CANCER DIAGNOSIS & PROGNOSIS
4: 515-520 (2024) doi: 10.21873/cdp.10357

Comparing the Effectiveness of Afatinib and Osimertinib for Patients With PD-L1-positive *EGFR*-mutant Non-small Cell Carcinoma

MINEHIKO INOMATA[1], YOSUKE KAWASHIMA[2], RYOTA SAITO[3], DAISUKE MORINAGA[4], HITOMI NOGAWA[5], MASAMICHI SATO[6], YOHEI SUZUKI[7], SATORU YANAGISAWA[8], TAKASHI KIKUCHI[9], DAISUKE JINGU[10], NARUO YOSHIMURA[11], TOSHIYUKI HARADA[12] and EISAKU MIYAUCHI[3]

[1]*First Department of Internal Medicine, Toyama University Hospital, Toyama, Japan;*
[2]*Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan;*
[3]*Department of Respiratory Medicine, Tohoku University Hospital, Sendai, Japan;*
[4]*Department of Respiratory Medicine, Faculty of Medicine, Hokkaido University, Sapporo, Japan;*
[5]*Department of Respiratory Medicine, Yamagata Prefectural Central Hospital, Yamagata, Japan;*
[6]*Department of Cardiology, Pulmonology, and Nephrology, Yamagata University Faculty of Medicine, Yamagata, Japan;*
[7]*Department of Thoracic Surgery, Omagari Kosei Medical Center, Daisen, Japan;*
[8]*Department of Respiratory Medicine, Saku Central Hospital Advanced Care Center, Saku, Japan;*
[9]*Department of Respiratory Medicine, Iwate Prefectural Isawa Hospital, Ohshu, Japan;*
[10]*Department of Respiratory Medicine, Saka General Hospital, Shiogama, Japan;*
[11]*Department of Respiratory Medicine, Tohoku Medical and Pharmaceutical University, Sendai, Japan;*
[12]*Department of Respiratory Medicine, Japan Community Health Care Organization Hokkaido Hospital, Sapporo, Japan*

Abstract. *Background/Aim: Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are effective for treating non-small cell lung cancer (NSCLC) harboring EGFR mutations. However, higher tumor programmed death ligand-1 (PD-L1) expression is associated with a poor response to EGFR-TKIs, and information on the comparison between afatinib and osimertinib in PD-L1-positive EGFR-mutant NSCLC is scarce. Patients and Methods: We retrospectively analyzed data of patients with PD-L1-positive EGFR-mutant NSCLC to compare the effectiveness of afatinib and osimertinib. Results: A total of 177 patients were included in the study. The Cox proportion hazard model was adjusted for age, sex, performance status, EGFR mutation status, PD-L1 expression level, and brain metastasis, revealing that there was no significant difference in risk for progression [hazard ratio (HR)=0.99, 95% confidence interval (CI)=0.64-1.53] or death (HR=0.96, 95% CI=0.54-1.73) between afatinib and osimertinib. Conclusion: In conclusion, the EGFR-TKI treatment duration and overall survival after the treatment with afatinib or osimertinib were similar in patients with PD-L1-positive EGFR-mutant NSCLC in the present study.*

Correspondence to: Minehiko Inomata, MD, Ph.D., First Department of Internal Medicine, Toyama University Hospital, 2630 Sugitani, Toyama, Toyama 930-0194, Japan. Tel: +81 764347287, Fax: +81 764345025, e-mail: 9446-tym@umin.org

Key Words: Non-small cell lung carcinoma, epidermal growth factor receptor-tyrosine kinase inhibitors, programmed death ligand-1, afatinib, osimertinib.

The standard therapy for advanced non-small cell lung carcinoma (NSCLC) is systemic drug therapy, which includes cytotoxic agents, targeted therapy, and immune checkpoint inhibitors. Among them, targeted therapy is particularly effective for treating NSCLC harboring driver mutations, and testing for multiple driver mutations is currently available in clinical practice.

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are the first targeted therapy developed for

NSCLC harboring driver mutations. First-generation EGFR-TKIs demonstrated improved progression-free survival (PFS) compared to cytotoxic agents in clinical trials (1). Furthermore, second-generation EGFR-TKIs showed improved PFS (2) and overall survival (OS) (3) compared to first-generation EGFR-TKIs, and third-generation EGFR-TKI, such as osimertinib, also showed improved PFS (4) and OS (5) compared with first-generation EGFR-TKIs.

