Efficacy And Safety of Ramucirumab and Docetaxel In Previously Treated Patients With Squamous Cell Lung Cancer: A Multicenter Retrospective Cohort Study

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Abstract

Objective: Ramucirumab plus docetaxel therapy (RAM/DOC) is currently the standard for previously treated advanced non-small cell lung cancer (NSCLC), irrespective of histology. However, the safety data of anti-angiogenic agents for squamous cell NSCLC (Sq) is lacking, with a higher reported rate of severe hemoptysis in a clinical trial setting. We conducted a multicenter retrospective cohort study to confirm the efficacy and safety of RAM/DOC for Sq in real-world settings.

Methods: We retrospectively analyzed previously treated patients with advanced NSCLC who underwent RAM/DOC at four institutions. Clinical data on the initiation of RAM/DOC were collected from medical records. Treatment outcomes of RAM/DOC were assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1. Incidence of pulmonary hemorrhage was assessed according to the Common Terminology Criteria for Adverse Events version 5.0.

Results: Overall, 237 patients with NSCLC were included and 38 (16%) had squamous cell carcinoma. There were no significant differences in median progression-free survival and overall survival between Sq and non-Sq patients (5.8 months vs. 4.3 months, $P=0.0937$; 15.2 months vs. 13.4 months, $P=0.714$, respectively). Of all patients, 13 (5%) developed pulmonary hemorrhage. According to histology, there was no significant difference in pulmonary hemorrhage proportion between Sq and non-Sq cohorts (2/38 vs. 11/199, respectively, $P=0.947$).

Conclusion: For previously treated patients with Sq, efficacy and safety data of RAM/DOC were confirmed in a real-world setting and were similar to non-Sq. Ramucirumab is the only vascular endothelial growth factor-blocker available for Sq.

Introduction

Lung cancer is a major cause of cancer-related mortality worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases, with the majority of NSCLC cases being diagnosed at advanced, unresectable, and metastatic disease stages [2]. Systemic chemotherapy is the standard anticancer treatment for advanced metastatic NSCLC. Currently, genetic and genomic profiling has developed, and advancements in molecular targeted therapies have improved the prognosis of patients with NSCLC [3]. Furthermore, immune checkpoint inhibitors (ICIs) and programmed death 1 (PD-1) programmed death ligand 1 (PD-L1) axis and cytotoxic T-lymphocyte antigen 4 (CTLA-4) axis inhibitors have demonstrated outstanding efficacy for first-line treatment of metastatic NSCLC, and they have been established as novel standard treatment options for NSCLC [4–12]. Despite an initial dramatic response and durable progression-free survival (PFS) using these agents, progressive disease (PD) is inevitable in most patients. Therefore, second-line chemotherapy after PD as first-line treatment is still important as salvage therapy.

Ramucirumab is a fully human recombinant IgG1 monoclonal antibody that specifically binds to the vascular endothelial growth factor (VEGF) receptor-2 extracellular domain with high affinity [13]. In a

preclinical study, VEGF blockade caused transient vascular normalization, leading to an enhanced effect of chemotherapy. In a large phase III trial, REVEL trial, ramucirumab plus docetaxel (RAM/DOC) therapy demonstrated improved overall survival (OS), PFS, and objective response rate (ORR) compared to placebo plus docetaxel for NSCLC patients with disease progression after first-line platinum-based chemotherapy [14]. Based on this result, RAM/DOC therapy has been approved and considered as one of the standard treatments for second-line therapy of metastatic NSCLC regardless of histology.

RAM/DOC therapy has been shown to be effective and safe in clinical trials; however, these clinical trials have eligibility criteria that outline who can participate in attempts of achieving accurate and meaningful results. Therefore, only limited patients in good general condition without organ failure can participate. Clinical trial outcomes are therefore not entirely representative of real-world patients [15]. Previous studies have shown that the majority of NSCLC patients in clinical settings are ineligible for clinical trials, with poorer treatment outcomes and higher toxicity rates in these ineligible patients [16, 17]. In particular, the safety of anti-angiogenic agents for squamous cell NSCLC (Sq) is controversial because a higher rate of severe hemoptysis was noted in Sq compared with adenocarcinoma in a randomized phase II study of bevacizumab, as another anti-VEGF agent approved for NSCLC. Consequently, the use of bevacizumab in squamous cell NSCLC has been routinely avoided [18]. Thus, we conducted a multicenter retrospective cohort study on the proportion, clinical characteristics, and prognoses of previously treated NSCLC patients who were administered RAM/DOC to confirm its efficacy and safety in the real-world setting, which provides a wider variety of patient characteristics compared to a clinical trial setting.

