ORIGINAL ARTICLE

Perioperative Pembrolizumab for Locally Advanced Thymic Epithelial Tumors: A Single-Arm, Phase 2 Trial

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ABSTRACT

Introduction: Complete surgical resection remains the only potentially curative option for thymic epithelial tumors (TETs). We hypothesized that adding perioperative pembrolizumab to standard therapy may improve response, resectability, and disease-free survival (DFS).

Methods: In this single-arm, prospective phase 2 trial, patients with potentially resectable TETs (Masaoka-Koga stages III–IV) received neoadjuvant docetaxel (75 mg/m^2), cisplatin (75 mg/m^2), and pembrolizumab (200 mg) every 3 weeks for 3 cycles, followed by surgery and maintenance pembrolizumab for 2 years. R1/R2-resected patients received adjuvant radiotherapy concomitant with pembrolizumab. The primary end point was a major pathologic response (MPR).

Results: From March 2020 to January 2025, 40 untreated patients were recruited, including those with WHO B3 thymoma (n = 7, 17.5%) or thymic carcinoma (n = 29, 72.5%). Most were diagnosed with stage IV disease (n = 31, 77.5%). The median follow-up duration was 27.5 months (95% confidence interval [CI]: 22.0–39.2), and 28 patients (70.0%) underwent surgical resection. Among the patients who received surgery, MPR and pathologic complete response were observed in 13 (46.4%) and five

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(17.9%) patients, respectively. Notably, all cases of MPR and pathologic complete response occurred exclusively in patients with thymic carcinoma, not in those with thymoma. The 1-year DFS rate was 91.0% (95% CI: 79.9–100.0), and the median DFS was 49.3 months (95% CI: 25.3–not reached) from the time point of surgery. Most of the adverse events were grade 1 or 2 (n = 21, 52.5%), with nine (22.5%) grade 3 and five (12.5%) grade 4. Two patients with thymoma died from myocarditis.

Conclusions: Perioperative pembrolizumab demonstrated promising rates of MPR, R0 resection, and long-term DFS in stage III to IV TETs.

Clinical trial registration: NCT03858582 (MK3475-971)

Keywords: Thymic epithelial tumor; Perioperative treatment; Immunotherapy; Locally advanced

Introduction

Thymic epithelial tumors (TETs) are rare neoplasms arising from the epithelial cells of the thymus, located in the anterior mediastinum, accounting for approximately 50% of anterior mediastinal masses.[1] TETs encompass a spectrum of histologic subtypes, broadly classified into thymomas and thymic carcinomas. These include high-risk subtypes, such as WHO type B3 thymoma and thymic carcinoma, which exhibit more aggressive clinical behavior, greater invasiveness, and a poorer prognosis.[2–4]

Complete surgical resection remains the only potentially curative treatment modality for TET.[5,6] However, when complete resection is not deemed feasible based on initial assessment, platinum-based induction chemotherapy is often considered as an alternative strategy to improve resectability and increase the likelihood of achieving a major pathologic response (MPR).[5–7] Nonetheless, previous studies evaluating neoadjuvant cytotoxic chemotherapy in high-risk TETs have reported MPR rates, including pathologic complete responses (pCR), of only 20% to 30%,[8–10] highlighting the need for more effective systemic therapies in the perioperative setting.

Chemoimmunotherapy has been found to improve pathologic response rates and long-term survival in the perioperative setting across several solid tumors,[11–14] by eradicating micrometastatic disease and enhancing antitumor immunity in the presence of intact tumor antigens.[15–17] In addition, programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors have demonstrated clinical efficacy in patients with metastatic TETs, particularly beyond the first-line setting, with reported objective response rate (ORR) ranging from 21.2% to 29.0%.[18–20] Furthermore, a recent study reported ORR of 56% with first-line combination therapy with atezolizumab, carboplatin, and paclitaxel in advanced thymic carcinoma, suggesting that immune checkpoint inhibitor (ICI), particularly when combined with cytotoxic chemotherapy, may also be effective in earlier lines of systemic TET treatment with manageable toxicity.[21]

In this context, we hypothesized that neoadjuvant pembrolizumab, when administered concurrently with chemotherapy, could improve tumor response, resectability, and disease-free survival (DFS). Here, we report the results of a phase 2, single-arm trial evaluating the efficacy and safety of neoadjuvant pembrolizumab in combination with docetaxel and cisplatin for potentially resectable TET.

Methods

Study Population

This was an open-label, single-arm phase II study at a single center (Samsung Medical Center) in Korea. This study investigated the efficacy and safety of neoadjuvant chemoimmunotherapy in patients with TETs not suitable for upfront surgery but potentially resectable after neoadjuvant therapy, based on multidisciplinary evaluation. Patients were included if they met the following criteria: (1) age above or equal to 19 years; (2) histologically confirmed TET; (3) localized advanced stage according to the modified Masaoka stage (III or IV); (4) have an Eastern Cooperative Oncology Group performance status of 0 to 1; (5) no prior treatment history of chemotherapy; (6) have measurable disease based on Response Evaluation Criteria in Solid Tumors 1.1; and (7) no other concurrent malignancy that could influence clinical outcomes.

