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Real-World Efficacy and Safety of Lenvatinib in Advanced or Recurrent Thymic Carcinoma: A Multicenter Retrospective Study in Japan

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ABSTRACT

Background: Lenvatinib is recommended for the treatment of advanced and recurrent thymic carcinomas. However, there is a paucity of data on lenvatinib's use in real-world clinical practice. The aim of this study was to evaluate the efficacy and safety of lenvatinib in patients with thymic carcinoma.

Methods: This multicenter retrospective cohort study assessed the efficacy and tolerability of lenvatinib in the treatment of patients with advanced or recurrent thymic carcinoma between March 2021 and March 2024.

Results: Twenty-seven patients from six institutions in Japan were enrolled in this study. The median progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR) were 9.0 months (95% confidence interval [CI] 4.8–14.5), 33% (95% CI 16.5%–54%), and 85% (95% CI 66.3%–95.8%), respectively. Although the number of patients was small, the median PFS of the first-, second-, and third- or later-line treatment groups was 21.3 months ($n = 5$), 9.0 months ($n = 13$), and 5.8 months ($n = 9$) ($p = 0.171$), respectively. Dose reduction was required in all patients, with 17 (63%) presenting grade ≥ 3 adverse events, including hypertension in seven patients and proteinuria in six. No grade ≥ 4 adverse events were observed.

Conclusion: The real-world efficacy and safety of lenvatinib are consistent with those reported in previous clinical trials of second-line lenvatinib. Furthermore, despite the relatively small sample size, our findings suggest that lenvatinib may be effective for the treatment of thymic carcinoma.

1 | Introduction

Thymic carcinoma is a rare malignancy with an incidence of approximately 0.02 per 100 000 individuals [1]. The prognosis of patients with advanced or recurrent thymic carcinoma remains poor [2, 3], and approximately half of patients present with advanced-stage disease at the initial diagnosis [4]. Historically, cytotoxic anticancer agents, including platinum-based drugs, have been used to control disease progression [5, 6]; however, no standard second-line treatment has been established.

Lenvatinib is a novel oral multikinase inhibitor that targets kinases such as the vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), and c-Kit and has presented antitumor effects in various malignancies [7–10]. In a phase II study of lenvatinib for previously treated patients with thymic carcinoma conducted in Japan (REMORA study), the objective response rate primary endpoint was 38.1%, and progression-free survival (PFS) was significantly prolonged compared with standard chemotherapy. These results led to the expansion of its use in Japan in March 2021 [11]. Consequently, lenvatinib has become the standard of care for thymic carcinomas refractory to first-line treatment in Japan. While its use is also recommended as a second-line treatment outside Japan, its inclusion in treatment labels varies across regions [12].

Despite these advancements, the efficacy and safety of lenvatinib for the treatment of thymic carcinoma in real-world clinical practice remain poorly understood. Therefore, this study aimed to evaluate the performance of lenvatinib in routine clinical practice, with a focus on efficacy outcomes and safety considerations in the treatment of advanced or recurrent thymic carcinoma.

2 | Patients and Methods

2.1 | Study Design and Patient Selection

This study was designed as a multicenter, noninterventional, retrospective cohort investigation conducted across six medical institutions in Japan. The study protocol outlined the specific eligibility criteria for patient inclusion. Participants were required to have a pathologically confirmed diagnosis of thymic carcinoma, with the disease status classified as either unresectable advanced disease (Masaoka-Koga classification stage IVa or IVb [13]) or postoperative recurrent disease. Patients who received lenvatinib between March 2021 and March 2024 were included in this study. This timeframe was selected to coincide with the regulatory approval of lenvatinib for thymic carcinoma in Japan and to ensure adequate follow-up for clinical evaluation.

2.2 | Data Collection and Management

A standardized data collection protocol was implemented to ensure consistency across the participating institutions. Medical records were systematically reviewed to extract relevant clinical information. The collected data included demographic details, smoking history, Eastern Cooperative Oncology Group performance status (ECOG-PS), tumor histology, clinical disease stage, and the presence of central nervous system metastases. Additionally, a complete treatment history prior to lenvatinib initiation was documented that encompassed all therapeutic interventions and their outcomes.

Lenvatinib-specific data collection focused on key parameters that included the initial dosing regimen, subsequent dose modifications or interruptions, treatment duration, and efficacy outcomes. Adverse events were meticulously recorded along with their management strategies to comprehensively evaluate safety.

