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Original Research

# Single-arm, multicentre, phase II trial of nivolumab for unresectable or recurrent thymic carcinoma: PRIMER study

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Nivolumab;
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**Abstract** ***Introduction:*** Thymic carcinoma (TC) is a rare cancer with a poor prognosis and limited treatment options, especially after relapse.
***Methods:*** In this open-label, two-stage, multicentre, single-arm and phase II trial, the main eligibility criteria were unresectable or recurrent TC, an Eastern Cooperative Oncology Group–performance status of 0 or 1, progression after at least one chemo(radio)therapy and no history of autoimmune disease. Nivolumab was administered at a dose of 3 mg/kg every 2 weeks. The primary end-point was response rate (RR) as evaluated by central review using Response Evaluation Criteria In Solid Tumours (RECIST), version 1.1. The planned sample size was 15 for each stage, with a threshold RR of 5%, an expected RR of 20%, one-sided

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alpha of 5% and power of 80%.
***Results:*** Between July 1 and August 16 2016, 15 patients were accrued in the first stage. Response was assessable in all patients, and 13 had squamous histology. Median follow-up time was 14.1 months (range: 2.4–17.5). The median number of nivolumab received was eight (range: 3–33). RR was 0% (95% confidential interval [CI]: 0–21.8). Eleven patients had stable disease (SD) including five patients with SD for 24 or more weeks. Median progression-free survival was 3.8 months (95% CI: 1.9–7.0). Two patients experienced immune-related serious adverse events (grade III aspartate aminotransferase (AST) increase and grade II adrenal insufficiency). Because the early termination criteria (less than one responder) were fulfilled during the first stage, the patient accrual was terminated.
***Conclusions:*** Despite the small number of patients, nivolumab was unable to produce tumour shrinkage by RECIST in previously treated unresectable or recurrent TC.
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## 1. Introduction

Thymic epithelial tumours originate in the thymus and include thymomas (World health organization [WHO] classification types A, AB and B) and thymic carcinomas (WHO classification type C). Thymic epithelial tumours are rare (0.15–0.32 cases per million), and thymic carcinomas comprise approximately 10%–15% of thymic epithelial tumours [1–3]. One third of thymomas produce autoimmune disease, while thymic carcinomas are asymptomatic until diagnosis at an advanced stage, resulting in a poor prognosis (5-year survival probability of 50.5%) [4]. Platinum doublet therapy is recommended as the first line therapy for unresectable or recurrent thymic carcinoma [5–8]. For the second line therapy, phase II studies of sunitinib and S-1 [9] have produced clinically significant responses; however, a standardised treatment has not been established because the efficacy and safety remain unsatisfactory. Immune checkpoint inhibitors have shown significant clinical activity across various tumour types and have well-tolerated toxicities. Our previous study using immunohistochemistry showed Programmed death-ligand 1 (PD-L1) positivity in 70% of thymic carcinomas [10], suggesting the possible efficacy of anti-PD-1 antibodies [11]. Immune checkpoint inhibitors are associated with a risk of immune-related adverse events (irAEs); thus, caution is needed when treating patients with autoimmune diseases [12,13]. In view of the above-mentioned findings, we conducted an investigator-initiated, registration-directed phase II trial of nivolumab, an anti-PD-1 antibody, in patients with unresectable or recurrent thymic carcinoma.

## 2. Methods

### 2.1. Study design and participants

This study was an open-label, two-stage, multicentre, single-arm, phase II trial for patients with unresectable or recurrent thymic carcinoma. All the patients had received a histological diagnosis of thymic carcinoma based on the 2015 WHO classification at each institution. The key inclusion criteria were unresectable or recurrent thymic carcinoma, no symptomatic central nervous system metastasis, an age of at least 20 years, an Eastern Cooperative Oncology Group (ECOG)-performance status (PS) of 0 or 1, the presence of measurable disease, progression after at least one previous course of platinum-based chemo(radio)therapy, no prior treatment with immune checkpoint inhibitors, no chronic systemic treatment with steroid (more than 10 mg of prednisolone per day) or other immune suppressant, no systemic therapy or surgery for at least 4 weeks before study enrolment, no thoracic radiation therapy for at least 8 weeks before study enrolment and adequate organ and bone marrow function. PD-L1 expression was not required. The key exclusion criteria were a history of active cancer, active infectious disease (hepatitis B or C carriers were eligible), treatment history for pneumonitis or pulmonary fibrosis or a history of autoimmune disease (several chronic autoimmune diseases such as type 1 diabetes were eligible, if stable).