However, there exist no reports comparing the efficacy of second- and third-generation EGFR-TKIs. A retrospective study using propensity analysis showed no significant difference in "time to discontinuation of any EGFR-TKIs" between patients treated with afatinib or osimertinib (6). Additionally, a meta-analysis reported no significant difference in OS between second-generation EGFR-TKIs and osimertinib (7), but another study suggested that afatinib showed a longer OS than osimertinib (8).

It has also been reported that the response to EGFR-TKIs is not consistent in *EGFR*-mutant NSCLC; higher tumor programmed death ligand-1 (PD-L1) expression is associated with a poor response to EGFR-TKIs (9, 10). The PD-L1 expression is induced by a variety of oncogene signals, including *EGFR* (11) and *ALK* (12), and increased PD-L1 expression may be the result of more activated oncogene signals in *EGFR*-mutant NSCLC (13). Moreover, AXL (14) and epiregulin (15, 16), which have been reported to confer resistance to EGFR-TKIs, were correlated with tumor PD-L1 expression.

There is limited information on the comparison between second- and third-generation EGFR-TKIs in PD-L1-positive *EGFR*-mutant NSCLC. Thus, we analyzed the survival in patients with PD-L1-positive *EGFR*-mutant NSCLC who were treated with afatinib and osimertinib, using data from a previous observational study, NJLCG2202 (17).

Patients and Methods

Patient selection. In the previous study (NJLCG2202) (17), we included patients who met the following criteria: 1) patients who had been cytologically or histopathologically diagnosed with NSCLC; 2) patients with tumors confirmed as harboring common *EGFR* mutations in clinical practice; 3) patients in whom tumor PD-L1 positivity was confirmed using the 22C3 antibody, with a tumor proportion score (TPS) of ≥1%; and 4) patients who had received EGFR-TKI therapy, including EGFR-TKI monotherapy or combined therapy, between January 2015 and June 2021. Among these candidates, we selected patients who were treated with afatinib or osimertinib and retrospectively analyzed them in the present study.

This study was conducted following the Declaration of Helsinki and Ethical Guidelines for Medical and Biological Research Involving Human Subjects (Ministry of Health, Labour and Welfare, Japan). The need to obtain written informed consent was waived under the approval of the ethical committee at the University of Toyama (Ethics Committee, University of Toyama), and we disclosed the study information to study participants (approval number: R2023192).

Outcome. In the NJLCG2202 study, PFS was calculated from the day EGFR-TKI treatment was initiated until the day that disease progression or death from any cause was noted. Disease progression was defined as progressive disease according to the Response Evaluation Criteria in Solid Tumors version 1.1 or clinically judged as progression, whichever occurred first. EGFR-TKI treatment duration was defined as the sum of PFS for first-line treatment with EGFR-TKIs and secondary osimertinib therapy after the acquisition of the T790M mutation. OS was calculated from the day EGFR-TKI treatment was initiated until the day that death was noted and censored at the last visit without death. If the treatment was discontinued due to adverse events and subsequent therapy was initiated without progression, PFS or EGFR-TKI treatment duration was censored at the initiation of the subsequent therapy. However, the change in treatment from afatinib to first-generation EGFR-TKIs without progression was considered an identical treatment and not censored.

Statistical analysis. In the present study, the endpoints are PFS, EGFR-TKI treatment duration, and OS. Kaplan–Meier curves were drawn and compared using the log-rank test. Multivariate analysis using the Cox proportional hazard model was conducted to analyze the association between treatment options and survival adjusting for age, sex, performance status (PS), *EGFR* mutation status, PD-L1 expression level, and brain metastasis. A p-value of <0.05 was considered significant. The statistical analysis was performed using JMP 15.0.0 (SAS, Cary, NC, USA).