2.3 | Assessment of Treatment Outcomes

Treatment response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 to ensure a standardized tumor response assessment across all centers. Radiological evaluations were conducted regularly following institutional protocols to monitor disease progression and response to therapy. Safety assessments were performed systematically throughout the treatment period, with adverse events graded using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). This approach has facilitated consistent documentation of treatment-related toxicities. Particular attention was given to adverse events that necessitated dose modification or treatment discontinuation. These therapeutic effects and toxicities were evaluated by the principal investigators at each institution.

2.4 | Statistical Considerations and Analysis

The statistical analysis was designed to comprehensively evaluate both efficacy and safety endpoints. Progression-free survival (PFS) was defined as the time from lenvatinib initiation to either disease progression or death from any cause, whichever occurred first. Overall survival (OS) was calculated from the start of treatment until death from any cause. Survival analysis was conducted using the Kaplan–Meier method, with 95% confidence intervals (CIs) calculated using the Brookmeyer–Crowley method.

To assess the impact of treatment sequencing, subgroup analyses were performed to compare PFS among patients receiving lenvatinib as first-line, second-line, third-line, or later-line therapy. Statistical comparisons between the groups were performed using the log-rank test. The mean PFS values were analyzed to explore the relationship between treatment timing and clinical outcomes.

All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing). This software was selected because of its robust capabilities in survival analysis and its suitability for the comprehensive statistical evaluations required for this study.

2.5 | Ethical Considerations

The study protocol was approved by the Osaka Toneyama Medical Center Ethics Review Board (approval number: TNH-R-2023045). This study adhered to the principles of the Declaration of Helsinki and Ethical Guidelines for Medical and Biological Research Involving Human Subjects. Given the retrospective nature of the study, patient consent was obtained using an opt-out methodology. The study information was disclosed through institutionally approved channels, and this approach was approved by the institutional review board.

TABLE 1 | Patient characteristics.

Characteristics	Patients ($n = 27$) *n* (%)
Age (years), median (range)	66 (42–83)
< 75 years	24 (88.9%)
≥ 75 years	3 (11.1%)
Sex	
Male	15 (55.6%)
Female	12 (44.4%)
Smoking history	
Never	11 (40.7%)
Former/current	16 (59.3%)
ECOG performance status	
0	6 (22.2%)
1	20 (74.1%)
2	1 (3.7%)
3	0 (0.0%)
4	0 (0.0%)
Stage (Masaoka-Koga classification)	
iva	6 (22.2%)
ivb	15 (55.6%)
Postoperative recurrence	6 (22.2%)
Histological type at initial diagnosis	
Squamous cell carcinoma	24 (88.9%)
Poorly differentiated carcinoma	2 (7.4%)
Basaloid cell carcinoma	1 (3.7%)
Previous surgery	
Yes	11 (40.7%)
No	16 (59.2%)
Previous radiotherapy	
Yes	8 (29.6%)
No	19 (70.4%)
Diagnostic test	
CT-guided needle biopsy	14 (51.9%)
Surgery	11 (40.7%)
Bronchoscopy	2 (7.4%)
Treatment line	
1	5 (18.5%)
2	13 (48.1%)
3	5 (18.5%)
≥ 4	4 (14.8%)
Treatment prior to lenvatinib	
Platinum combination therapy	21 (77.8%)
ADOC	4 (14.8%)

Abbreviation: ADOC, cisplatin + doxorubicin + vincristine + cyclophosphamide.

3 | Results

3.1 | Patient Demographics and Baseline Characteristics

The study cohort was composed of 27 patients enrolled from six medical institutions in Japan, and the characteristics of the enrolled patients are summarized in Table 1. The median age at lenvatinib initiation was 66 years (range, 42–83 years), with a slight male predominance (15 males and 12 females), and a smoking history was documented in 16 patients (59.2%). Performance status (PS) evaluation showed that most patients had good functional capacity: six patients (22.2%) had an ECOG PS of 0, 20 patients (74.0%) had a PS of 1, and only one patient (3.7%) had a PS of 2.

Histological analysis revealed that squamous cell carcinoma was the predominant subtype in 24 patients (88.8%). The remaining patients had poorly differentiated carcinoma (two patients, 7.4%) and basaloid cell carcinoma (one patient, 3.7%). Clinical staging before lenvatinib initiation indicated that six patients (22.2%) had stage IVa disease, 15 patients (55.6%) had stage IVb disease, and six patients (22.2%) presented with postoperative recurrence. One patient had central nervous system metastases at the start of treatment.