Patients And Methods

In this retrospective multicenter cohort study, we included consecutive previously treated patients with advanced NSCLC (unresectable stage III or IV, including postoperative recurrence) who received RAM/DOC at four institutions in Japan between June 2016 and March 2020.

Clinical data at the time of initiating DOC/RAM were collected from electronic medical records, including age, sex, smoking status, Eastern Cooperative Oncology Group performance status (ECOG-PS) score, histology (Sq and non-Sq), EGFR mutation, PD-L1 status, treatment line history of prior ICI therapy, and history of prophylactic administration of pegylated-granulocyte-colony stimulating factor (PEG-G-CSF). The incidence of pulmonary hemorrhage was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [19]. Tumor assessment was performed according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1 [20]. PFS was calculated from the start of RAM/DOC treatment until the first instance of lung cancer progression or death due to any cause. Overall survival (OS) was calculated from the start of DOC/RAM treatment until the first instance of death from any cause. The data cut-off date was June 30, 2020. Our study protocol was approved by the respective review boards of each of the four institutions. Patient consent was waived due to the retrospective nature of the study, and we used an opt-out method so that patients and families could refuse to participate in the study.

Statistical analysis

The Kaplan–Meier method was used to estimate survival outcomes and groups, according to metastatic organs, were compared using the log-rank test. Cox proportional hazard models were used to determine associations between patient characteristics and survival outcomes. Only factors with a P-value of <0.10 on univariate analysis were included in the multivariate analysis. Results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical significance was defined as having a two-tailed P-value of <0.05. All analyses were performed using JMP 14 software (SAS Institute, Cary, NC, USA).

Results

1.1. Patient characteristics

A total of 237 previously treated patients with NSCLC were included in the study; 38 (16%) had squamous cell carcinoma on histology (Table 1). The median patient age was 66 years (range, 33–82 years). The majority were men (63%), had a smoking history (76%), and had an ECOG PS score of 0 or 1 (80%). At the time of administering RAM/DOC, 64 (27%) patients were treated with RAM/DOC as second-line treatment, while 124 (52%) patients had previously been treated with ICIs. PEG-G-CSF was prophylactically administered to 190 patients (80%).

Table 1
Patient characteristics.

Patient characteristics	Total (%) (N=237)	Squamous cell carcinoma (%) (N=38)	Non-Squamous cell carcinoma (%) (N=199)	P-value
Age (years)				
Median (range)	66 (33-82)	69 (54-80)	66 (33-82)	0.020
Age group				
≥75 years	30 (13)	7 (18)	23 (12)	0.244
<75 years	207 (87)	31 (82)	176 (88)	
Sex				
Male	150 (63)	32 (84)	118 (59)	0.003
Female	87 (37)	6 (16)	81 (41)	
Smoking status				
Never-smoker	58 (24)	0 (0)	58 (29)	< 0.001
Current or former smoker	179 (76)	38 (100)	141 (71)	
ECOG PS				
0-1	189 (80)	33 (87)	156 (78)	0.235
2-4	48 (20)	5 (13)	43 (22)	
Histology				
Squamous cell carcinoma	38 (16)	38 (100)		
Adenocarcinoma	180 (76)		180 (90)	
Other	19 (8)		19 (10)	
<i>EGFR</i> mutation status				
Positive	66 (28)	0 (0)	66 (33)	< 0.001
Negative or not investigated	171 (72)	38 (100)	133 (67)	
PD-L1 status				
≥50%	31 (13)	10 (26)	21 (11)	

ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor gene; PD-L1, programmed death ligand 1; ICI, immune checkpoint inhibitor; G-CSF, granulocyte-colony stimulating factor.