Results

Patient characteristics. A total of 177 patients with PD-L1-positive *EGFR*-mutant NSCLC were investigated, including 45 and 132 who were treated with afatinib or osimertinib, respectively. Table I shows the patient characteristics. Patients with stage I-III were included because they were treated with EGFR-TKIs, as they were ineligible for local therapy. Patients aged <75 years, male patients, and patients with a PS of 0-1 were more prevalent in the afatinib group. The proportion of patients having brain metastasis was similar.

Survival. Figure 1 shows the Kaplan–Meier curves for PFS, EGFR-TKI treatment duration, and OS from the initiation of the treatment with afatinib or osimertinib. The median 95% confidence interval (CI) of PFS was 15.3 (11.0-22.9) and 17.0 (13.7-22.3) months in patients treated with afatinib and osimertinib, respectively (p=0.632, log-rank test). Of the 45 patients treated with afatinib, 33 showed disease progression during the treatment. Among them, the T790M mutation was detected in 9/33 patients (27.3%). Additionally, the T790M mutation was detected in a patient in whom afatinib therapy was discontinued due to adverse events. A total of 10 patients subsequently received the administration of osimertinib. The median (95% CI) of EGFR-TKI treatment duration was 18.2 (11.6-31.1) and 17.0 (13.7-22.3) months in patients treated with afatinib and osimertinib, respectively (p=0.925, log-rank test). The median (95% CI) of OS was 52.4 (26.8-not

Table I. *Patient characteristics*.

		Afatinib		Osimertinib		*p*-Value
N		45		132		
Age	<75	36	80.0%	85	64.4%	0.064
	≥75	9	20.0%	47	35.6%	
Sex	Male	23	51.1%	43	32.6%	0.033
	Female	22	48.9%	89	67.4%	
PS	0-1	44	97.8%	114	86.4%	0.047
	≥2	1	2.2%	18	13.6%	
Histology	Adeno	43	95.6%	124	93.9%	1.000
	Others	2	4.4%	8	6.1%	
EGFR	del 19	29	64.4%	68	51.5%	0.166
	L858R	16	35.6%	64	48.5%	
PD-L1 TPS	1%-49%	32	71.1%	96	72.7%	0.849
	≥50%	13	28.9%	36	27.3%	
Stage	1-3	0	0.0%	12	9.1%	0.106
	4A	12	26.7%	25	18.9%	
	4B	22	48.9%	56	42.4%	
	Recurrence	11	24.4%	39	29.5%	
Brain metastasis	Yes	16	35.6%	45	34.1%	0.858
	No	29	64.4%	87	65.9%	

Adeno, Adenocarcinoma; EGFR, epidermal growth factor receptor; del 19, exon 19 deletion; L858R, exon 21 L858R; PD-L1 TPS, programmed death ligand-1 tumor proportion score; PS, performance status.