3.2 | Treatment Implementation and Exposure

Lenvatinib was used as first-line therapy in five patients (18.5%), second-line therapy in 13 patients (48.1%), and third- or later-line therapy in nine patients (33.3%). The treatment lines and treatments prior to lenvatinib administration are presented in Table 1. All patients underwent cytotoxic therapy during the course of their overall treatment, with 26 patients (96.2%) specifically receiving platinum-based combination therapy. The median duration of lenvatinib administration was 7.3 months.

3.3 | Efficacy Outcomes

The median follow-up period was 22.8 months (range: 3.6–35.9 months), and in the final analysis, three patients (11.1%) remained on active lenvatinib treatment. During follow-up, eight patients (29.6%) died due to primary disease progression.

The response evaluation using the RECIST criteria showed no complete responses (CR, 0%), while nine patients (33.3%)

TABLE 2 | Clinical efficiency data of lenvatinib treatment.

Treatment response	All patients ($n=27$)	1st line ($n=5$)	2nd or later line ($n=22$)
CR	0 (0.0%)	0 (0.0%)	0 (0.0%)
PR	9 (33.3%)	3 (60.0%)	6 (27.3%)
SD	14 (51.8%)	1 (20.0%)	13 (59.1%)
PD	3 (11.1%)	1 (20.0%)	2 (9.0%)
NE	1 (3.7%)	0 (0.0%)	1 (4.5%)
ORR (%)	9 (33.3%) [16.5–54]	3 (60.0%) [23.1–88.2]	6 (27.3%) [13.2–48.2]
DCR (%)	23 (85.1%) [66.3–95.8]	4 (80.0%) [37.6–96.4]	19 (86.4%) [66.7–95.3]

Note: [confidence interval].
Abbreviations: CR, complete response; DCR, disease control rate; NE, not evaluated; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

achieved a partial response (PR). Stable disease (SD) was observed in 14 patients (51.8%), progressive disease (PD) was observed in three patients (11.1%), and one patient (3.7%) was not evaluable (NE). The objective response rate (ORR) was 33.3% (95% CI: 16.5%–54%), and the disease control rate (DCR) was 85.1% (95% CI: 66.3%–95.8%) (Table 2). Additionally, when limited to patients who received lenvatinib as second-line or later therapy, the ORR was 27.2%, and the DCR was 86.3%.

The survival analysis revealed a median progression-free survival (mPFS) of 9.0 months (95% CI: 4.8–14.4) (Figure 1A). In contrast, the median overall survival (mOS) was not reached (95% CI: 29.1–not calculable) (Figure 1B). Figure 1 presents the Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) in the study population. Stratified PFS analysis by treatment line showed a trend toward longer PFS in earlier treatment lines: the median PFS was 21.3 months for first-line treatment ($n=5$), 9.0 months for second-line treatment ($n=13$), and 5.8 months for third- or later-line treatment ($n=9$); however, these differences were not statistically significant ($p=0.171$) (Figure 2). Additionally, in the overall cohort of patients receiving second-line or later treatment, the median PFS was 7.8 months (95% CI: 4.7–14.7), and the median OS was not reached (95% CI: 16.8–not calculable).

3.4 | Safety and Tolerability

The safety analysis included all 27 patients with adverse events reported in each case. Grade 3 or higher adverse events occurred in 17 patients (63.0%), with hypertension (seven patients, 25.9%) and proteinuria (six patients, 22.2%) being the most frequent (Table 3). No Grade 4 adverse events were observed.

Treatment modifications were common, with 26 patients (96.2%) requiring dose reductions or temporary interruptions owing to adverse events. Treatment was discontinued due to adverse events in 10 patients (37.0%). Multivariate logistic regression identified a significant association between first-line lenvatinib use and the incidence of grade 3 hypertension ($p=0.0116$), and the clinical data of patients treated with lenvatinib as first-line treatment are shown in Table 4. No other significant associations were observed between patient characteristics and severe adverse events. Notably, no treatment-related deaths occurred during the study period.

