ANTICANCER RESEARCH *40*: 4229-4236 (2020)
doi:10.21873/anticanres.14424

A Multivariable Regression Model-based Nomogram for Estimating the Overall Survival of Patients Previously Treated With Nivolumab for Advanced Non-small-cell Lung Cancer

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Abstract. *Aim: Although nivolumab improves progression-free (PFS) and overall (OS) survival of patients previously treated for metastatic non-small-cell lung cancer (NSCLC), approximately 50% of treated patients experience disease progression within 3 months. As predictive biomarkers of response are not yet established, development of biomarkers to predict longer PFS and OS of patients treated with nivolumab is crucial. Therefore, we analyzed the impact of predictive markers of response to nivolumab and quantified the impact of each factor using nomograms. Patients and Methods: Clinical data at nivolumab commencement were retrospectively collected from 201 patients treated with nivolumab between December 2015 and July 2016. Immunohistochemistry for programmed cell death ligand 1 (PD-L1) was performed using two assay systems (22C3 and 28-8). OS was calculated from nivolumab treatment initiation. Multivariate Cox regression analysis was conducted to identify independent predictors of OS. A nomogram was constructed to estimate OS. Results: The median patient age was 68 years (135 males). Thirty-nine patients had driver mutations (epidermal growth factor receptor mutations and anaplastic lymphoma kinase rearrangement). In 22C3 and 28-8 immunostaining assays, 36.3% and 36.8% patients had PD-L1-negative cells, 17.4% and 14.4% had 1-49% PD-L1-positive cells, 11.9% and 14.9% had ≥50% PD-L1-positive cells, and 34.3% and 33.8% had unknown PD-L1 status, respectively. Kendall's rank correlation coefficient between the staining assays was 0.8414. The median OS of the whole patient cohort was 12.27 months [95% confidence interval (CI)=10.87-15.6]. Performance status ≥2 [hazard ratio (HR)=2.15, 95% CI=1.35-3.42, p=0.001) and high baseline lactate dehydrogenase (HR=1.15, 95% CI=1.05-1.26, p=0.004] were independent predictors of shorter OS. There was no significant correlation between PD-L1 status and OS. We constructed a nomogram to estimate the OS of patients previously treated with nivolumab. Conclusion: The multivariate analysis-based nomogram might be useful to estimate the OS of patients previously treated with nivolumab for advanced NSCLC.*

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Key Words: Non-small-cell lung cancer, nivolumab, nomogram.

Lung cancer is the leading cause of cancer-related death worldwide, and it has a high incidence of metastasis (1) Immune-checkpoint inhibitors (ICIs), including those targeting the interaction between programmed-death 1(PD1) and PD1 ligand 1 (PD-L1), significantly prolong survival in patients with advanced non-small-cell lung cancer (NSCLC) (2). ICIs are more effective than standard therapies (3-8) and have become the standard of care.

PD-L1 staining is a useful approach for treatment selection but it does not provide a satisfactory result for predicting the effect of ICIs. Therefore, it is important to

identify markers predictive of ICI efficacy. Many laboratory studies have explored factors capable of predicting the effects of ICIs but there is still no predictive biomarker of treatment effect. Clinical studies have also examined predictive factors of ICI response. In our previous studies, we analyzed factors predictive of treatment effect of nivolumab, including patient characteristics and laboratory data, and we identified several candidates (9-12). However, we have not evaluated the relationship between clinical factors and overall survival (OS) after the start of nivolumab treatment. In the present study, we analyzed the impact of these predictive factors on nivolumab OS by multivariate analysis and quantified the impact of each factor into a nomogram. This nomogram is an intuitive graph of a predictive statistical model created by incorporating biological and clinical variables to generate a numerical probability of a clinical event (13).

Patients and Methods

Patients. Consecutive patients previously treated with nivolumab for NSCLC at two respiratory specialty hospitals and one cancer specialty hospital in Japan between December 17, 2015, and July 31, 2016, were retrospectively reviewed. At the time of commencement of nivolumab administration, we collected clinical data of age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), histology, smoking status, stage, driver mutation if data were available, serum albumin, lactate dehydrogenase (LDH) level, metastasis, steroid use, and best response to the most recent chemotherapy regimen.

Nivolumab was administered intravenously at a dose of 3 mg/kg every 2 weeks until disease progression or development of unacceptable toxicity.