### 2.2. Procedures

Patients were treated with 3 mg/kg of nivolumab intravenously every 2 weeks until disease progression. No dose reductions were allowed. Treatment was withheld in patients with any toxicities of grade III or more and any symptoms of autoimmune diseases or pneumonitis. Treatment was discontinued in patients with obvious disease progression and a worsening of clinical symptoms or in patients with severe or life-threatening adverse events requiring treatment to be withheld for more than 6 weeks after the last administration. Supportive care and the management of irAEs were performed in accordance with standard guidelines. Toxicity was graded using the Common Terminology Criteria for Adverse Events, version 4.0. Treatment was

discontinued in cases with clinical disease progression, unacceptable toxicity or at the patient's request.

A physical examination, blood tests and urine analysis were carried out every 2 weeks before dosing, and an electrocardiogram, thyroid function tests and serum KL-6 and SP-D tests were done every 8 weeks.

We assessed the tumour response using computed tomography scans every 8 weeks for 6 months, followed by every 12 weeks thereafter. The response was independently assessed by a central review board in accordance with the Response Evaluation Criteria In Solid Tumours (RECIST), version 1.1 [14].

The biomarker study was conducted separately.

### 2.3. Outcomes

All the analyses were completed for all the eligible patients (full analysis set). The primary end-point of this study was the response rate (RR) as evaluated by the central review. The secondary end-points were progression-free survival (PFS), overall survival (OS), disease control rate (DCR) and safety. The PFS was calculated from the date of registration to the date of progression or death due to any cause, whichever came first. In the absence of progression or death during the follow-up period, the PFS was censored on the last date of a verified lack of progression. The OS was calculated from the date of registration until the date of death from any cause. In the absence of death during the follow-up period, the OS was censored on the date that the patient was last known to be alive.

### 2.4. Statistical analysis

We tested the null hypothesis that 5% or fewer patients would have a response against the one-sided alternative hypothesis, which was more than 20% of the patients would respond to nivolumab. We used a Southwest Oncology Group (SWOG) two-stage design. In the first stage, 15 patients were accrued. If at least one response was seen at the preplanned interim analysis after the first 15 patients had been followed for 24 weeks, the study would then accrue an additional 15 patients. Assuming a few ineligible cases, a total of 33 patients were to be enrolled. If no response was observed during the first stage, then the study would be deemed futile and terminated. The null hypothesis would be rejected if four or more responses were observed in 30 patients. This design yields a one-sided type I error of 5% and a power of 80%. The planned accrual period was 2 years. We calculated the Clopper-Pearson exact 95% confidential interval (CI) for the proportion of patients with a response. The median PFS and OS times were estimated using the Kaplan–Meier method, and the 95% CI of the median time was calculated using the Brookmeyer and Crowley method. The survival probability was estimated using the Kaplan–Meier method, and the 95% CI was calculated using Greenwood's formula. The statistical analysis was performed using SAS, version 9.4. This trial was registered as UMIN000022007.

## 3. Results

### 3.1. Patient characteristics

From July 1, 2016 to August 16, 2016, 15 patients were enrolled from five institutions. All the patients were eligible. The baseline characteristics are shown in Table 1. All the patients were Japanese, 12 were male, the median age was 55 years (range, 34–70 years) and 11 had an ECOG-PS of 1. A squamous histology was dominant (13/15), about half of the patients (7/15) had undergone prior radiotherapy and six patients had undergone three or more prior chemotherapy regimens. Seven patients had been treated with S-1, and two patients had been treated with sunitinib. One patient was still receiving treatment at the time of the data cut-off (February 5, 2018).