Study Design

As a neoadjuvant regimen, patients received 3 cycles of docetaxel (75 mg/m^2), cisplatin (75 mg/m^2), and pembrolizumab (200 mg), administered every 3 weeks. After neoadjuvant treatment, treatment response was assessed using both computed tomography (CT) and positron emission tomography-computed tomography (PET/CT). Both imaging studies were performed at baseline and after completion of neoadjuvant therapy for treatment response and surgical decision-making. SUVmax, evaluated from the primary lesion, was defined as the highest standardized uptake value and was measured consistently using the same protocol

across baseline and post-treatment PET/CT scans. Operability was assessed approximately 3 weeks (±1 wk) after the final cycle of neoadjuvant treatment through multidisciplinary team evaluation, and surgical resection was subsequently performed within 2 weeks based on post-treatment resectability. The intensity of subsequent treatment was determined according to surgical outcomes. For patients who achieved R0 resection, pembrolizumab was administered as maintenance therapy for up to 32 cycles every 3 weeks. For patients with R1 or R2 resection, adjuvant radiotherapy (52.8 Gy in 24 fractions for R1, and 59.4 Gy in 27 fractions for R2) was added to pembrolizumab maintenance (Fig. 1*A*). Patients underwent chest CT (extending to the adrenal glands) after 4 weeks of surgery, then every 3 cycles of pembrolizumab maintenance phase during the first 12 months, and every 4 cycles for the next 12 months of the study.

The primary end point of the study was the MPR rate, defined as less than or equal to 10% of residual viable tumor cells in the resected specimen. Secondary end points included the complete resection rate, ORR, DFS, progression-free survival (PFS), overall survival (OS), safety profile, and treatment feasibility. DFS was assessed among patients who underwent curative-intent resection (R0 or R1) and was defined as the time from surgery to the first documented recurrence. For patients who underwent R2 resection, DFS was also calculated as an exploratory measure, defined as the time from surgery to radiological or clinical progression. PFS and OS were evaluated from the time of study enrollment. PFS was defined as the time from enrollment to documented disease progression: recurrence after R0 or R1 resection, progression after R2 resection, or initial progression in patients who did not undergo surgery.

All adverse events were graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Immune-related adverse events (irAEs) were defined as events of clinical interest with potentially drug-related immunologic causes. The detailed study design, including the full eligibility criteria, is provided in the protocol (Supplementary Material).

The study was approved and conducted under the supervision of the Samsung Medical Center Institutional Review Board (No: 2018-11-105) and registered at ClinicalTrials.gov (NCT 03858582). The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. This study was supported by Merck Sharp & Dohme. The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Study Assessment and Sample Size

This phase II, single-arm study aimed to enroll up to approximately 40 eligible patients, with an anticipated accrual period of 36 months. The primary end point was the MPR rate. The study was designed based on a one-arm binomial model to detect an increase in the MPR rate from a null hypothesis (H0) of less than or equal to 25% to an alternative hypothesis (H1) of more than or equal to 50%, with 90% power and a one-sided alpha level of 0.05. A total of 32 assessable patients were required for statistical analysis. Considering an anticipated dropout rate of 20%, the target sample size was set at 40 patients. The results were considered positive if more than 50% of the assessable patients achieved an MPR.

PD-L1 Immunohistochemistry

PD-L1 immunohistochemistry (IHC) was conducted using the PD-L1 IHC 22C3 PharmDx assay on the Dako Autostainer Link 48 system (Agilent Technologies, CA), in accordance with the manufacturer's protocol. PD-L1 expression was evaluated using the tumor proportion score (TPS), defined as the percentage of PD-L1–positive tumor cells among all viable tumor cells. Scoring was performed by an academic pathologist (Y-LC) with regular training in the interpretation of the 22C3 PharmDx assay.

Data Analysis

All patients participating in the clinical trial were included in the analysis, and those who were followed up after the actual test drug administration were considered the target group for the analysis of the primary efficacy analysis and safety evaluation. Best radiographic response was assessed based on imaging performed immediately before surgery or, in patients who did not undergo surgery, at the last assessable imaging time point. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors version 1.1 criteria. Survival was estimated using the Kaplan–Meier method. Safety evaluation was performed to determine the incidence of adverse events (AEs). Prespecified subgroup analyses to assess the consistency of the treatment effect on DFS and OS rates were performed using unstratified hazard ratios estimated from a Cox proportional-hazards model. All analyses were performed using R statistical software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

A total of 40 patients were enrolled in this study. The median age of the patients was 52 (range, 35–78) years,