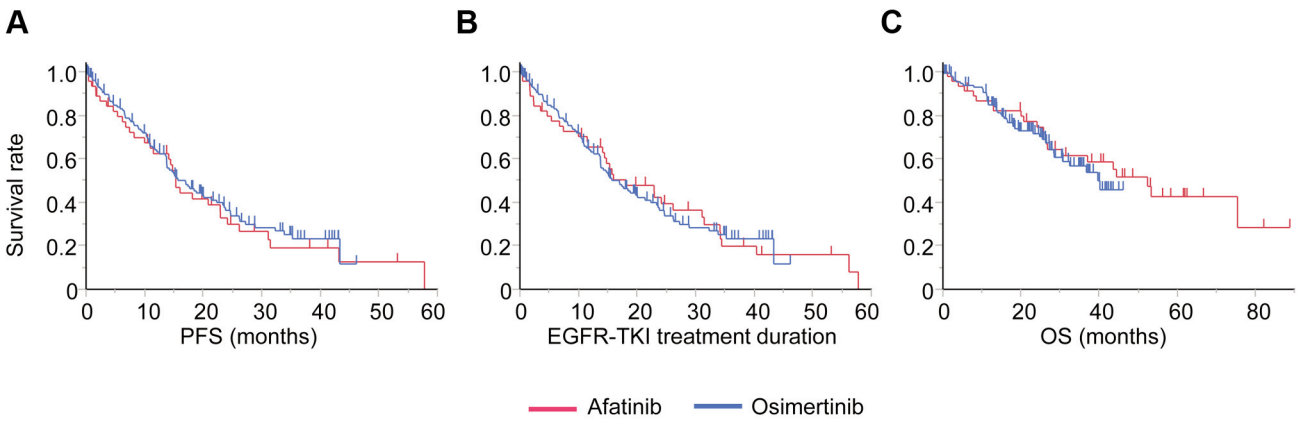

Figure 1. *Kaplan–Meier curves for PFS (A), EGFR-TKI treatment duration (B), and OS (C) in patients with PD-L1-positive EGFR-mutant NSCLC who were treated with afatinib or osimertinib. EGFR-TKI, Epidermal growth factor receptor inhibitor; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PD-L1, programmed death ligand-1.*

estimated (NE)) and 39.7 (28.5-NE) months in patients treated with afatinib and osimertinib, respectively (p=0.492, log-rank test). In addition, 10 patients who were treated with afatinib and osimertinib presenting the T790M mutation showed a median (95% CI) OS of 44.5 (20.7-NE) months.

We evaluated the hazard ratio (HR) of the EGFR-TKI treatment duration (Table II) and OS (Table III), adjusting for clinical parameters, including age, sex, PS, *EGFR* mutation status, PD-L1 expression level, and brain metastasis, using the Cox proportional hazard model. The results revealed no significant difference in risk for progression (HR=0.99, 95% CI=0.64-1.53) or death (HR=0.96, 95% CI=0.54-1.73) between afatinib and osimertinib.

Discussion

Despite accumulating evidence on the association between PD-L1 expression and prognosis in *EGFR*-mutant NSCLC, information on the effectiveness of different treatments for patients with PD-L1-positive *EGFR*-mutant NSCLC is

Table II. *Multivariate analysis for the association between treatment option and EGFR-TKI treatment duration.*

	HR	95% CI	*p*-Value
Age			
≥75	0.98	0.64-1.51	0.937
<75	1.00		
Sex			
Male	1.26	0.85-1.86	0.250
Female	1.00		
PS			
0-1	1.04	0.52-2.10	0.907
≥2	1.00		
EGFR			
L858R	1.54	1.06-2.25	0.025
del 19	1.00		
PD-L1 TPS			
1%-49%	0.98	0.64-1.50	0.921
≥50%	1.00		
Brain metastasis			
No	0.79	0.53-1.19	0.261
Yes	1.00		
Treatment			
Afatinib	0.99	0.64-1.53	0.977
Osimertinib	1.00		

EGFR, Epidermal growth factor receptor; del 19, exon 19 deletion; L858R, exon 21 L858R; PD-L1 TPS, programmed death ligand-1 tumor proportion score; PS, performance status.

Table III. *Multivariate analysis for the association between treatment option and overall survival.*

	HR	95% CI	*p*-Value
Age			
≥75	1.93	1.12-3.33	0.019
<75	1.00		
Sex			
Male	1.91	1.14-3.21	0.015
Female	1.00		
PS			
0-1	0.60	0.25-1.44	0.252
≥2	1.00		
EGFR			
L858R	2.02	1.23-3.32	0.005
del 19	1.00		
PD-L1 TPS			
1%-49%	1.23	0.68-2.24	0.492
≥50%	1.00		
Brain metastasis			
No	0.81	0.48-1.37	0.441
Yes	1.00		
Treatment			
Afatinib	0.96	0.54-1.73	0.900
Osimertinib	1.00		

EGFR, Epidermal growth factor receptor; del 19, exon 19 deletion; L858R, exon 21 L858R; PD-L1 TPS, programmed death ligand-1 tumor proportion score; PS, performance status.

lacking. The present study showed a comparable PFS, EGFR-TKI treatment duration, and OS between afatinib and osimertinib in PD-L1-positive *EGFR*-mutant NSCLC. Furthermore, the detection rate of the T790M mutation after treatment with afatinib was as low as 27.3%, which was consistent with previous studies showing lower detection rates of the T790M mutation in PD-L1-positive EGFR-mutant NSCLC (9, 13, 18, 19).