The present study was conducted in accordance with the Declaration of Helsinki. The final version of the protocol was approved by the Institutional Ethics Committee (Osaka International Cancer Institute: No. 1612149202).

Immunohistochemistry. We examined two PD-L1 immunohistochemistry (IHC) assay systems (22C3 and 28-8). For the 22C3 and 28-8 assays conducted at SRL, Inc., Tokyo, Japan, sections were stained with 22C3 mouse monoclonal primary antibody and 28-8 rabbit monoclonal primary antibody, respectively, against PD-L1. The percentage of PD-L1-positive cells in the overall tumor sections was estimated in increments of 5%, except for 1%. The pathologists were blinded to the clinical data. Patients were then divided into groups according to the tumor proportion score: 0%, 1-49%, ≥50% PD-L1-positive cells. We compared the scores from both IHC methods by Kendall's rank correlation coefficient.

Definitions. Tumor response was assessed by the investigators' clinical practice until disease progression using the Response Evaluation Criteria in Solid Tumors (14). Progression-free survival (PFS) was defined as the time from nivolumab administration until the first documented tumor progression or death from any cause, and OS was defined as the time from nivolumab administration to death from any cause. The data cutoff date for survival estimation was October 31, 2017.

Table I. *Patient characteristics (N=201)*.

Characteristic	Value
Age, years	
Median (range)	68 (27-87)
Gender, n	
Male	135
Female	66
Smoking history, n	
Yes	157
No	44
Performance status, n	
0	32
1	121
2	33
3	12
4	3
Histological type, n	
SCC	42
ADC	142
Other	17
Stage, n	
≤3C	6
4	183
Post operation	9
Driver mutation, n	
EGFR+	37
ALK+	2
Wild-type or unknown	162
Liver metastasis, n	
Yes	29
No	172
Response to prior treatment, n	
CR	2
PR	57
SD	66
PD	67
NE	8
Steroid use, n	
Yes	24
No	177
Previous treatment lines, n	
≤2	123
≥3	78
LDH (U/l)	
Median (range)	214 (120-1880)
ALI	
Median (range)	22.7 (0.7-133.5)
PFS on nivolumab, months	
Median (range)	2.86 (2.01-3.62)

SCC: Squamous cell; ADC: adenocarcinoma; EGFR: epidermal growth factor receptor; *ALK*: anaplastic lymphoma kinase; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable; LDH: lactate dehydrogenase; ALI: advanced lung cancer inflammation index; PFS: progression-free survival.

Statistical analysis. We evaluated OS using the Kaplan–Meier method [the median and 95% confidence intervaI (CI) were determined] and log-rank tests. We also conducted multivariable Cox regression analysis including laboratory data and clinical factors at the time of nivolumab initiation to assess the impact of clinical variables on OS.