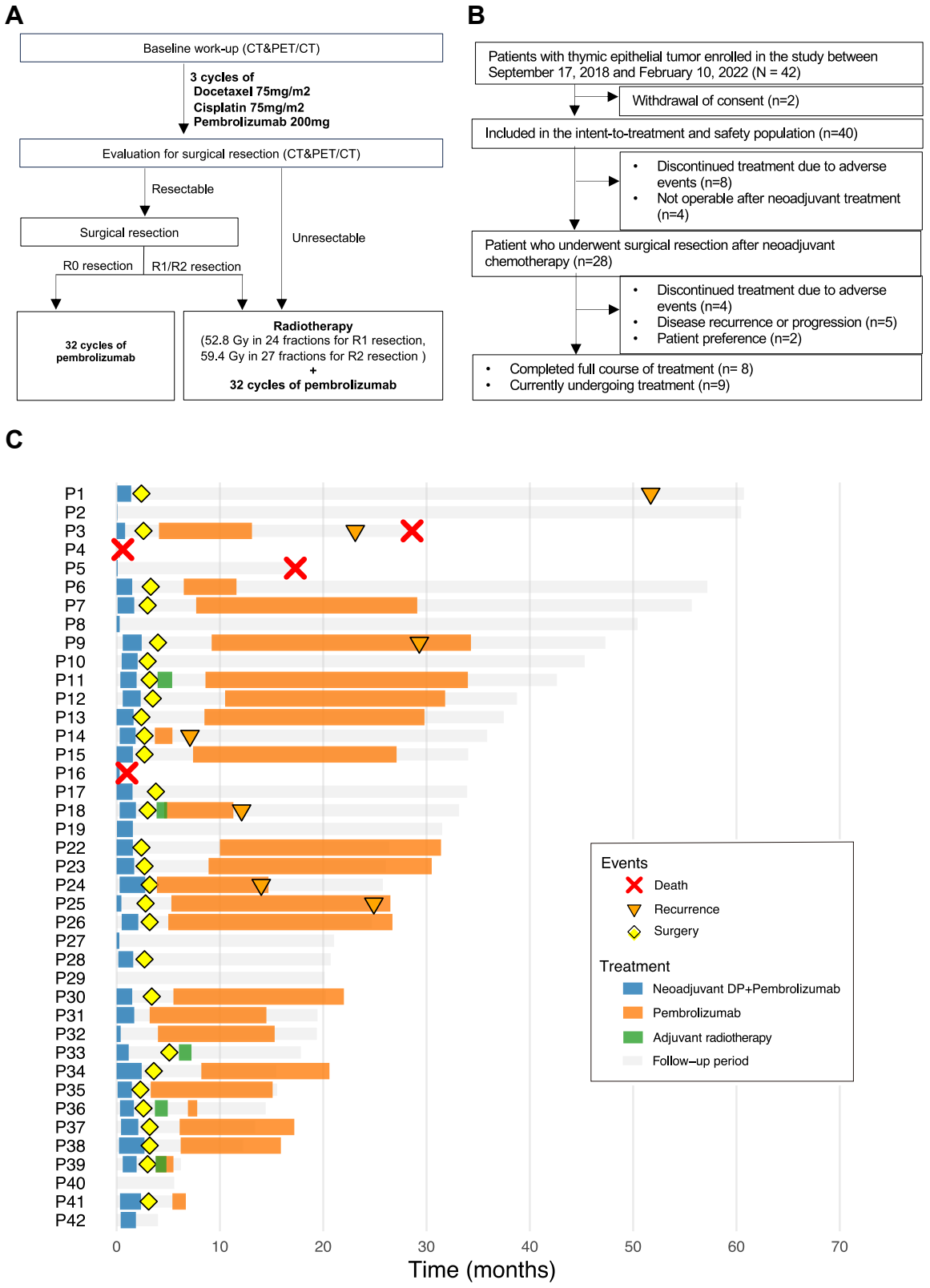

Figure 1. Overview of study design and patient cohort. (*A*) Scheme overview of the study. (*B*) Flow diagram of patient enrollment and treatment. (*C*) Swimmer plot depicting the treatment course of each patient. The duration of treatment administration is indicated with different colors. Y-axis labels from P1 to P42 represent individual patients (e.g., P1 = patient #1).

and 17 patients were male (42.5%). Most patients had Eastern Cooperative Oncology Group performance status of 1 (n = 34, 85.0%). Thymic carcinoma was the predominant histology (n = 29, 72.5%), followed by thymoma B3 (n = 7, 17.5%). Most of the patients were stage IV according to the TNM staging system of the American Joint Committee on Cancer (AJCC) eighth edition (n = 31, 77.5%) and the Masaoka-Koga staging system (n = 33, 82.5%). Baseline PD-L1 TPS was more than or equal to 50% in 18 (45.0%), 1% to 49% in 10 (25.0%), less than 1% in 11 (27.5%), and unassessable in one patient (2.5%) (Table 1). At data cutoff on June 11, 2025, nine of 40 patients (36.0%) remained on treatment with maintenance therapy. Among the 40 enrolled patients, 12 did not undergo curative-intent surgery after neoadjuvant therapy. Of these, eight were unable to proceed to surgery due to treatment-related adverse events, but four remained inoperable despite completing neoadjuvant treatment. Among the 28 patients who underwent surgery, four discontinued maintenance therapy due to adverse events. In addition, five patients discontinued treatment due to disease recurrence. Two patients discontinued follow-up based on personal preference (Fig. 1*B* and *C*). The median number of administered cycles was 3 (range, 1–3) for induction therapy and 21 (range, 1–32) for maintenance therapy. A total of five patients received adjuvant radiotherapy: four with R1 resection received 52.8 Gy in 24 fractions, but one with R2 resection received 59.5 Gy in 27 fractions.