Patient characteristics	Total (%) (N=237)	Squamous cell carcinoma (%) (N=38)	Non-Squamous cell carcinoma (%) (N=199)	P-value
1-49%	69 (29)	13 (34)	56 (28)	
< 1%	65 (27)	5 (13)	60 (30)	
Not evaluated	72 (30)	10 (26)	62 (31)	
Treatment line				
second line	64 (27)	10 (26)	54 (27)	0.917
third or later line	173(73)	28 (74)	145 (73)	
Prior ICI therapy				
Administered	124 (52)	33 (87)	91 (46)	< 0.001
ICI monotherapy	116 (49)	32 (84)	84 (42)	
ICI plus chemotherapy	14 (6)	3 (8)	11 (6)	
None	113 (48)	5 (13)	108 (54)	
Prophylactic G-CSF				
Administered	190 (80)	32 (84)	158 (79)	0.495
None	47 (20)	6 (16)	41 (21)	
ECOG PS, Eastern Cooperative Oncology Group Performance Status; <i>EGFR</i> , epidermal growth factor receptor gene; PD-L1, programmed death ligand 1; ICI, immune checkpoint inhibitor; G-CSF, granulocyte-colony stimulating factor.				

Patients with squamous cell carcinoma had significantly higher proportions of those with older age (69 years vs. 66 years, respectively, $P=0.020$), male sex (32/38 vs. 118/199, respectively, $P=0.003$), smoking history (38/38 vs. 141/199, respectively, $P<0.001$), no *EGFR* mutation status (0/38 vs. 66/199, respectively, $P<0.001$), and prior ICI therapy history (33/38 vs. 91/199, respectively, $P<0.001$).

1.2. Treatment outcomes

In all patients, the objective response rate (ORR) and disease control rate (DCR) was 25% and 64%, respectively (Table 2). At the time of analysis, the median PFS and OS were 4.5 months (95.0% CI: 3.6–5.5 months) and 13.4 months (95.0% CI: 11.5–15.6 months), respectively (Fig. 1A and Fig. 1B).

Table 2
Treatment outcome for Docetaxel plus Ramucirumab.

	All patients (%) (N=237)	Squamous cell carcinoma (%) (N=38)	Non-Squamous cell carcinoma (%) (N=199)	P-value
Response to Docetaxel plus Ramucirumab				
Complete Response	2 (1)	1 (3)	1 (1)	
Partial Response	56 (24)	9 (24)	47 (24)	
Stable Disease	89 (38)	17 (45)	72 (36)	
Progression Disease	83 (35)	10 (26)	73 (37)	
Not Evaluable	7 (3)	1 (3)	6 (3)	
Objective Response	58 (25)	10 (27)	48 (25)	0.782
Disease Control	147 (64)	27 (72)	120 (62)	0.210

We also investigated treatment outcomes according to histology. The ORR and DCR were not significantly different between the Sq and non-Sq groups (27% vs. 25%, $P=0.782$; 72% vs. 62%, $P=0.210$, respectively) (Table 2). Additionally, there were no significant differences in the median PFS and OS between the Sq and non-Sq groups (5.8 months vs. 4.3 months, $P=0.0937$; 15.2 months vs 13.4 months, $P=0.714$, respectively) (Fig. 2A and Fig. 2B).

The PFS according to patient characteristics is shown in Table 3. Univariate analysis using Cox proportional hazards models indicated that a good ECOG PS (HR, 0.57, 95.0% CI: 0.40–0.81; $P=0.002$) was significantly associated with a longer PFS. In contrast, factors not significantly associated with a longer PFS were: age (HR: 0.98, 95.0% CI: 0.63–1.51; $P=0.914$), sex (HR: 1.21, 95.0% CI: 0.90–1.62; $P=0.197$), smoking status (HR: 0.76, 95.0% CI: 0.55–1.06; $P=0.103$), histology (HR: 0.72, 95.0% CI: 0.49–1.06; $P=0.096$), EGFR mutation (HR: 1.19, 95.0% CI: 0.87–1.62; $P=0.267$), treatment line (HR: 1.03, 95.0% CI: 0.75–1.42; $P=0.840$), prior ICI treatment history (HR: 0.81, 95.0% CI: 0.61–1.08; $P=0.146$), and prophylactic G-CSF administration history (HR: 0.98, 95.0% CI: 0.72–1.45; $P=0.919$). Furthermore, on the multivariate Cox proportional hazards regression model, only a good ECOG PS (HR, 0.56, 95.0% CI: 0.38–0.81; $P=0.002$) was an independent predictor of longer PFS in patients treated with RAM/DOC.