The PFS after the initial treatment with osimertinib is relatively short in PD-L1-positive *EGFR*-mutant NSCLC (10, 20). The relevant mechanisms may include AXL (14) and epiregulin expression (15, 16). AXL is a tyrosine kinase receptor associated with resistance to a variety of chemotherapy and targeted drugs (14). Epiregulin, from the ErbB family of ligands, is also associated with the aggressive nature of tumors, including cell proliferation, invasion, metastasis, angiogenesis, and resistance to apoptosis (15). AXL (21) and epiregulin (16) expression are correlated with PD-L1 expression. These factors may explain the low effectiveness of front-line treatment with osimertinib. Additionally, PD-L1-positive *EGFR*-mutant NSCLC shows a lower detection rate of the T790M mutation after treatment with first-/second-generation EGFR-TKIs (9, 13, 18, 19). Therefore, although the efficacy of sequential therapy with afatinib plus osimetinib has been reported from real-world data (22), a long survival may not be expected by employing sequential therapy with first-/second-generation EGFR-TKIs plus osimertinib in patients with PD-L1-positive *EGFR*-mutant NSCLC. For this population, combined therapy may improve prognosis. In the NJLCG2202 study, combined therapy with EGFR-TKIs plus vascular endothelial growth factor inhibitor or cytotoxic agents showed a significant risk reduction in progression against first-/second-generation EGFR-TKIs (17). Moreover, a recent clinical trial demonstrated the novel combination therapy of amivantamab plus lazertinib for *EGFR*-mutant NSCLC (23). On the other hand, *EGFR*-mutant NSCLC with PD-L1-negative or lower expression showed a longer PFS with osimertinib therapy and a higher detection rate of the T790M mutation. Therefore, a favorable prognosis is expected for both the front-line treatment with osimertinib and sequential therapy with first-/second-generation EGFR-TKIs plus osimertinib (19, 20).

The tumor response to EGFR-TKIs is not consistent in patients with *EGFR*-mutant NSCLC. Thus, it may be appropriate to select a treatment option based on tumor background including PD-L1 expression. One issue, however, is the cutoff value for PD-L1 expression: the NJLCG2202 study included patients with *EGFR*-mutated NSCLC with a PD-L1 TPS of ≥1% (17), while other

previous studies used a cutoff value of TPS of ≥50% (20). It has been reported that *EGFR*-mutant NSCLC with PD-L1 TPS of 1%-49% showed a more favorable clinical course compared with those with TPS of ≥50%.

The present study was limited by its small sample size. Thus, especially in the afatinib-treated group, it is not clear whether the study sample is representative of PD-L1-positive *EGFR*-mutant NSCLC. Although the present study revealed no significant difference in PFS, EGFR-TKI treatment duration, or OS between the afatinib and osimertinib groups, the small sample size may have provided insufficient statistical power.

In summary, there was no significant difference in the risk of progression (HR=0.99, 95% CI=0.64-1.53) or death (HR=0.96, 95% CI=0.54-1.73) between afatinib and osimertinib, suggesting that the EGFR-TKI treatment duration and OS are similar in patients with PD-L1-positive *EGFR*-mutant NSCLC. EGFR-TKI monotherapy may have limited efficacy in PD-L1-positive NSCLC harboring an *EGFR* mutation, and combined therapy may provide improved outcome in this population. Further validation through accumulation of more evidence is warranted.

Conflicts of Interest

The Authors do not have any conflicts of interest to declare.

Authors' Contributions

MI and EM designed the study. YK, RS, DM, HN, MS, YS, SY, TK, DJ, NY, and TH contributed to the data collection and investigation. MI wrote the main manuscript. All the Authors read and approved the final manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1 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: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 362(25): 2380-2388, 2010. DOI: 10.1056/NEJMoa0909530

2 Park K, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T, Hirsh V, Yang JC, Lee KH, Lu S, Shi Y, Kim SW, Laskin J, Kim DW, Arvis CD, Kölbeck K, Laurie SA, Tsai CM, Shahidi M, Kim M, Massey D, Zazulina V, Paz-Ares L: Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol 17(5): 577-589, 2016. DOI: 10.1016/S1470-2045(16)30033-X

3 Mok TS, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, Lee M, Linke R, Rosell R, Corral J, Migliorino MR, Pluzanski A, Sbar EI, Wang T, White JL, Wu YL: Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. J Clin Oncol 36(22): 2244-2250, 2018. DOI: 10.1200/JCO.2018.78.7994