Table 1. Baseline Characteristics

	Overall Cohort (N = 40)
Age, y	52 (35-78)
Sex	
Male	17 (42.5%)
Female	23 (57.5%)
ECOG	
0	6 (15.0%)
1	34 (85.0%)
Smoking history	
Never	13 (32.5%)
Past	12 (30.0%)
Current	5 (12.5%)
Masaoka-Koga stage	
III	7 (17.5%)
IVA	24 (60.0%)
IVB	9 (22.5%)
TNM stage	
II	1 (2.5%)
IIIA	1 (2.5%)
IIIB	7 (17.5%)
IVA	17 (42.5%)
IVB	14 (35.0%)
Histologic subtype	
Thymoma A	1 (2.5%)
Thymoma B1	2 (5.0%)
Thymoma B2	1 (2.5%)
Thymoma B3	7 (17.5%)
Thymic SqCC	22 (55.0%)
Thymic carcinoma-NOS	7 (17.5%)
Baseline PD-L1 TPS (22C3)[a]	
<1%	11 (27.5%)
1%-49%	10 (25.0%)
≥ 50%	18 (45.0%)
NA	1 (2.5%)

Note: The data are presented as numbers (%).
[a]Baseline PD-L1 TPS was evaluated in pretreatment tumor tissue samples.
ECOG, Eastern Cooperative Oncology Group; NA, not available; NOS, not otherwise specified; SqCC, squamous cell carcinoma; TPS, tumor proportion score.

Neoadjuvant Efficacy Outcomes

The median follow-up duration was 27.5 months (95% confidence interval [CI]: 22.0–39.2). The ORR to neoadjuvant therapy was 57.5%, with 23 patients (57.5%) achieving partial responses (PRs). Furthermore, 10 patients (25.0%) had stable disease and seven patients (17.5%) were not assessable due to treatment discontinuation before the first response assessment (Table 2). Median reduction in tumor size from baseline in target lesions was observed after neoadjuvant treatment in 31 patients (77.5%), with a median decrease of 35.6% (range, 1.2%–79.5%) (Fig. 2*A* and *B*). There was no significant difference in tumor volume decrease according to pathology (median reduction: 36.2% in thymic carcinoma versus 30.8% in thymoma; $p = 0.509$) or PD-L1 TPS status (43.1% in ≥50%, 32.3% in 1%–49%, and 33.5% in 0%; $p = 0.364$).

Pre- and post-treatment PET/CT evaluations were available for 26 patients (18 with thymic carcinoma and eight with thymoma), allowing for paired SUVmax analysis. Overall, the median SUVmax significantly decreased from 9.5 to 4.2 after neoadjuvant therapy ($p = 0.001$). When analyzed by histologic subtype, patients with thymic carcinoma demonstrated a significant reduction in SUVmax (from 11.8 to 4.0, $p < 0.001$), whereas those with thymoma exhibited no significant change (from 6.1 to 5.0, $p = 0.208$) (Fig. 2*C*).

Surgical, Pathologic, and Survival Outcomes

Among the 40 patients, 28 (70.0%) underwent surgical resection. The median interval from the end of neoadjuvant treatment to surgery was 4.9 weeks (range, 3.1–15.8). Two patients did not undergo surgery within the planned 3- to 6-week window due to treatment-related adverse events. One patient developed grade 3 aspartate aminotransferase/alanine aminotransferase (ALT) elevation and grade 3 cytopenia, leading to surgery at 10.0 weeks after the end of neoadjuvant