Table 3
Analyses of progression free survival time (N=237).

Characteristics	No of patients (%)	Progression free survival time (months)	Univariate		Multivariate	
			HR (95% CI)	P-value	HR (95% CI)	P-value
Age	30 (13)	5.8	0.98 (0.63-1.51)	0.914	1.02 (0.65-1.60)	0.942
≥75 years	207 (87)	4.4	reference		reference	
<75 years						
Sex	150 (63)	4.1	1.21 (0.90-1.62)	0.197	1.25 (0.86-1.82)	0.243
Male	87 (37)	5.3	reference		reference	
Female						
Smoking status	58 (24)	6.3	0.76 (0.55-1.06)	0.103	0.73 (0.47-1.12)	0.152
Never-smoke	179 (76)	4.1	reference		reference	
current or former smoker						
ECOG PS	189 (80)	5.5	0.57 (0.40-0.81)	0.002	0.56 (0.38-0.81)	0.002
0-1	48 (20)	2.8	reference		reference	
2-4						
Histology	38 (16)	5.8	0.72 (0.49-1.06)	0.096	0.75 (0.49-1.14)	0.178
Squamous cell carcinoma	199 (84)	4.3	reference		reference	
Non-squamous cell carcinoma						
EGFR mutation	66 (28)	4.1	1.19 (0.87-1.62)	0.267	1.29 (0.86-1.93)	0.227
Yes	171 (72)	4.8			reference	
No or not investigated						
Treatment line	64 (27)	4.3	1.03 (0.75-1.42)	0.840	1.01 (0.67-1.55)	0.945
second line	173 (73)	4.5	reference		reference	
Third or later line						

ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor gene; ICI, immune checkpoint inhibitor; G-CSF, granulocyte-colony stimulating factor; HR, hazard risk; CI, confidence interval.

Characteristics	No of patients (%)	Progression free survival time (months)	Univariate		Multivariate	
			HR (95% CI)	P-value	HR (95% CI)	P-value
Prior ICI treatment	124 (52)	5.1	0.81 (0.61-1.08) reference	0.146	0.83 (0.58-1.20)	0.327
Administered	113 (48)	4.1				
None						
Prophylactic G-CSF	190 (80)	4.5	0.98 (0.72-1.45)	0.919	0.98 (0.68-1.41)	0.919
Administered	47 (20)	4.8				
None						
ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor gene; ICI, immune checkpoint inhibitor; G-CSF, granulocyte-colony stimulating factor; HR, hazard risk; CI, confidence interval.						

1.3. Adverse events of pulmonary hemorrhage

Of the 237 patients, 13 (5%) developed pulmonary hemorrhage of any grade (eight patients had grade 1, four had grade 2, and one had grade 5). There was no significant difference regarding the proportion of patients who developed pulmonary hemorrhage of any grade between the Sq and non-Sq groups (2/38 vs. 11/199, respectively, $P=0.947$), nor in those who developed grade ≥ 3 hemorrhage (0/38 vs. 1/199, respectively, $P=0.662$).

Discussion

In this study, we demonstrated treatment outcomes of RAM/DOC in previously treated patients with NSCLC in a real-world setting. Additionally, we found that RAM/DOC was a suitable treatment for both Sq and non-Sq in clinical settings, in terms of effectiveness and tolerability.

The results of the present study revealed that the treatment outcome in a real-world setting was consistent with the efficacy data reported from previous key clinical trials [14, 21]. Since the eligibility criteria of clinical trials have become increasingly detailed and strict, only selected patients in good general condition can participate [15]. Therefore, clinical trial outcomes may not be entirely representative of outcomes in real-world scenarios and careful attention should be paid to these differences when applying clinical trial data to real-world patients. In the REVEL and JVCg trials, only patients with disease progression despite first-line platinum-based therapy were included [14, 21]. Recently, ICI monotherapy or combination therapy has become the standard of care as a first-line treatment for patients with advanced NSCLC [4–12]. Therefore, it is still unknown whether these clinical trial data can be applied to patients who were previously treated with ICI or with more than one chemotherapy regimen, although this question seems to be an important problem in clinical practice settings. In our study, we found that both ICI treatment history and multi-line chemotherapy treatment history did not negatively affect treatment

outcome, but the patients with poor ECOG PS being the only independent predictor of a shorter PFS. Based on this data, RAM/DOC is considered a reasonable treatment option, irrespective of prior treatment history.