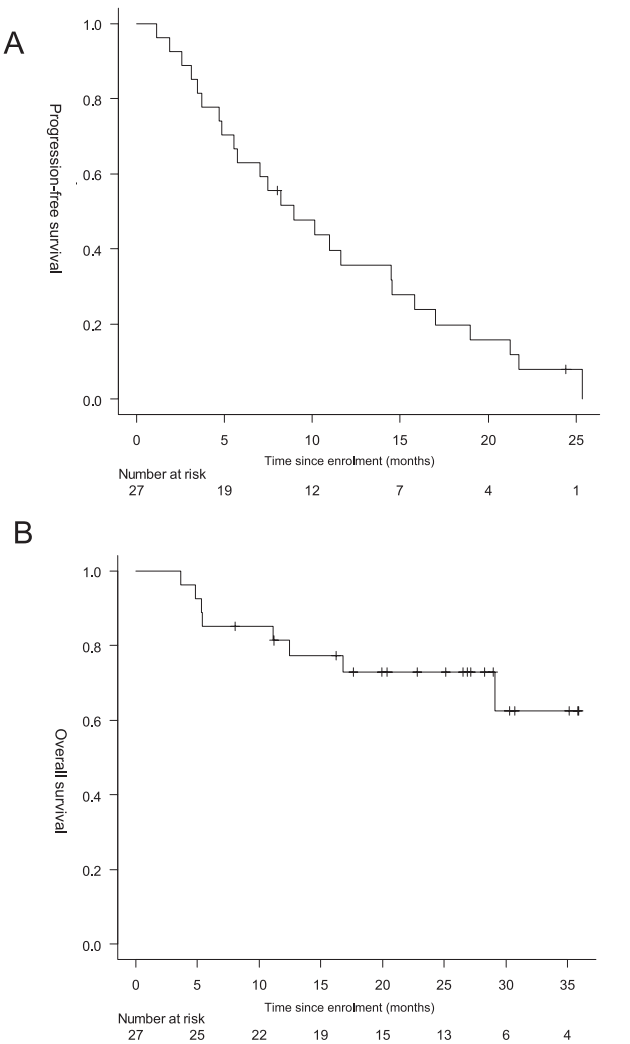

FIGURE 1 | Kaplan–Meier plots for progression-free survival (PFS) (A) and overall survival (OS) (B) in the study population. The median PFS was 9.0 months (95% confidence interval [CI] 4.8–14.5), and the median OS was not reached (95% CI 29.1-not calculable).

4 | Discussion

We retrospectively assessed the efficacy and tolerability of lenvatinib in patients with advanced or recurrent thymic carcinoma.

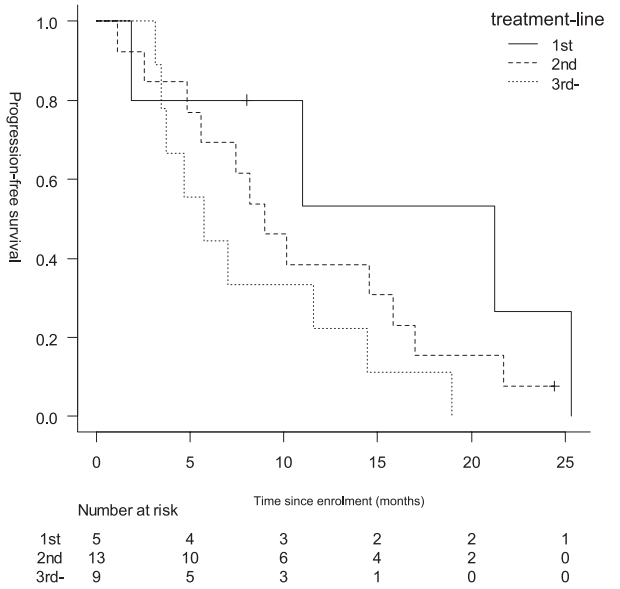

FIGURE 2 | Kaplan–Meier plots for PFS according to treatment line. The median PFS tended to be shorter in the third- or later line treatment group (first-line [$n = 5$], 21.3 months; second-line [$n = 13$], 9.0 months; third- or later line [$n = 9$], 5.8 months; $p = 0.171$).

TABLE 3 | Lenvatinib-related adverse events.

	Grade1-2	Grade3
Hypertension	10 (37.0%)	7 (25.9%)
Proteinuria	11 (40.7%)	6 (22.2%)
Platelet count decreased	8 (29.6%)	3 (11.1%)
Bacterial pneumonitis	0 (0.0%)	2 (7.4%)
Hypothyroidism	12 (44.4%)	1 (3.7%)
Appetite loss	8 (29.6%)	1 (3.7%)
Anemia	0 (0.0%)	1 (3.7%)
Alanine aminotransferase increased	0 (0.0%)	1 (3.7%)
Diarrhea	10 (37.0%)	1 (3.7%)
Creatinine increased	0 (0.0%)	1 (3.7%)
Palmar-plantar erythrodysesthesia syndrome	11 (40.7%)	0 (0.0%)
Nausea	2 (7.4%)	0 (0.0%)

To the best of our knowledge, these results represent the first real-world data on first-line treatment in Japan, and we believe that they will provide meaningful information for future treatment strategies.