Table 2. Safety Profiles by Histological Subtype

	Total (N = 40)				Thymoma (N = 11)				Thymic Carcinoma (N = 29)				
Variables	Any	Gr 1–2	Gr 3–4	Gr 5	Any	Gr 1–2	Gr 3–4	Gr 5	Any	Gr 1–2	Gr 3–4	Gr 5	*p* Value
Nausea	10 (25.0%)	10 (25.0%)	0 (0.0%)	0 (0.0%)	4 (36.4%)	4 (36.4%)	0 (0.0%)	0 (0.0%)	6 (20.7%)	6 (20.7%)	0 (0.0%)	0 (0.0%)	0.418
Neutropenia	13 (32.5%)	8 (20.0%)	5 (12.5%)	0 (0.0%)	6 (54.5%)	3 (27.3%)	3 (27.3%)	0 (0.0%)	7 (24.1%)	5 (17.2%)	2 (6.9%)	0 (0.0%)	0.146
Thrombocytopenia	3 (7.5%)	3 (7.5%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	2 (6.9%)	2 (6.9%)	0 (0.0%)	0 (0.0%)	0.999
Anemia	21 (52.5%)	21 (52.5%)	0 (0.0%)	0 (0.0%)	5 (45.5%)	5 (45.5%)	0 (0.0%)	0 (0.0%)	16 (55.2%)	16 (55.2%)	0 (0.0%)	0 (0.0%)	0.845
Mucositis	7 (17.5%)	7 (17.5%)	0 (0.0%)	0 (0.0%)	3 (27.3%)	3 (27.3%)	0 (0.0%)	0 (0.0%)	4 (13.8%)	4 (13.8%)	0 (0.0%)	0 (0.0%)	0.369
Diarrhea	6 (15.0%)	6 (15.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	5 (17.2%)	5 (17.2%)	0 (0.0%)	0 (0.0%)	0.999
Myalgia	12 (30.0%)	12 (30.0%)	0 (0.0%)	0 (0.0%)	3 (27.3%)	3 (27.3%)	0 (0.0%)	0 (0.0%)	9 (31.0%)	9 (31.0%)	0 (0.0%)	0 (0.0%)	0.999
Gastritis	10 (25.0%)	10 (25.0%)	0 (0.0%)	0 (0.0%)	3 (27.3%)	3 (27.3%)	0 (0.0%)	0 (0.0%)	7 (24.1%)	7 (24.1%)	0 (0.0%)	0 (0.0%)	0.999
Alopecia	15 (37.5%)	15 (37.5%)	0 (0.0%)	0 (0.0%)	4 (36.4%)	4 (36.4%)	0 (0.0%)	0 (0.0%)	11 (37.9%)	11 (37.9%)	0 (0.0%)	0 (0.0%)	0.999
Potentially immune-mediated adverse events													
Rash	13 (32.5%)	11 (27.5%)	2 (5.0%)	0 (0.0%)	4 (36.4%)	3 (27.3%)	1 (9.1%)	0 (0.0%)	9 (31.0%)	8 (27.6%)	1 (3.4%)	0 (0.0%)	0.999
Hypothyroidism	8 (20.0%)	7 (17.5%)	1 (2.5%)	0 (0.0%)	3 (27.3%)	2 (18.2%)	1 (9.1%)	0 (0.0%)	5 (17.2%)	5 (17.2%)	0 (0.0%)	0 (0.0%)	0.660
Hyperthyroidism	2 (5.0%)	2 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.9%)	2 (6.9%)	0 (0.0%)	0 (0.0%)	0.999
Increased alanine aminotransferase	15 (37.5%)	11 (27.5%)	4 (10.0%)	0 (0.0%)	5 (45.5%)	4 (36.4%)	1 (9.1%)	0 (0.0%)	10 (34.5%)	7 (24.1%)	3 (10.3%)	0 (0.0%)	0.783
Pneumonitis	3 (7.5%)	2 (5.0%)	1 (2.5%)	0 (0.0%)	1 (9.1%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	2 (6.9%)	1 (3.4%)	1 (3.4%)	0 (0.0%)	0.999
Myocarditis	6 (15.0%)	0 (0.0%)	4 (10.0%)	2 (5.0%)	3 (27.3%)	0 (0.0%)	1 (9.1%)	2 (18.2%)	3 (10.3%)	0 (0.0%)	3 (10.3%)	0 (0.0%)	0.319
Pericarditis	1 (2.5%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0.999
Myositis	3 (7.5%)	2 (5.0%)	1 (2.5%)	0 (0.0%)	3 (27.3%)	2 (18.2%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.017
Pancreatitis	1 (2.5%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0.999

Note: Data are presented as number (%). *p* values were calculated based on the proportion of patients experiencing each toxicity of any grade, without stratification by severity.

