence of *de novo* resistance between the group with high TPS and the other two groups, despite of the inferior PFS in the group with high TPS. Accordingly, physicians should be aware of the acquired resistance to osimertinib for patients with high PD-L1 expression, even though they initially had favorable anti-tumor response. There was a discrepancy in the anti-tumor response and *de novo* resistance rate between the previous and present studies. Previous studies reported that patients with high PD-L1 expression had lower ORR and more frequent *de novo* resistance to EGFR-TKIs compared with the group with low or no PD-L1 expression (14, 15). It remains controversial whether increased PD-L1 expression contributed to primary or acquired resistance to osimertinib treatment. One speculation to the result of the present study is the association between Yes-associated protein (YAP) activity and PD-L1 expression on the EGFR signaling
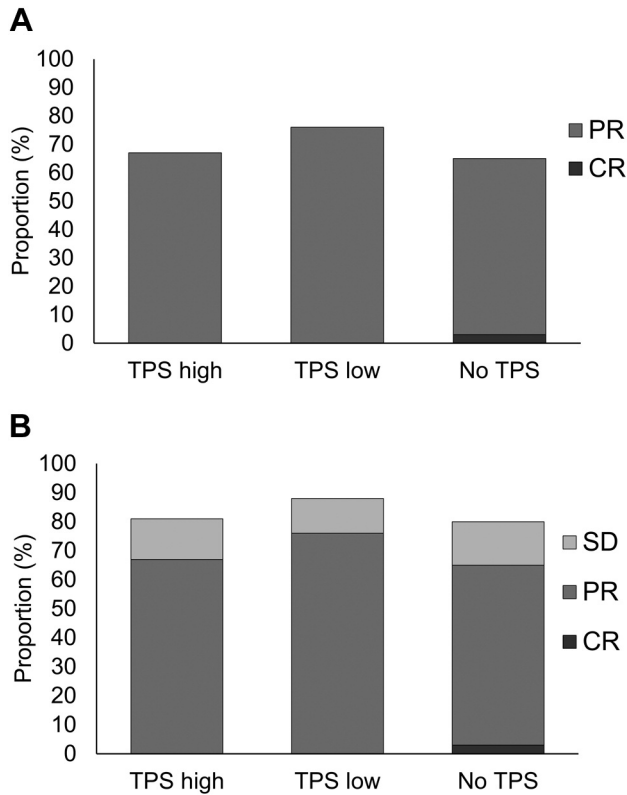
A

B

Figure 2. *Best overall response according to tumor proportion score (TPS). Objective response rate stratified by TPS (A) and disease control rate stratified by TPS (B). CR: Complete response; PR: partial response; SD: stable disease.*

Table III. *Relationship between PD-L1 expression and de-novo resistance to osimertinib.*

		TPS			
	N	None	Low	High	*p*-value
De novo	15	5 (33%)	5 (33%)	5 (33%)	
Non-*de novo*	99	19 (19%)	33 (33%)	47 (48%)	0.39

PD-L1: Programmed death-ligand 1; TPS: tumor proportion score.

This study had some limitations. First, there was a bias originating from the study's retrospective nature. Second, OS was not reached owing to the short observation period. Third, information regarding TPS was not obtained in approximately 20% of the participants. Finally, the current study included only Japanese patients; hence, ethnic differences may affect the results.

In conclusion, the present study provided clinically relevant data on the outcomes of first-line osimertinib for advanced or recurrent NSCLC with *EGFR* mutations. The favorable efficacy of osimertinib in this study was similar to that observed in the FLAURA trial. High TPS could be an independent adverse prognostic factor for PFS in osimertinib therapy, though the ORR and incidence of *de novo* resistance were similar regardless of PD-L1 expression. For patients with *EGFR*-mutated advanced NSCLC with high PD-L1 expression, physicians should be aware of the risk of acquired resistance to osimertinib, even though osimertinib initially showed favorable anti-tumor response.

Conflicts of Interest

There are no relevant conflicts of interest to be disclosed.

Authors' Contributions

Toshihiro Shiozawa, Hiroaki Satoh, and Nobuyuki Hizawa planned and designed this study. Toshihiro Shiozawa, Takeshi Numata, Tomohiro Tamura, Takeo Endo, Takayuki Kaburagi, Yusuke Yamamoto, Hideo Ichimura, Hideyasu Yamada, Norihiro Kikuchi, Kazuhito Saito, Masaharu Inagaki, Koichi Kurishima, Yasunori Funayama, Kunihiko Miyazaki, Nobuyuki Koyama, Kinya Furukawa, Hiroyuki Nakamura, Shinji Kikuchi, Yukio Sato, Ikuno Sekine, and Hiroaki Satoh collected the data. Toshihiro Shiozawa and Tomohiro Tamura analyzed the data. Toshihiro Shiozawa and Takeshi Numata wrote the original draft. Nobuyuki Hizawa supervised the manuscript preparation. All Authors discussed the results and agreed on the final draft.