4 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, FLAURA Investigators: Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 378(2): 113-125, 2018. DOI: 10.1056/NEJMoa1713137

5 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, FLAURA Investigators: Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med 382(1): 41-50, 2020. DOI: 10.1056/NEJMoa1913662

6 Ito K, Morise M, Wakuda K, Hataji O, Shimokawaji T, Takahashi K, Furuya N, Takeyama Y, Goto Y, Abe T, Kato T, Ozone S, Ikeda S, Kogure Y, Yokoyama T, Kimura M, Yoshioka H, Murotani K, Kondo M, Saka H: A multicenter cohort study of osimertinib compared with afatinib as first-line treatment for EGFR-mutated non-small-cell lung cancer from practical dataset: CJLSG1903. ESMO Open 6(3): 100115, 2021. DOI: 10.1016/j.esmoop.2021.100115

7 Zhao Y, Liu J, Cai X, Pan Z, Liu J, Yin W, Chen H, Xie Z, Liang H, Wang W, Guo Z, Zhao S, Liang W, He J: Efficacy and safety of first line treatments for patients with advanced epidermal growth factor receptor mutated, non-small cell lung cancer: systematic review and network meta-analysis. BMJ 367: l5460, 2019. DOI: 10.1136/bmj.l5460

8 Chang HC, Huang KT, Tseng CC, Chen YM, Lai CH, Chang YP, Chen YC, Chuang HY, Wang CC: Survival outcomes of east Asian patients with advanced non-small cell lung cancer treated with first-line EGFR tyrosine kinase inhibitors: A network meta-analysis of real-world evidence. Thorac Cancer 14(32): 3217-3225, 2023. DOI: 10.1111/1759-7714.15112

9 Inomata M, Azechi K, Takata N, Hayashi K, Tokui K, Taka C, Okazawa S, Kambara K, Imanishi S, Miwa T, Hayashi R, Matsui S, Tobe K: Association of tumor PD-L1 expression with the T790M mutation and progression-free survival in patients with EGFR-mutant non-small cell lung cancer receiving EGFR-TKI therapy. Diagnostics (Basel) 10(12): 1006, 2020. DOI: 10.3390/diagnostics10121006

10 Shiozawa T, Numata T, Tamura T, Endo T, Kaburagi T, Yamamoto Y, Yamada H, Kikuchi N, Saito K, Inagaki M, Kurishima K, Funayama Y, Miyazaki K, Koyama N, Furukawa K, Nakamura H, Kikuchi S, Ichimura H, Sato Y, Sekine I, Satoh H, Hizawa N: Prognostic implication of PD-L1 expression on osimertinib treatment for EGFR-mutated non-small cell lung cancer. Anticancer Res 42(5): 2583-2590, 2022. DOI: 10.21873/anticanres.15736

11 Chen N, Fang W, Zhan J, Hong S, Tang Y, Kang S, Zhang Y, He X, Zhou T, Qin T, Huang Y, Yi X, 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. DOI: 10.1097/JTO.0000000000000500

12 Ota K, Azuma K, Kawahara A, Hattori S, Iwama E, Tanizaki J, Harada T, Matsumoto K, Takayama K, Takamori S, Kage M, Hoshino T, Nakanishi Y, Okamoto I: Induction of PD-L1 expression by the EML4–ALK oncoprotein and downstream signaling pathways in non–small cell lung cancer. Clin Cancer Res 21(17): 4014-4021, 2015. DOI: 10.1158/1078-0432.Ccr-15-0016

13 Yang CY, Liao WY, Ho CC, Chen KY, Tsai TH, Hsu CL, Su KY, Chang YL, Wu CT, Hsu CC, Liao BC, Hsu WH, Lee JH, Lin CC, Shih JY, Yang JC, Yu CJ: Association between programmed death-ligand 1 expression, immune microenvironments, and clinical outcomes in epidermal growth factor receptor mutant lung adenocarcinoma patients treated with tyrosine kinase inhibitors. Eur J Cancer 124: 110-122, 2020. DOI: 10.1016/j.ejca.2019.10.019