### 3.2. Efficacy

The median number of nivolumab doses that were received was eight (range: 3–33). The median follow-up time was 14.1 months (range: 2.4–17.5). Fourteen patients discontinued study treatment because of disease progression. No discontinuation because of adverse events or patient decisions occurred. The RR determined by the central review was 0% (95% CI = 0–21.8), and the DCR was 73.3% (95% CI = 44.9–92.2). No complete responses (CRs) or partial responses (PRs) were seen. Eleven patients had stable disease (SD) (including five patients with SD for 24 or more weeks [patient # 003, 011, 013, 014, 015]), and four patients had progressive disease (PD) (Table 2, Fig. 1). Among the five patients with SD for 24 or more weeks, three were ex-smokers, two had undergone prior radiotherapy and all patients had undergone one or two prior chemotherapy regimens. The median PFS was 3.8 months (95% CI = 1.9–7.0), and the 12-month PFS

Table 1
Patient characteristics.

| | | N |
|---|---|---|
| Age (median) | | 55 (34–70) |
| Sex | Male/Female | 12/3 |
| ECOG-PS | 0/1 | 4/11 |
| Histology | Sq/Ad/others | 13/1/1 |
| Masaoka-Koga Stage | IIIa/IVa/IVb | 1/3/11 |
| Smoking history | Never or light/ex/current | 5/9/1 |
| Prior surgery | Yes/no | 3/12 |
| Prior radiotherapy | Yes/no | 7/8 |
| Prior chemotherapy (line) | 1/2/3/4 or more | 4/5/2/4 |

Sq = squamous cell carcinoma, Ad = adenocarcinoma; ECOG-PS = Eastern Cooperative Oncology Group-performance status.

Table 2
Response to treatment as evaluated by a central review.

| | | |
|---|---|---|
| Best response | Complete response (CR) | 0 |
| | Partial response (PR) | 0 |
| | Stable disease (SD) | 11[a] |
| | Progressive disease (PD) | 4 |
| | Not evaluable | 0 |
| Response rate (CR+PR) (%) | 0 (95% CI: 0–21.8) | |
| Disease control rate (CR+PR+SD) (%) | 73.3 (95% CI: 44.9–92.2) | |
| Median number of nivolumab cycles | 8 (range: 3–33) | |

[a] Including SD for ≥ 24 weeks in 5 patients.

probability was 9.0% (95% CI = 0.6–32.7). The median OS was 14.1 months (95% CI = 11.1–not estimable [NE]), and the 12-month OS probability was 60.0% (95% CI = 31.8–79.7) (Fig. 2). In a subgroup analysis of patients with squamous cell carcinoma (N = 13), the median PFS was 3.8 months (95% CI = 1.9–5.6), and the 12-month PFS probability was 11.0% (95% CI = 0.7–37.8). The median OS was 14.1 months (95% CI = 11.1–NE), and the 12-month OS probability was 61.5% (95% CI = 30.8–81.8). In a subgroup analysis of patients with previous radiation therapy (N = 7), the