Our study highlighted the efficacy and safety of RAM/DOC in patients with Sq. In the present study, outcomes regarding ORR, DCR, PFS, and OS were not significantly different between the Sq and non-Sq groups. Since the evidence for kinase inhibitors in Sq was substantially restricted, compared with non-Sq, the treatment options for Sq are still limited [22]. Therefore, it is considered important to confirm the efficacy data for Sq patients treated with RAM/DOC in a real-world setting. Whereas, RAM/DOC in real-world setting revealed that the frequency of treatment-related pulmonary hemorrhage was not associated with histology, which seemed to be unique as the previous trial of bevacizumab, another anti-VEGF antibody increased that in Sq-group. It is well known that blockade are different; bevacizumab binds to VEGF-A and interferes with the interaction between VEGF-A and VEGFR-2, whereas ramucirumab targets VEGFR-2 [23]. However, the reason for the difference of risk against pulmonary hemorrhage in Sq between ramucirumab and bevacizumab treatment remains unclear. Clarifying the precise mechanism may provide clues for safer treatment strategies with antiangiogenic agents for NSCLC. Further studies are needed.

Our study demonstrated the efficacy and safety data of ramucirumab for Sq in a real-world setting, which may provide a novel treatment strategy combined with VEGF inhibitors for Sq. In a preclinical study, VEGF inhibitors caused transient vascular normalization, leading to reduced tumor hypoxia and increased immune-cell infiltration, which modulates and reprograms the immunosuppressive tumor microenvironment, which may lead to increased antitumor immunity [24–26]. Therefore, ICIs plus VEGF inhibitors are considered a reasonable combination treatment option. In a phase 3 clinical trial, chemotherapy combined with atezolizumab and bevacizumab demonstrated significantly longer survival compared to platinum doublet chemotherapy and established standard therapies in treatment-naïve advanced non-Sq patients [8]. Furthermore, to clarify the effect of adding a VEGF inhibitor to ICI plus chemotherapy more precisely, a randomized phase 3 study for non-Sq patients has been conducted [27]. These findings in a clinical setting support the benefit of such combination therapy; however, this treatment strategy is eligible for only non-Sq patients. Since ramucirumab is the only anti-angiogenic agent available for Sq, combination with ICI and ramucirumab may be a reasonable treatment option for Sq. A phase 1 study revealed a manageable safety profile of first-line therapy with ramucirumab plus pembrolizumab in patients with NSCLC, including Sq [28]. Further studies are warranted to validate the efficacy of this combination treatment for Sq.

The present study had several limitations. First, this study had a multicenter retrospective design. Therefore, although the results of our study were clinically important, selection bias was inevitable. Second, this study included only Japanese patients, which precludes the generalization of our findings to patients from other countries.

In conclusion, the results of the present study revealed the efficacy and safety data of RAM/DOC for previously treated patients with Sq and non-Sq in a real-world setting. Ramucirumab is the only VEGF-blocker available for Sq. Further studies are needed to investigate novel combination therapies for Sq.

Declarations

Author Declarations

Ethics approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the review board of each of the four institutions.

Consent for publication: The patient's informed consent was waived for the retrospective nature of study, and we used an opt-out method so that patients and families could refuse to participate in the study.

Availability of data and materials: The datasets during the current study available from the corresponding author on reasonable request.