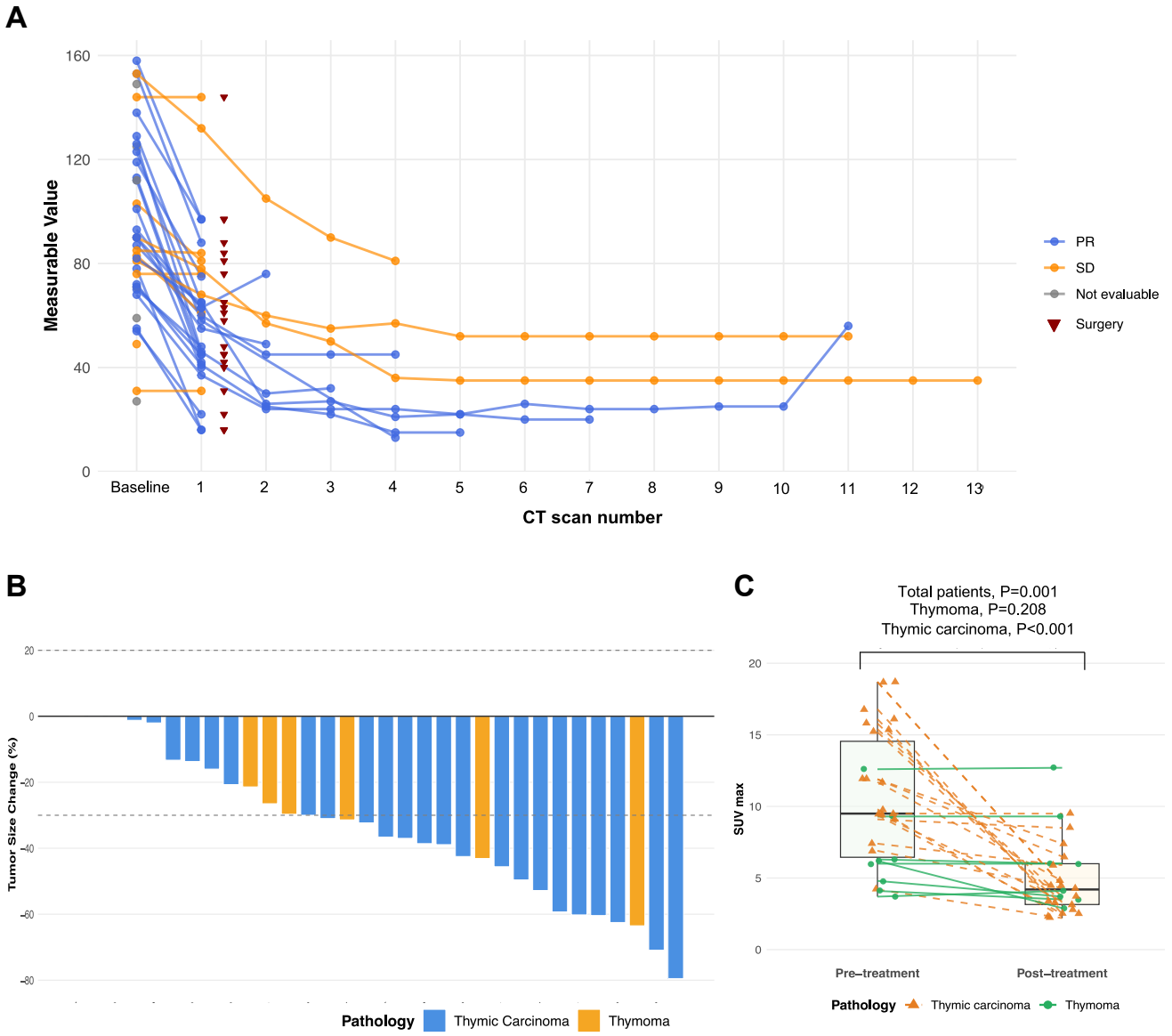

Figure 2. Efficacy outcomes of the study. (*A*) Waterfall plot of the percentage change in target lesions after neoadjuvant treatment. (*B*) Spider plot illustrating percentage change in target lesion size for individual patients. (*C*) Change in SUVmax of the target lesion after neoadjuvant treatment (n = 26).

treatment. The other patient experienced a grade 3 rash, delaying surgery to 15.8 weeks post-treatment. R0 resection was achieved in 20 patients (50.0% of the total cohort, 71.4% among those who underwent surgery). MPR and pCR were observed in 13 and five patients, respectively (32.5% and 12.5% of the total cohort; 46.4% and 17.9% among patients who underwent surgery). Both MPR and pCR were observed exclusively in thymic carcinoma (59.1% and 22.7% among patients with thymic carcinoma who underwent surgery), with no cases reported in thymoma (Fig. 3*A*, Supplementary Table 1). The rates of MPR and pCR were not significantly different according to PD-L1 TPS. MPR was observed in 45.5% of patients with PD-L1–negative tumors (0%), 20.0% in those with low expression (1%–49%), and 27.8% in those with high expression (≥50%) ($p = 0.282$). Similarly, pCR was achieved in 9.1%, 20.0%, and 11.1% of patients in the PD-L1 TPS 0%, 1% to 49%, and more than or equal to 50% groups, respectively ($p = 0.848$) (Fig. 3*B*).