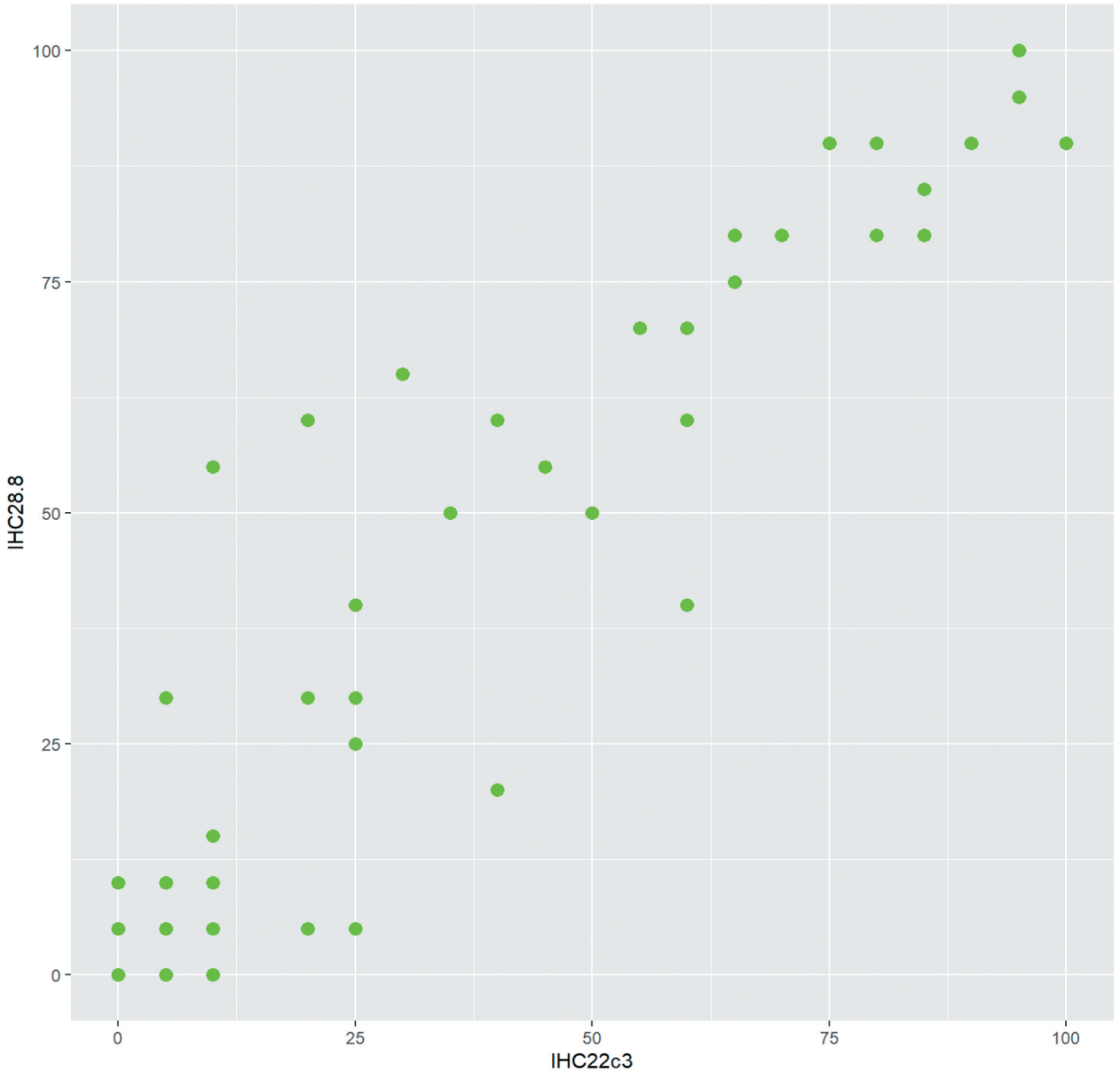

Figure 1. *The correlation between the tumor proportion score by 22C3 and 28-8 staining assays for programmed cell death ligand 1. Kendall's rank correlation coefficient was 0.8414.*

Furthermore, using the results of the multivariable analysis, a nomogram was created to estimate the OS in patients previously treated with nivolumab for advanced NSCLC. Statistical significance was defined as $p<0.05$. Statistical analysis was performed using Easy R software (version 2.8.1; http://www.R-project.org).

Results

Patients. A total of 201 consecutive patients were enrolled in this study. Overall, the median age was 68 years (range=27-87 years), 135 patients were male, and 76.1% of patients had an ECOG PS of 2 or less. Thirty-nine patients had driver mutations: 37 with epidermal growth factor receptor mutations and 2 with anaplastic lymphoma kinase rearrangement. Twenty-four patients received continuous steroids, 29 patients had liver metastases, and 67 patients experienced disease progression with their most recent chemotherapy (Table I).

In the 22C3 and 28-8 assays, 36.3% and 36.8% of patients had PD-L1-negative cells, 17.4% and 14.4% had 1-49% PD-L1-positive cells, 11.9% and 14.9% had ≥50% PD-L1-positive cells, and 34.3% and 33.8% had unknown PD-L1

Table II. *The multivariate Cox hazards model of survival in patients with non-small-cell lung cancer.*

Factor	Comparison/difference**	HR	95% CI	*p*-Value
Baseline age, years	11**	1.02	0.81-1.28	0.862
LDH, U/l	94**	1.15	1.05-1.26	**0.004**
ALI	22.45**	0.82	0.62-1.10	0.194
Gender	Male *vs*. Female	0.97	0.57-1.67	0.925
EGFR mutation	Yes *vs*. No	0.99	0.60-1.65	0.977
Histology	Squamous *vs*. Non-squamous	1.41	0.86-2.33	0.257
Baseline PS	2-4 *vs*. 0,1	2.15	1.35-3.42	**0.001**
Stage*	IV *vs*. Other	0.90	0.44-1.86	0.776
Smoking	Yes *vs*. No	0.99	0.55-1.80	0.975
Steroid use	Yes *vs*. No	1.70	0.97-2.99	0.066
Liver metastasis	Yes *vs*. No	1.31	0.69-2.49	0.411
Last response	PD *vs*. Non-PD	1.49	0.99-2.23	0.058
IHC 22C3	≥50 *vs*. Other	0.90	0.40-2.02	0.298