Lenvatinib was administered to patients with thymic carcinoma in 2018 based on the findings of the REMORA trial, a single-arm phase 2 trial that enrolled Japanese patients with pathologically confirmed advanced or recurrent thymic carcinoma that progressed following at least one line of platinum-based chemotherapy. In the REMORA trial, patients with advanced or recurrent thymic carcinoma showed an ORR, mPFS, and mOS of 38.1%, 9.3 months, and 28.3 months, respectively [11, 14]. While these outcomes were observed in second-line or subsequent treatments, the efficacy of first-line treatment remains unexplored. Nevertheless, the use of lenvatinib as a first-line treatment is anticipated to increase in the future. In this study, lenvatinib was given as a first-line treatment to five patients, and lenvatinib is currently recommended in Japan for thymic carcinoma refractory to primary treatment. Patients with previously treated disease were eligible for treatment in the REMORA study, which was the basis for approval in Japan; in addition, there have been no trials of lenvatinib as a first-line treatment. However, no drugs have previously been approved for the treatment of thymic carcinoma in Japan, and carboplatin plus paclitaxel has been used as a first-line treatment based on prior reports. At present, lenvatinib is the only drug approved for thymic carcinoma in Japan, and its use as a first-line treatment was deemed acceptable. Furthermore, in second-line and later treatment settings, which are generally considered to be less effective, lenvatinib has shown efficacy in the REMORA study comparable to that of first-line carboplatin plus paclitaxel. Taken together, clinical findings reveal that lenvatinib provides an option for first-line treatment in real practice.

Therefore, the aim of this retrospective observational study was to provide real-world clinical data, including that of first-time patients. In this study, the ORR was 33.3%, the mPFS was 9.0 months, and all but one of the patients had an ECOG-PS of 0–1; thus, the efficacy was comparable to that observed in the REMORA trial (mPFS, 9.3 months; ORR, 38.1%; DCR, 95.2%). However, when limited to the second-line or later treatment group, the mPFS was 7.8 months, the ORR was 27.2%, and the DCR was 86.3%. Although these results indicate lower efficacy compared to the REMORA trial, they were slightly higher than those reported in real-world data from Western countries [15]. This difference may be attributed to the older age distribution of patients in this trial compared to those of the REMORA trial and the initial dose reduction of lenvatinib (14 mg/day) at some institutions, which is similar to practices in Western real-world settings that aim to mitigate adverse effects. There was no significant difference in mPFS among the first-line ($n = 5$), second-line ($n = 13$), or third-line or later ($n = 9$) treatment groups; however, efficacy may be higher with earlier use. These findings suggest that early use may also be an option in the treatment of thymic carcinoma. Grade ≥ 3 adverse events were observed in 17 patients (63.0%), with hypertension and proteinuria being the most common. The adverse event profile is consistent with that observed in previous reports [11], and while all patients required temporary or permanent drug discontinuation or dose adjustments, no treatment-related deaths occurred.

The use of lenvatinib is supported by evidence from strategies such as the weekend-off strategy, which manages adverse effects [15–17]. These findings indicate that the antitumor activity of lenvatinib can be maintained by implementing an appropriate dose reduction in response to adverse events. However, in recent years, a relationship between the relative dose intensity (RDI) of lenvatinib and efficacy outcomes has been reported. Previous studies have also shown that patients with an eight-week RDI of $\geq 75\%$ had improved efficacy outcomes, including mOS and mPFS [18]. The REMORA study indicated that a certain level of drug exposure is necessary to achieve optimal lenvatinib

TABLE 4 | Clinical data of patients receiving lenvatinib as first-line treatment.