Among the 26 patients with paired pre- (baseline) and post-treatment (surgical) samples available for PD-L1 expression analysis, the overall median TPS remained unchanged at 10.0% ($p = 0.122$). In patients with thymic carcinoma, PD-L1 expression revealed no significant change (from 5.0% to 10.0%, $p = 0.507$). However, those with thymoma (n = 6) demonstrated a

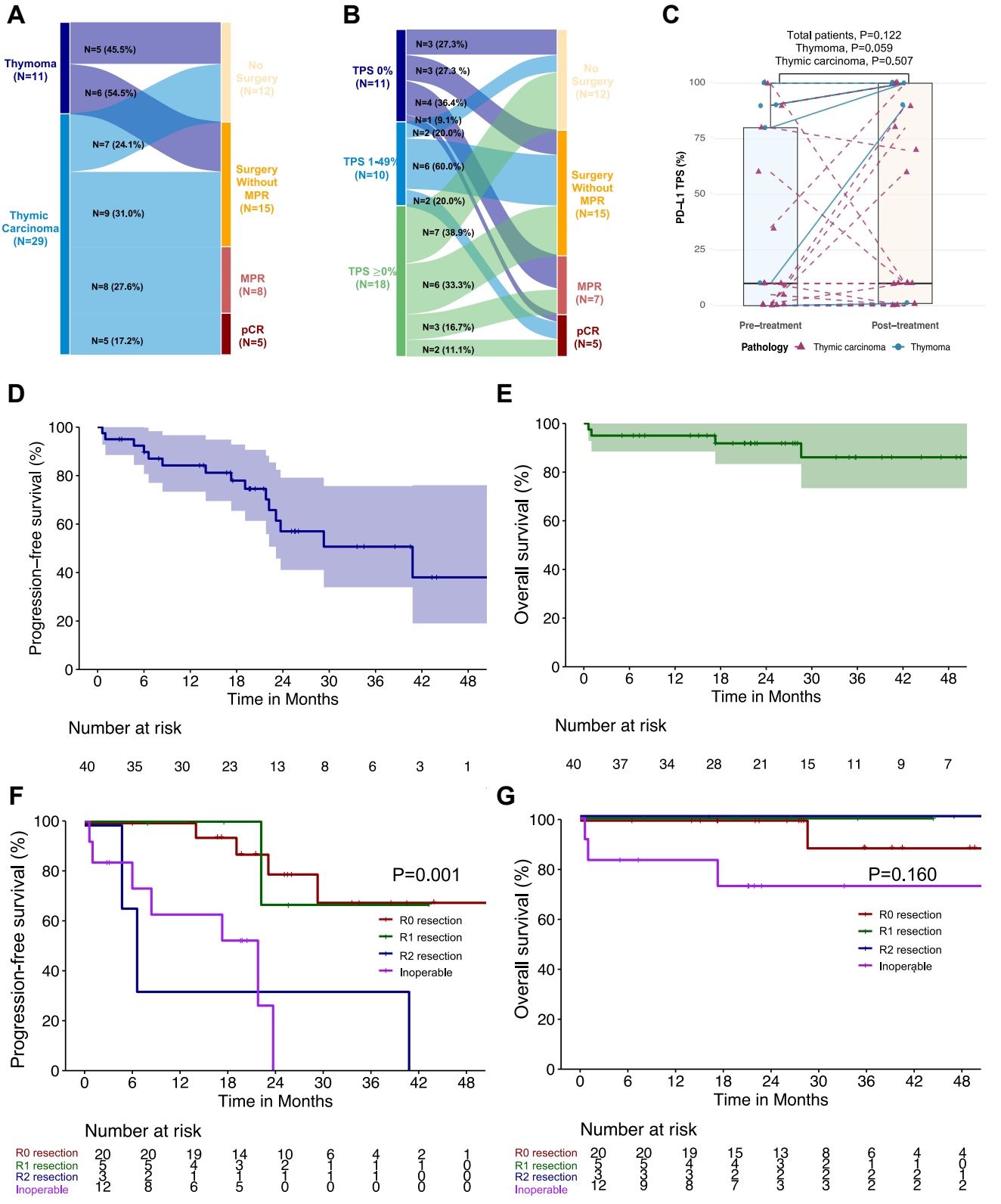

Figure 3. PD-L1 expression, dynamics, and overall clinical outcomes. (*A* and *B*) Alluvial plot illustrating surgical outcomes stratified by pathologic subtype (*A*) and PD-L1 TPS (*B*). (*C*) Dynamic change in PD-L1 TPS after neoadjuvant treatment, based on paired pretreatment biopsies and post-treatment surgical specimens. (*D* and *E*) Progression-free survival in patients (*D*) and overall survival of the study cohort patients (*E*). (*F*) Comparison of progression-free survival according to resection status (R0, R1, R2, and no surgery). (*G*) Comparison of overall survival according to resection status (R0, R1, R2, and no surgery). TPS, tumor proportion score.

trend toward increased expression, with the median TPS rising from 85.0% to 100.0% ($p = 0.059$) (Fig. 3*C*).