LDH: Lactate dehydrogenase; ALI: advanced lung cancer inflammation index; *EGFR*: epidermal growth factor receptor; PS: performance status; PD: progressive disease; IHC: immunohistochemistry; HR: hazard ratio. *According to the eighth edition of the TNM Classification of Malignant Tumours. **Continuous variables were analyzed by difference. Statistically significant *p*-values are shown in bold.

status, respectively. The Kendall's rank correlation coefficient between the 22C3 and 28-8 staining assays was 0.8414 (Figure 1).

Prognostic factors and nomogram development. In the present study, the median PFS was 2.87 (95% CI=2.03-3.57) months, and median OS was 12.27 (95% CI=10.87-15.6) months.

In the multivariate Cox regression analysis (Table II), PS had the greatest impact on OS, followed by the LDH level. High PS and a high LDH level were associated with significantly shorter OS [PS ≥2: hazard ratio (HR)=2.15, 95% CI: 1.35-3.42, p=0.001; high LDH level at baseline: HR=1.15, 95% CI=1.05-1.26, p=0.004]. Additionally, patients receiving continuous steroids before nivolumab and those who had a poor response to their most recent chemotherapy tended to have shorter OS. Liver metastasis, histology, smoking status, and PD-L1 positivity had no significant effect on OS.

Based on the estimated regression coefficients in the multivariate Cox analysis, a nomogram was created to estimate the OS of patients previously treated with nivolumab for advanced NSCLC (Figure 2).

Discussion

In the present study, high ECOG PS and a high LDH level at the start of nivolumab therapy had the highest impact on OS. Other prognostic factors included response to the most recent chemotherapy before nivolumab and steroid administration at the start of nivolumab. Liver metastasis, histology, smoking status, and PD-L1 positivity were not associated with nivolumab OS. The factors predictive of nivolumab OS differed from the predictive biomarkers of the effect of nivolumab; few of these biomarkers were predictive of OS after starting nivolumab therapy. Therefore, it may be important to combine multiple factors to create a prognostic model of OS after nivolumab. Using the results of the multivariate Cox analysis, we constructed a nomogram to estimate nivolumab OS in patients previously treated for advanced NSCLC.

In previous reports, poor PS and steroid administration were prognostic factors of poor response to ICIs (10, 15). Similarly, our analysis revealed that these factors affected the OS after commencing nivolumab. Firstly, patients with a high PS are immunosuppressed due not only to tumor progression but also to comorbidities, leading to immunodeficiency. Therefore, ICIs are insufficient to prolong survival. Furthermore, poor PS is closely related to the effect of ICIs (10, 16), and when they are ineffective, the patient generally cannot receive further treatment. Secondly, corticosteroids are commonly administered to patients with NSCLC to treat various indications, including fatigue, reduced appetite, and symptomatic brain metastases (15, 17-19). Given the immunosuppressive properties of corticosteroids and the potential effect on T-cell function (20), steroids might reduce the efficacy of nivolumab.

High serum LDH was also significantly associated with poor survival. There are several potential reasons for this association. Firstly, an increased LDH result in increased lactic acid and acidification of the extracellular fluid (21). An acidic extracellular pH contributes to increased invasive ability of cancer cells (22). Furthermore, activation of macrophage-mediated angiogenesis by lactate may also facilitate metastasis (23, 24). Secondly, increased LDH production by cancer cells can be a direct marker of intratumoral hypoxia and is a strong marker of tumor