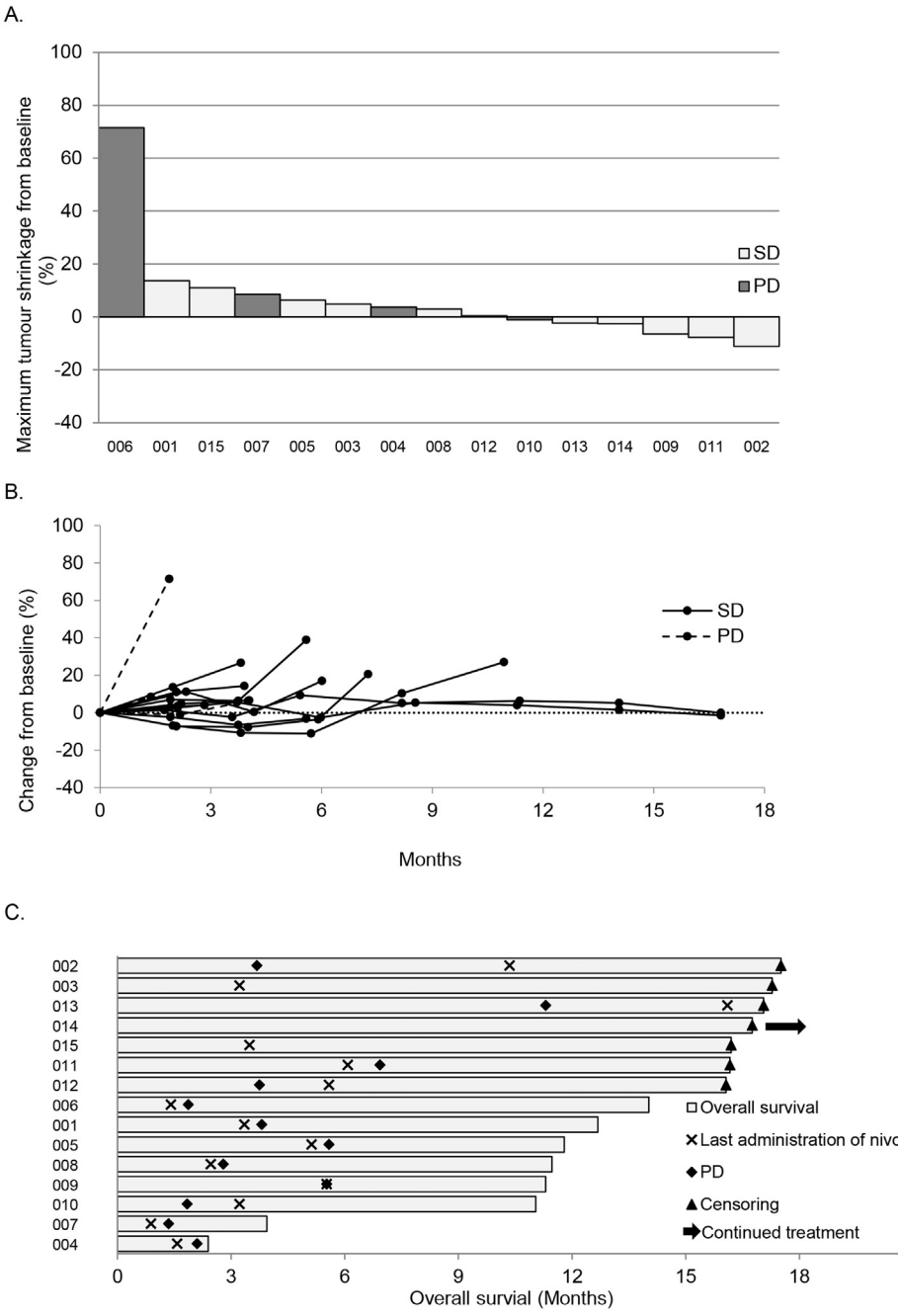
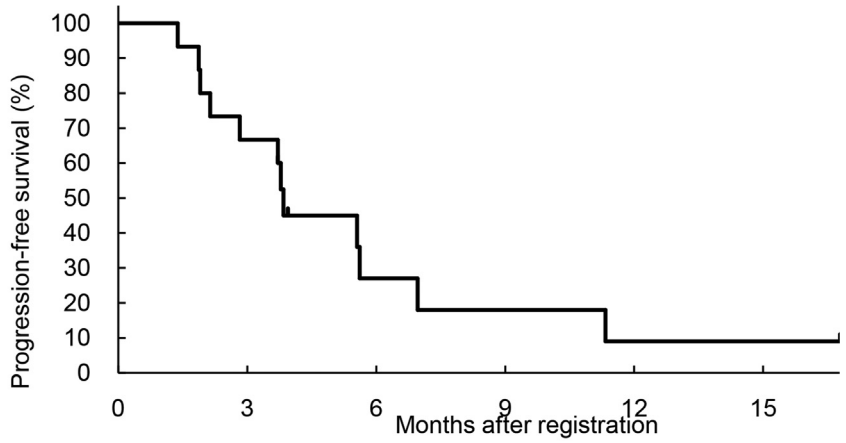