14 Yoshimura A, Yamada T, Serizawa M, Uehara H, Tanimura K, Okuma Y, Fukuda A, Watanabe S, Nishioka N, Takeda T, Chihara Y, Takemoto S, Harada T, Hiranuma O, Shirai Y, Shukuya T, Nishiyama A, Goto Y, Shiotsu S, Kunimasa K, Morimoto K, Katayama Y, Suda K, Mitsudomi T, Yano S, Kenmotsu H, Takahashi T, Takayama K: High levels of AXL expression in untreated EGFR-mutated non-small cell lung cancer negatively impacts the use of osimertinib. Cancer Sci 114(2): 606-618, 2023. DOI: 10.1111/cas.15608

15 Sunaga N, Kaira K: Epiregulin as a therapeutic target in non-small-cell lung cancer. Lung Cancer (Auckl) 6: 91-98, 2015. DOI: 10.2147/LCTT.S60427

16 Wu Y, Lin L, Liu X: Identification of PDL1-related biomarkers to select lung adenocarcinoma patients for PD1/PDL1 inhibitors. Dis Markers 2020: 7291586, 2020. DOI: 10.1155/2020/7291586

17 Inomata M, Kawashima Y, Saito R, Morinaga D, Nogawa H, Sato M, Suzuki Y, Yanagisawa S, Kikuchi T, Jingu D, Yoshimura N, Harada T, Miyauchi E: A retrospective study of the efficacy of combined EGFR TKI plus VEGF inhibitor/cytotoxic therapy vs. EGFR TKI monotherapy for PD L1 positive EGFR mutant non small cell lung cancer: North Japan Lung Cancer Study Group 2202. Oncol Lett 26(2): 334, 2023. DOI: 10.3892/ol.2023.13920

18 Yoon BW, Chang B, Lee SH: High PD-L1 expression is associated with unfavorable clinical outcome in EGFR-mutated lung adenocarcinomas treated with targeted therapy. Onco Targets Ther 13: 8273-8285, 2020. DOI: 10.2147/OTT.S271011

19 Inomata M, Matsumoto M, Mizushima I, Seto Z, Hayashi K, Tokui K, Taka C, Okazawa S, Kambara K, Imanishi S, Miwa T, Hayashi R, Matsui S, Tobe K: Association of tumor PD-L1 expression with time on treatment using EGFR-TKIs in patients with EGFR-mutant non-small cell lung cancer. Cancer Diagn Progn 2(3): 324-329, 2022. DOI: 10.21873/cdp.10112

20 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, 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. DOI: 10.21037/tlcr-21-461

21 Tsukita Y, Fujino N, Miyauchi E, Saito R, Fujishima F, Itakura K, Kyogoku Y, Okutomo K, Yamada M, Okazaki T, Sugiura H, Inoue A, Okada Y, Ichinose M: Axl kinase drives immune checkpoint and chemokine signalling pathways in lung adenocarcinomas. Mol Cancer 18(1): 24, 2019. DOI: 10.1186/s12943-019-0953-y

22 Chen CH, Chang JW, Chang CF, Huang CY, Yang CT, Kuo CS, Fang YF, Hsu PC, Wu CE: Real-world afatinib outcomes in advanced non–small cell lung cancer harboring EGFR mutations. Anticancer Res 42(4): 2145-2157, 2022. DOI: 10.21873/anticanres.15697

23 Passaro A, Wang J, Wang Y, Lee SH, Melosky B, Shih JY, Wang J, Azuma K, Juan-Vidal O, Cobo M, Felip E, Girard N, Cortot AB, Califano R, Cappuzzo F, Owen S, Popat S, Tan JL, Salinas J, Tomasini P, Gentzler RD, William WN Jr, Reckamp KL, Takahashi T, Ganguly S, Kowalski DM, Bearz A, MacKean M, Barala P, Bourla AB, Girvin A, Greger J, Millington D, Withelder M, Xie J, Sun T, Shah S, Diorio B, Knoblauch RE, Bauml JM, Campelo RG, Cho BC, MARIPOSA-2 Investigators: Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study. Ann Oncol 35(1): 77-90, 2024. DOI: 10.1016/j.annonc.2023.10.117

Received March 31, 2024
Revised April 25, 2024
Accepted May 16, 2024