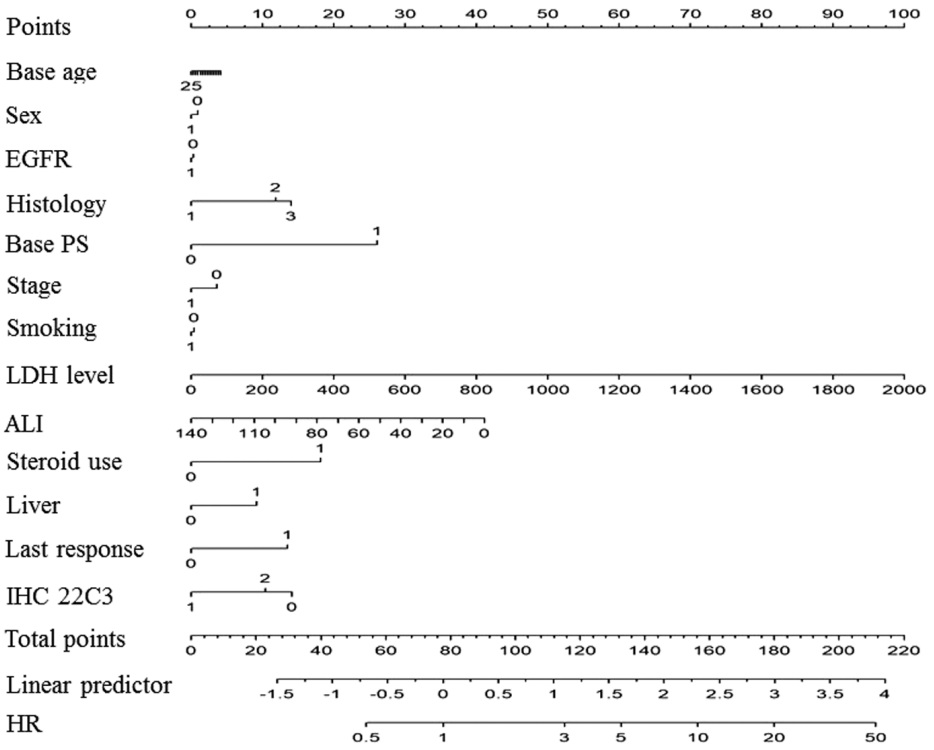

Figure 2. *Nanogram based on multivariate analysis developed for overall survival of patients after starting nivolumab therapy. To use this nomogram, a vertical line is drawn upward to the Points bar is used to identify the points for each. Based on the sum of the points, a line is drawn vertically downward from the Total points bar to calculate the hazard ratio (HR). Points were assigned from the Points scale according to the following factors: Baseline age: from 25 years old; sex: female 0, male 1; EGFR mutation: none 0, present 1; histology: adenocarcinoma 1, squamous 2, other 3; PS: PS 0-1 0, PS 2-4 1; stage: other (stage III, recurrence after surgery) 0, stage IV 1; smoking history: none 0, 1 positive; LDH, according to LDH level (U/l); ALI: according to the ALI score; steroid use: none 0, present 1; Liver: no liver metastasis 0, liver metastasis 1; last response: not progressive disease 0, progressive disease 1; IHC 22C3, programmed cell death ligand 1 staining: unknown/0% 0, 1-49% 1, >50% 2.*

resistance to radiotherapy and chemotherapy (25). A high LDH level might affect OS after starting nivolumab because it reflects tumor progression and insensitivity to post-nivolumab therapy.

The status of PD-L1 expression was assessed using two immunostaining methods (22C3 and 28-8), and there was no significant difference in the PD-L1 status between the two, in concordance with the results of previous reports (26-28). We did not observe any relationship between OS from nivolumab and PD-L1 status. The updated analyses from the Check-Mate 017 and Check-Mate 057 trials showed long-term clinical benefit with nivolumab in patients previously treated for advanced squamous and non-squamous NSCLC, regardless of the PD-L1 expression status (29). Unlike clinical trials, studies in the real-world setting include various patients, such as patients with poor PS or patients who have multiple comorbidities (30). In our study, patients had differences in histology and the number of lines of treatment and had poor PS and various mutation statuses. Any of these factors may affect the PD-L1 status.

The prognostic factors of OS after starting nivolumab differed from the biomarkers for response to nivolumab; therefore, we believe that it is important to combine multiple factors to create a prognostic model of OS after starting nivolumab. In this study, we used the results of multivariate Cox analysis to construct a nomogram to estimate individualized OS in a real-world cohort of patients with advanced NSCLC after starting nivolumab as second-line or later treatment. Recently, nomograms have been widely used to quantify risk in several types of cancer (31-34). A nomogram integrates multiple risk factors to predict survival, and they are useful and convenient tools in lung cancer study to predict prognosis because they can calculate and visualize risks using the nomogram.

The study has several limitations that need to be acknowledged. Firstly, given the retrospective nature of the study, the results need to be cautiously interpreted. Secondly, PD-L1 testing is not mandatory when ICIs are administered as second or subsequent lines of treatment. Therefore, there were some patients for whom we were unable to determine

the PD-L1 status. Finally, external prospective validation is warranted to assess the reproducibility and generality of this analysis.