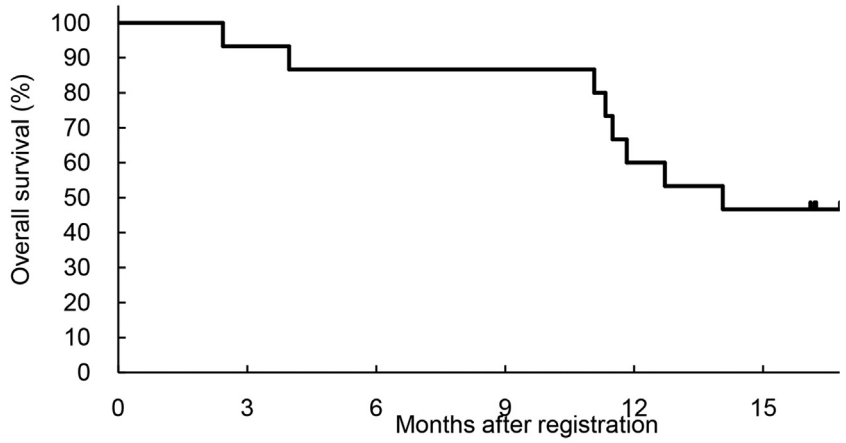

Fig. 1. Overall tumour responses as evaluated by a central review. (A) Greatest change from baseline target lesion diameters. (B) Change in sum of target lesions from baseline. (C) Duration of treatment, overall survival and best response.

A.




| Months | 0 | 3 | 6 | 9 | 12 | 15 | 18 |
|---|---|---|---|---|---|---|---|
| At risk | 15 | 10 | 3 | 2 | 1 | 1 | 0 |
| Censoring | - | 0 | 2 | 0 | 0 | 0 | 1 |

B.




| Months | 0 | 3 | 6 | 9 | 12 | 15 | 18 |
|---|---|---|---|---|---|---|---|
| At risk | 15 | 14 | 13 | 13 | 9 | 7 | 0 |
| Censoring | - | 0 | 0 | 0 | 0 | 0 | 7 |

Fig. 2. (A) Progressive-free survival and (B) overall survival as evaluated by a central review.

median PFS was 3.8 months (95% CI = 1.9–7.0), and the 12-month PFS probability was 0% (95% CI = NE). The median OS was 12.7 months (95% CI = 2.4–NE), and the 12-month OS probability was 57.1% (95% CI = 17.2–83.7).

Because the early termination criterion (less than one responder) was fulfilled during the first stage, the study was deemed futile and was terminated.

### 3.3. Safety

Most of the patients had mild adverse events consistent with previous data for nivolumab, with no new safety signals observed. A total of seven grade III or higher adverse events were seen in three patients (patient # 002, 004, 014): two of these events were obviously not related to the nivolumab treatment (Table 3). Two patients experienced serious irAEs requiring admission. One (patient # 004) had a grade III aspartate aminotransferase (AST) increase 7 days after the first administration, and the other (patient # 014) had a grade II adrenal insufficiency occurring 8 days after the 10th administration. The former patient had liver metastasis; treatment was withheld, and the patient recovered 19 days thereafter. The patient restarted treatment after an additional 12 days, but the best response was PD. The

Table 3
(A) Adverse events observed in 3 or more patients or with grade 3 or higher, and (B) immune-related adverse events regardless of nivolumab causality.

| AE | Any Grade | Grade 3 or 4 |
|---|---|---|
| Hypoalbuminemia | 13 | 1 |
| Anemia | 13 | 0 |
| Lymphocyte count decreased | 8 | 1 |
| Hyperglycemia | 8 | 0 |
| Hyperkalemia | 7 | 0 |
| Hyponatremia | 6 | 1 |
| Fatigue | 4 | 0 |
| Proteinuria | 3 | 0 |
| Fever | 3 | 0 |
| Hypercalcemia | 2 | 1 |
| Retinopathy | 1 | 1 (not treatment-related) |
| Malignant neoplasm progression | 1 | 1 (not treatment-related) |

| irAE | | Any Grade | Grade 3 or 4 |
|---|---|---|---|
| Skin | Rash maculopapular | 4 | 0 |
| Hepatic | AST increased | 8 | 1[a] |
| | Alanine transaminase (ALT) increased | 3 | 0 |
| Endocrine | Adrenal insufficiency | 1[a] | 0 |
| | Hypothyroidism | 1 | 0 |
| GI | Diarrhea | 3 | 0 |
| Myositis | Creatine phosphokinase (CPK) increased | 3 | 0 |
| Renal | Creatinine increased | 2 | 0 |
| Pulmonary | Drug-induced pneumonitis | 0 | 0 |

[a] Serious AE which required admission.

latter patient was treated with hydrocortisone, prolonging treatment for 28 days. The patient exhibited tumour shrinkage within the range of SD for 24 or more weeks. To sum up, one patient showed SD for 24 or more weeks among three patients who experienced G3 or higher adverse events or serious irAEs requiring admission, while four patients showed SD for 24 or more weeks among 12 patients who did not experience such adverse events.