Competing interests: Hayato Kawachi reports personal fees from Ono Pharmaceutical, personal fees from Chugai Pharmaceutical, personal fees from AstraZeneca, personal fees from Taiho Pharmaceutical, personal fees from Eli Lilly, personal fees from MSD, outside the submitted work. Motohiro Tamiya reports grants and personal fees from Boehringer Ingelheim, grants and personal fees from Ono Pharmaceutical, grants and personal fees from Bristol-Myers Squibb, personal fees from Chugai Pharmaceutical, personal fees from AstraZeneca, personal fees from Taiho Pharmaceutical, personal fees from Eli Lilly, personal fees from Asahi Kasei Pharmaceutical, personal fees from MSD, outside the submitted work. HS reports personal fees from Chugai Pharmaceutical, personal fees from MSD, personal fees from AstraZeneca, outside the submitted work. Akihiro Tamiya reports personal fees from Chugai Pharmaceutical, grants and personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, grants and personal fees from Ono Pharmaceutical, grants and personal fees from Bristol-Myers Squibb, personal fees from MSD, personal fees from Taiho Pharmaceutical, personal fees from Pfizer, personal fees from Eli Lilly, personal fees from Takeda Pharmaceutical, personal fees from Kissei, personal fees from Amgen, personal fees from Merck Bio Pharma, outside the submitted work. Toru Kumagai reports grants and personal fees from Ono Pharmaceutical, grants from MSD, grants and personal fees from Chugai Pharmaceutical, grants and personal fees from AstraZeneca, grants and consulting fees from Takeda Pharmaceutical, consulting fees from Nitto Denko Corporation, grants and personal fees from Eli Lilly, grants from Merck Bio Pharma, grants and personal fees from Pfizer, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Taiho Pharmaceutical, personal fees from Bristol-Myers Squibb, personal fees from Novartis Pharma, grants from The Osaka Foundation for The Prevention of Cancer and Life-style related Diseases (Public Interest Incorporated Foundation), outside the submitted work.

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest

Hayato Kawachi reports personal fees from Ono Pharmaceutical, personal fees from Chugai Pharmaceutical, personal fees from AstraZeneca, personal fees from Taiho Pharmaceutical, personal fees from Eli Lilly, personal fees from MSD, outside the submitted work. Motohiro Tamiya reports grants and personal fees from Boehringer Ingelheim, grants and personal fees from Ono Pharmaceutical, grants and personal fees from Bristol-Myers Squibb, personal fees from Chugai Pharmaceutical, personal fees from AstraZeneca, personal fees from Taiho Pharmaceutical, personal fees from Eli Lilly, personal fees from Asahi Kasei Pharmaceutical, personal fees from MSD, outside the submitted work. HS reports personal fees from Chugai Pharmaceutical, personal fees from MSD, personal fees from AstraZeneca, outside the submitted work. Akihiro Tamiya reports personal fees from Chugai Pharmaceutical, grants and personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, grants and personal fees from Ono Pharmaceutical, grants and personal fees from Bristol-Myers Squibb, personal fees from MSD, personal fees from Taiho Pharmaceutical, personal fees from Pfizer, personal fees from Eli Lilly, personal fees from Takeda Pharmaceutical, personal fees from Kissei, personal fees from Amgen, personal fees from Merck Bio Pharma, outside the submitted work. Toru Kumagai reports grants and personal fees from Ono Pharmaceutical, grants from MSD, grants and personal fees from Chugai Pharmaceutical, grants and personal fees from AstraZeneca, grants and consulting fees from Takeda Pharmaceutical, consulting fees from Nitto Denko Corporation, grants and personal fees from Eli Lilly, grants from Merck Bio Pharma, grants and personal fees from Pfizer, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Taiho Pharmaceutical, personal fees from Bristol-Myers Squibb, personal fees from Novartis Pharma, grants from The Osaka Foundation for The Prevention of Cancer and Life-style related Diseases (Public Interest Incorporated Foundation), outside the submitted work.

Research involving Human Participants and/or Animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration

and its later amendments or comparable ethical standards. The study protocol was approved by the review board of each of the four institutions.

Informed consent

The patient's informed consent was waived for the retrospective nature of study, and we used an opt-out method so that patients and families could refuse to participate in the study.

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Figures

Figure 1

Kaplan–Meier survival curves showing the progression-free survival (A) and overall survival (B) of all patients.

Figure 2

Kaplan–Meier survival curves showing the progression-free survival (A) and overall survival (B) in Sq and Non-Sq patients.