Conclusion

An ECOG PS score of two or more, steroid administration at baseline, and a high LDH level at baseline were important factors predictive of poor OS after nivolumab administration. Steroid use at baseline and disease progression with most recent chemotherapy might be predictive of poor OS after nivolumab. We identified multiple prognostic factors of OS after nivolumab; therefore, it may be important to combine multiple factors to create such prognostic indicators. Our nomogram might be useful to estimate the OS after administration of nivolumab in patients previously treated for advanced NSCLC.

Conflicts of Interest

Dr. A Tamiya, Dr. M Tamiya, Dr. Y Taniguchi, Dr. S Isa, Dr. K Nakahama, Dr. T Shiroyama, Dr. H Suzuki, Dr. T Inoue, Dr. T Kumagai, Dr. T Hirashima, Dr. A Shintani, Dr. F Imamura, and Dr. S Atagi report grants from Ono Pharmaceutical and Bristol-Myers Squibb. Dr. Y Taniguchi, Dr. A Tamiya, Dr. H Suzuki, Dr. M Tamiya, Dr. T Inoue, Dr. T Kumagai, and Dr. S Atagi report personal fees from Ono Pharmaceutical. Dr. Y Taniguchi, Dr. A Tamiya, Dr. M Tamiya, Dr. T Inoue, Dr. T Kumagai, and Dr. S Atagi report personal fees from Bristol-Myers Squibb during the conduct of the study. Dr. Y. Taniguchi reports personal fees from Chugai Pharmaceutical, Boehringer Ingelheim, MSD, AstraZeneca, Mundipharma, and Taiho Pharmaceutical outside the submitted work. Dr. A. Tamiya reports grant from AstraZeneca, and personal fees from Chugai Pharmaceutical, Taiho Pharmaceutical, AstraZeneca, Eli Lilly, Kissei, Pfizer, MSD, and Boehringer Ingelheim outside the submitted work. Dr. H Suzuki reports personal fees from MSD, AstraZeneca, and Chugai Pharmaceutical outside the submitted work. Dr. T Inoue reports personal fees from AstraZeneca, and Chugai Pharmaceutical outside the submitted work. Dr. M. Tamiya reports grant from Boehringer Ingelheim, and personal fees from Chugai Pharmaceutical, AstraZeneca, Taiho Pharmaceutical, Eli Lilly, Asahi Kasei Pharmaceutical, and Boehringer Ingelheim outside the submitted work. Dr. K. Nishino reports personal fees from Chugai Pharmaceutical, Boehringer Ingelheim, Novartis Pharmaceutical, MSD, Eli Lilly, Roche, and AstraZeneca outside the submitted work. Dr. T. Kumagai reports grant from Chugai Pharmaceutical, Takeda Pharmaceutical, Regeneron Pharmaceuticals, Merck Serono, Delta-Fly Pharma, Taiho Pharmaceutical, Eli Lilly, Pfizer, Astra Zeneca, MSD, AbbVie GK, Novartis Pharmaceutical, The Osaka Foundation for The Prevention of Cancer and Life-style related Diseases, and Boehringer Ingelheim outside the submitted work, and personal fees from Chugai Pharmaceutical, Taiho Pharmaceutical, Eli Lilly, Pfizer, Astra Zeneca, MSD, TEIJIN PHARMA LIMITED, Novartis Pharmaceutical, and Boehringer Ingelheim outside the submitted work. Dr. S Atagi reports grants and personal fees from MSD, Eli Lilly, AstraZeneca, Chugai Pharmaceutical, Taiho Pharmaceutical, Pfizer, and Boehringer Ingelheim, grants from Roche, and personal fees from Hisamitsu, Kyowa Hakko Kirin.

Authors' Contributions

A.T, M.T, T.I, K.N, Y.T, T.S, S.I, H.S, and F.I developed the study concept and initiated the project. A.T, M.T, Y.T, S.I, T.S, H.S, and F.I coordinated the study concept and protocol design. H.G and A.S were responsible for the statistical analysis. All Authors have read and approved the final article.

Acknowledgements

The Authors wish to thank all the patients who participated in this study.

Funding

This study was supported by Ono Pharmaceutical Co., Ltd and Bristol-Myers Squibb Co., Ltd. The sponsors had not role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

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Received May 8, 2020
Revised June 21, 2020
Accepted June 25, 2020