## 4. Discussion

This report describes the first multicentre, phase II trial of nivolumab for patients with previously treated unresectable or recurrent thymic carcinoma. The DCR was 73% (11/15), and SD for 24 or more weeks was observed in 33% (5/15), suggesting some clinical benefit. Only two patients developed serious irAEs (G3 AST increased, G2 adrenal insufficiency), both of which were resolved. Grade III or more toxicities or serious irAEs were not clearly related to disease control, while treatment with nivolumab in earlier line suggested improved outcomes. The patient accrual was terminated because of the preplanned early termination criterion: no responders were seen among the 15 patients accrued during the first stage.

Nivolumab produced a lower RR than in previous studies for patients with thymic carcinoma, though cross-trial comparison should be performed with caution. In a phase II trial of sunitinib, six of the 23 evaluable patients with thymic carcinoma (26%) had PR, and the DCR was 91%. The median PFS was 7.2 months; however, treatment discontinuation because of adverse events was seen in 21% of the patients, including a decline in the left-ventricular ejection fraction, intolerable tumour pain and mucositis [15]. In a retrospective study, S-1 treatment resulted in a PR in six out of 14 patients (43%), the DCR was 85.7% and the median PFS was 8.1 months [9]. In a phase II trial of pembrolizumab for unresectable or recurrent thymic carcinoma (48% squamous cell carcinoma and 15% neuroendocrine cancer) performed in the United States, the RR was 22.5% in 40 evaluable patients, and the median PFS was 4.2 months, while serious irAEs developed in 15% (including myocarditis in 5%) [16]. In another phase II trial of pembrolizumab conducted in Korea in 26 patients, the efficacy and safety were similar to those in the US study despite the different in racial background (Asian) and a higher rate of squamous histology (73%) [17]. Thymic carcinoma is known as a 'cold tumour' and has a low tumour mutation burden [18,19]. Previous studies have reported mutations in tumour suppressor genes (*TP53, CYLD* and *CDKN2A*), chromatin remodelling genes (*BAP1* and *PBRM1*) and other genes (*HRAS* and *KRAS* ) [20], though no targetable mutation or genes associated with costimulatory and coinhibitory T-cell signalling were included [21]. Such genetic information did not strongly support the activity of immune checkpoint inhibitors, while a high PD-L1 expression was still related to a better treatment effect in the pembrolizumab trials. The patient and tumour background did not seem to be responsible for the relatively low treatment effect observed in our study.

We set RR as the primary end-point in the present study because of comparable historical controls used in previous phase II trials. Considering the low toxicity and clinically meaningful DCR in our study, an early stopping rule based on toxicity could have been used rather than an assessment of efficacy at the interim analysis. From another viewpoint, the difficulty in evaluating thymic carcinoma including lesions of the pleura using RECIST has been pointed out by the International Thymic Malignancy Interest Group [22]. For example, in trials for soft-tissue sarcoma, which are also difficult to evaluate using RECIST, the end-points are often set as a 3-month or 6-month PFS to suggest drug activity [23]. A recent meta-analysis on defining the most appropriate primary end-point in phase II trials of immune checkpoint inhibitors has pointed out that RR is poorly correlated with the 12-month OS ($r = 0.08$), so the 6-month PFS is recommended as an end-point ($r = 0.74$) [24]. The ideal end-point remains controversial. For now, several prospective studies are being conducted: nivolumab is being evaluated using European Organisation for Research and Treatment of

Cancer for thymoma and thymic carcinoma (NCT03134118, NIVOTHYM trial, primary outcome is 6-month PFS), avelumab is being evaluated for thymoma and thymic carcinoma (NCT03076554, primary outcome is RR) and pembrolizumab plus epacadostat (NCT02364076, primary outcome is RR) is being evaluated for thymus cancer.

Of note, the rapid patient accrual and accurate diagnosis for ruling out thymomas suggests a well-established network among regional expert centres in Japan and high-quality pathology departments.

In conclusion, although the number of patients in the present study was small, nivolumab was unable to cause tumour shrinkage according to RECIST in previously treated patients with unresectable or recurrent thymic carcinoma. Our study does, however, suggest a clinically meaningful benefit of nivolumab, and further investigation in other research groups is awaited.

## Conflict of interest statement

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