Acknowledgements

pathway. Positive association was reported between EGFR pathway activation and PD-L1 expression in *EGFR*-mutated NSCLC (16). Specifically, the activated EGFR signaling pathway increased PD-L1 expression *via* IL-6/JAK/STAT3, or p-ERK1/2/p-c-JUN signaling pathway. Previous studies also reported that PD-L1 expression was decreased due to the blockade of the EGFR signaling pathway by EGFR-TKI administration (17-19). Recent studies reported that YAP, known to be associated with acquired resistance to EGFR-TKI therapy, had an important role as a regulator of PD-L1 expression (20-22). Accordingly, in patients with high PD-L1 expression, down-regulation of PD-L1 by osimertinib administration might lead to YAP-1 activation, resulting in the induction of acquired resistance to osimertinib treatment. Resistance to osimertinib is a current unmet need in EGFR-mutant NSCLC, and the development of novel therapeutic strategy to overcome it is under investigation (23). Further basic research to reveal the molecular mechanism of the correlation between response to osimertinib and PD-L1 expression and clinical validation with a large cohort are warranted.

References

1 Jorissen RN, Walker F, Pouliot N, Garrett TP, Ward CW and Burgess AW: Epidermal growth factor receptor: mechanisms of activation and signalling. Exp Cell Res *284(1)*: 31-53, 2003. PMID: 12648464. DOI: 10.1016/s0014-4827(02)00098-8

2 Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, Ando M, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Morita S, Nukiwa T and North-East Japan Study Group: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med *362(25)*: 2380-2388, 2010. PMID: 20573926. DOI: 10.1056/NEJMoa0909530

3 Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L, Hu C, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Y, Xiu Q, Ma J, Zhang L and You C: Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol *12(8)*: 735-742, 2011. PMID: 21783417. DOI: 10.1016/S1470-2045(11)70184-X

4 Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazulina V, Shahidi M and Schuler M: Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol *31(27)*: 3327-3334, 2013. PMID: 23816960. DOI: 10.1200/JCO.2012.44.2806

5 Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, Cho BC, Cheng Y, Cho EK, Voon PJ, Planchard D, Su WC, Gray JE, Lee SM, Hodge R, Marotti M, Rukazenkov Y, Ramalingam SS and FLAURA Investigators: Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med *378(2)*: 113-125, 2018. PMID: 29151359. DOI: 10.1056/NEJMoa1713137

6 Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, Zhou C, Reungwetwattana T, Cheng Y, Chewaskulyong B, Shah R, Cobo M, Lee KH, Cheema P, Tiseo M, John T, Lin MC, Imamura F, Kurata T, Todd A, Hodge R, Saggese M, Rukazenkov Y, Soria JC and FLAURA Investigators: Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. N Engl J Med *382(1)*: 41-50, 2020. PMID: 31751012. DOI: 10.1056/NEJMoa1913662

7 Hanna NH, Robinson AG, Temin S, Baker S Jr, Brahmer JR, Ellis PM, Gaspar LE, Haddad RY, Hesketh PJ, Jain D, Jaiyesimi I, Johnson DH, Leighl NB, Moffitt PR, Phillips T, Riely GJ, Rosell R, Schiller JH, Schneider BJ, Singh N, Spigel DR, Tashbar J and Masters G: Therapy for stage IV non-small-cell lung cancer with driver alterations: ASCO and OH (CCO) joint guideline update. J Clin Oncol *39(9)*: 1040-1091, 2021. PMID: 33591844. DOI: 10.1200/JCO.20.03570

8 Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, Majem M, Fidler MJ, de Castro G Jr, Garrido M, Lubiniecki GM, Shentu Y, Im E, Dolled-Filhart M and Garon EB: Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet *387(10027)*: 1540-1550, 2016. PMID: 26712084. DOI: 10.1016/S0140-6736(15)01281-7

9 Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR and KEYNOTE-024 Investigators: Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med *375(19)*: 1823-1833, 2016. PMID: 27718847. DOI: 10.1056/NEJMoa1606774

10 Jackman D, Pao W, Riely GJ, Engelman JA, Kris MG, Jänne PA, Lynch T, Johnson BE and Miller VA: Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. J Clin Oncol *28(2)*: 357-360, 2010. PMID: 19949011. DOI: 10.1200/JCO.2009.24.7049

11 Nakashima K, Ozawa Y, Daga H, Imai H, Tamiya M, Tokito T, Kawamura T, Akamatsu H, Tsuboguchi Y, Takahashi T, Yamamoto N, Mori K and Murakami H: Osimertinib for patients with poor performance status and EGFR T790M mutation-positive advanced non-small cell lung cancer: a phase II clinical trial. Invest New Drugs *38(6)*: 1854-1861, 2020. PMID: 32424780. DOI: 10.1007/s10637-020-00943-0

12 Reungwetwattana T, Nakagawa K, Cho BC, Cobo M, Cho EK, Bertolini A, Bohnet S, Zhou C, Lee KH, Nogami N, Okamoto I, Leighl N, Hodge R, McKeown A, Brown AP, Rukazenkov Y, Ramalingam SS and Vansteenkiste J: CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. J Clin Oncol: JCO2018783118, 2018. PMID: 30153097. DOI: 10.1200/JCO.2018.78.3118