Age	Sex	ECOG-PS	Histotype	Stage	PFS (months)	Treatment response	Grade 3 adverse events
43	Female	1	Squamous	Postoperative recurrence	11.0	PR	Hypertension Proteinuria
51	Female	1	Squamous	iva	21.3	PR	Liver dysfunction
55	Female	1	Squamous	ivb	1.9	PD	Hypertension
68	Female	0	Basaloid	ivb	25.3	SD	Hypertension Proteinuria Platelet count decreased
77	Female	1	Squamous	iva	8.0	PR	Hypertension

efficacy, and these findings emphasize the need to recognize the significance of maintaining therapeutic intensity during early treatment [14]. A higher incidence of severe hypertension was also observed in the cohort that received lenvatinib as primary treatment, although its significance was difficult to determine due to the small number of patients.

Data on lenvatinib for the treatment of thymic carcinoma remains limited. At present, lenvatinib is primarily used in previously treated patients, based on the findings of the REMORA trial. This study evaluated the real-world efficacy and safety of lenvatinib, and our findings suggested that, although the number of patients was small, the efficacy of lenvatinib in the first-line setting may be comparable to or even greater than that in the second-line or later settings. However, several limitations of this study should be noted when interpreting our findings, including the relatively small sample size, short follow-up period, lack of randomization, and restriction to Japanese patients. These factors may limit the generalizability of our findings to a broader population. Therefore, careful consideration is required to determine whether these results can be extrapolated to real-world settings beyond those of these specific clinical trials. In the future, the accumulation of additional patient information and long-term follow-up studies will be essential to further clarify the clinical role of lenvatinib in the treatment of thymic carcinoma.

In summary, this study provides information on the good efficacy and controllable adverse events of lenvatinib for the treatment of unresectable thymic carcinoma in real-world practice.

Author Contributions

Concept/design: Satoshi Miyamoto and Masahide Mori. Data collection and/or assembly: Satoshi Miyamoto, Akihiro Tsukaguchi, Hanako Kuhara, Taiichiro Otsuki, Takayuki Shiroyama, and Motohiro Tamiya. Manuscript writing: Satoshi Miyamoto and Masahide Mori. Final approval of the manuscript: Satoshi Miyamoto, Akihiro Tsukaguchi, Hanako Kuhara, Taiichiro Otsuki, Takayuki Shiroyama, Motohiro Tamiya, Akihiro Tamiya, Nishino Kazumi, Takeda Yoshito, Takashi Kijima, Meinoshin Okumura, Atsushi Kumanogoh, and Masahide Mori.

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Conflicts of Interest

Satoshi Miyamoto received honoraria from AstraZeneca. Akihiro Tsukaguchi has received honoraria from AstraZeneca, Japan. Taiichiro Otsuki has received honoraria from AstraZeneca, Bristol Myers Squibb, Chugai, Daiichi-Sankyo, Kyowa-kirin, MSD, Nihon-kayaku, Ono, Pfizer, and Takeda. Takayuki Shiroyama received honoraria from AstraZeneca, Bristol Myers Squibb, Chugai, Eli Lilly, MSD, and Ono. Motohiro Tamiya received honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, Eli Lilly, Kyowa-kirin, MSD, Ono, Pfizer, Taiho, and Takeda and research funding from Boehringer Ingelheim, Chugai, Daiichi-Sankyo, Eisai, MSD, and Ono. Akihiro Tamiya received honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, BMS, Chugai, Daiichi-Sankyo, Eli Lilly, Kyowa-kirin, MSD, Merck, Nihon-kayaku, Novartis, Ono, Pfizer, Taiho, and Takeda and research funding from Daiichi-Sankyo and Taiho. Kazumi Nishino received honoraria from AMGEN, Astrazeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Daiichi-Sankyo, Eli Lilly, Merck, MSD, Nihon-kayaku, Novartis, Ono, Pfizer, and Takeda, and research funding from AMGEN, Astrazeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Daiichi-Sankyo, Eli Lilly, Janssen, Merck, MSD, Nihon-kayaku, Novartis, Ono, Pfizer, and Takeda. Takashi Kijima received honoraria from AstraZeneca, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, Eli Lilly, Kyowa-kirin, MSD, Merck, Nihon-kayaku, Novartis, Ono, Pfizer, Taiho, and Takeda, and research funding from AstraZeneca, Chugai, Daiichi-Sankyo, MSD, Ono, and Taiho. Meinoshin Okumura received honoraria from Eisai, Japan. Masahide Mori received honoraria from AbbVie, AstraZeneca, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, Eli Lilly, Kyowa-kirin, MSD, Nihon-kayaku, Novartis, Ono, Pfizer, Taiho, and Takeda and research funding from Chugai, Daiichi-Sankyo, Delta Fly, Janssen, and Ono. The authors declare no conflicts of interest.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon request.

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