13 Brown H, Vansteenkiste J, Nakagawa K, Cobo M, John T, Barker C, Kohlmann A, Todd A, Saggese M, Chmielecki J, Markovets A, Scott M and Ramalingam SS: Programmed cell death ligand 1 expression in untreated EGFR mutated advanced NSCLC and response to osimertinib *versus* comparator in FLAURA. J Thorac Oncol *15(1)*: 138-143, 2020. PMID: 31605792. DOI: 10.1016/j.jtho.2019.09.009

14 Yoshimura A, Yamada T, Okuma Y, Fukuda A, Watanabe S, Nishioka N, Takeda T, Chihara Y, Takemoto S, Harada T, Hiranuma O, Shirai Y, Nishiyama A, Yano S, Goto Y, Shiotsu S, Kunimasa K, Morimoto Y, Iwasaku M, Kaneko Y, Uchino J, Kenmotsu H, Takahashi T and Takayama K: Impact of tumor programmed death ligand-1 expression on osimertinib efficacy in untreated *EGFR*-mutated advanced non-small cell lung cancer: a prospective observational study. Transl Lung Cancer Res *10(8)*: 3582-3593, 2021. PMID: 34584858. DOI: 10.21037/tlcr-21-461

15 Su S, Dong ZY, Xie Z, Yan LX, Li YF, Su J, Liu SY, Yin K, Chen RL, Huang SM, Chen ZH, Yang JJ, Tu HY, Zhou Q, Zhong WZ, Zhang XC and Wu YL: Strong programmed death ligand 1 expression predicts poor response and de novo resistance to EGFR tyrosine kinase inhibitors among NSCLC patients with EGFR mutation. J Thorac Oncol *13(11)*: 1668-1675, 2018. PMID: 30056164. DOI: 10.1016/j.jtho.2018.07.016

16 Bassanelli M, Sioletic S, Martini M, Giacinti S, Viterbo A, Staddon A, Liberati F and Ceribelli A: Heterogeneity of PD-L1 expression and relationship with biology of NSCLC. Anticancer Res *38(7)*: 3789-3796, 2018. PMID: 29970498. DOI: 10.21873/anticanres.12662

17 Zhang N, Zeng Y, Du W, Zhu J, Shen D, Liu Z and Huang JA: The EGFR pathway is involved in the regulation of PD-L1 expression

via the IL-6/JAK/STAT3 signaling pathway in EGFR-mutated non-small cell lung cancer. Int J Oncol *49(4)*: 1360-1368, 2016. PMID: 27499357. DOI: 10.3892/ijo.2016.3632

18 Chen N, Fang W, Zhan J, Hong S, Tang Y, Kang S, Zhang Y, He X, Zhou T, Qin T, Huang Y, Yi X and Zhang L: Upregulation of PD-L1 by EGFR activation mediates the immune escape in EGFR-driven NSCLC: Implication for optional immune targeted therapy for NSCLC patients with EGFR mutation. J Thorac Oncol *10(6)*: 910-923, 2015. PMID: 25658629. DOI: 10.1097/JTO.0000000000000500

19 Lin K, Cheng J, Yang T, Li Y and Zhu B: EGFR-TKI down-regulates PD-L1 in EGFR mutant NSCLC through inhibiting NF-κB. Biochem Biophys Res Commun *463(1-2)*: 95-101, 2015. PMID: 25998384. DOI: 10.1016/j.bbrc.2015.05.030

20 McGowan M, Kleinberg L, Halvorsen AR, Helland Å and Brustugun OT: NSCLC depend upon YAP expression and nuclear localization after acquiring resistance to EGFR inhibitors. Genes Cancer *8(3-4)*: 497-504, 2017. PMID: 28680534. DOI: 10.18632/genesandcancer.136

21 Lee JE, Park HS, Lee D, Yoo G, Kim T, Jeon H, Yeo MK, Lee CS, Moon JY, Jung SS, Kim JO, Kim SY, Park DI, Park YH, Lee JC, Oh IJ, Lim DS and Chung C: Hippo pathway effector YAP inhibition restores the sensitivity of EGFR-TKI in lung adenocarcinoma having primary or acquired EGFR-TKI resistance. Biochem Biophys Res Commun *474(1)*: 154-160, 2016. PMID: 27105908. DOI: 10.1016/j.bbrc.2016.04.089

22 Tung JN, Lin PL, Wang YC, Wu DW, Chen CY and Lee H: PD-L1 confers resistance to EGFR mutation-independent tyrosine kinase inhibitors in non-small cell lung cancer *via* upregulation of YAP1 expression. Oncotarget *9(4)*: 4637-4646, 2017. PMID: 29435131. DOI: 10.18632/oncotarget.23161

23 Takano N, Seike M, Sugano T, Matsuda K, Hisakane K, Yoshikawa A, Nakamichi S, Noro R and Gemma A: A novel molecular target in *EGFR*-mutant lung cancer treated with the combination of osimertinib and pemetrexed. Anticancer Res *42(2)*: 709-722, 2022. PMID: 35093869. DOI: 10.21873/anticanres.15529