Among the patients who underwent surgery (n = 28), the 1-year DFS rate was 87.9% (95% CI: 75.9–100.0) and the median DFS was 49.3 months (95% CI: 25.3–not reached [NR]) from the time point of surgery (Supplementary Fig. 1A). According to resection status, the median DFS was 49.3 months (95% CI: 25.3–NR) for R0 resection, NR (95% CI: 19.2–NR) for R1 resection, and 20.6 months (95% CI: 3.64–NR) for R2 resection ($p = 0.077$) (Supplementary Fig. 1B). When limited to patients who achieved R0 or R1 resection (n = 25), the 1-year DFS rate was 91.0% (95% CI: 79.9–100.0) and the median DFS was 49.3 months (95% CI: 25.3–NR), measured from the time point of surgery (Supplementary Fig. 1C), and there was no difference in DFS, according to the resection status (R0 resection versus R1 resection; $p = 0.908$), pathology type (thymoma versus thymic carcinoma; $p = 0.746$), or PD-L1 status (TPS $\geq$50% versus <50%; $p = 0.263$) (Supplementary Fig. 1D–F).

In the overall cohort (N = 40), the median PFS and OS from enrollment were 40.8 months (95% CI: 23.1–NR) and NR (95% CI: 8.4–NR), respectively (Fig. 3*D* and *E*). By surgical outcome, the median PFS was NR for both R0 (95% CI: 29.3–NR) and R1 (95% CI: 22.2–NR) resections, 6.6 months (95% CI: 4.7–NR) for R2 resections, and 21.8 months (95% CI: 8.4–NR) for patients who did not undergo surgery ($p = 0.001$) (Fig. 3*F*). No significant difference in OS was observed according to surgical status or resection margin status ($p = 0.160$) (Fig. 3*G*). There were no significant differences in PFS or OS according to PD-L1 status (TPS $\geq$50% versus <50%; $p = 0.906$ and $p = 0.408$, respectively) or pathology type (thymoma versus thymic carcinoma; $p = 0.170$ and $p = 0.316$, respectively) (Supplementary Fig. 2).

Safety Outcomes

The safety profile is described in Table 2 and Supplementary Tables 2 to 3. A total of 37 patients (92.5%) experienced at least one treatment-related adverse event. The most frequently observed adverse event of any grade was anemia (n = 21, 52.5%), followed by increased ALT (n = 15, 37.5%) and neutropenia (n = 13, 32.5%), which might be related to the cytotoxic chemotherapy. A total of 16 patients (40.0%) reported grade 3 to 5 adverse events (Table 2 and Supplementary Table 2). Patients with thymoma experienced a significantly higher rate of severe toxicity (grade $\geq$3) compared with those with thymic carcinoma (63.6% versus 31.0%, $p = 0.043$). Myositis was uniquely observed in the thymoma group, occurring in 27.3% of patients, but no cases were reported in the thymic carcinoma group ($p = 0.017$) (Table 2). A total of 12 patients discontinued the study due to treatment-related adverse events, and eight discontinued before surgery as a result of treatment-related adverse events. More patients with thymoma (n = 5, 45.5%) were unable to undergo surgery due to toxicity-related treatment discontinuation, including grade 4 myocarditis (n = 1), grade 5 myocarditis (n = 2), grade 4 neutropenia (n = 1), and grade 4 aspartate aminotransferase/ALT elevation (n = 1), compared with those with thymic carcinoma (n = 3, 10.3%; all myocarditis; $p = 0.025$). Of note, all six myocarditis cases occurred during the neoadjuvant phase and resulted in withdrawal from the study. Four of them recovered after receiving high-dose steroid pulse therapy (methylprednisolone [mPD] 1000 mg for 3 d), followed by corticosteroid tapering and intravenous immunoglobulin (IVIG) or steroid pulse and tapering therapy in combination with ruxolitinib (a JAK1/2 inhibitor) and abatacept (2 mg/kg, administered four times). However, two patients with thymoma developed myocarditis approximately 3 weeks after initiating neoadjuvant treatment and died despite receiving steroid pulse therapy and IVIG (Supplementary Table 3). Meanwhile, four patients discontinued treatment during the maintenance period due to grade 3 gastritis, pancreatitis, cholangitis, and pericarditis. All other adverse events resolved after treatment discontinuation.

Representative and Discussed Cases

Figure 4*A* illustrates the clinical course of patient #13, who was initially diagnosed with Masaoka-Koga stage III thymic squamous cell carcinoma. The patient achieved PR after neoadjuvant treatment, with a decrease in SUVmax from 9.7 to 2.3 on PET/CT, indicating a partial metabolic response. The patient subsequently underwent surgical resection and achieved a pCR. Adjuvant pembrolizumab was administered for 32 cycles, and the patient has remained recurrence free for more than 3 years. Figure 4*B* and *C* illustrates the clinical course of patient #40, who discontinued treatment due to myocarditis. The patient presented to the emergency department with chest and back pain and generalized myalgia 3 weeks after completing 1 cycle of neoadjuvant therapy. Initial cardiac markers were elevated (CK-MB 1.5 ng/mL, troponin-I 2.3 ng/mL). mPD 50 mg was initiated on admission, but due to worsening markers, pulse therapy with mPD 500 mg for 3 days was administered on hospital day 3, followed by tapering. On day 12, the patient developed high-grade atrioventricular block requiring a temporary pacemaker, which failed to capture on day 17 and required repositioning. Abatacept (2 mg/kg weekly) and

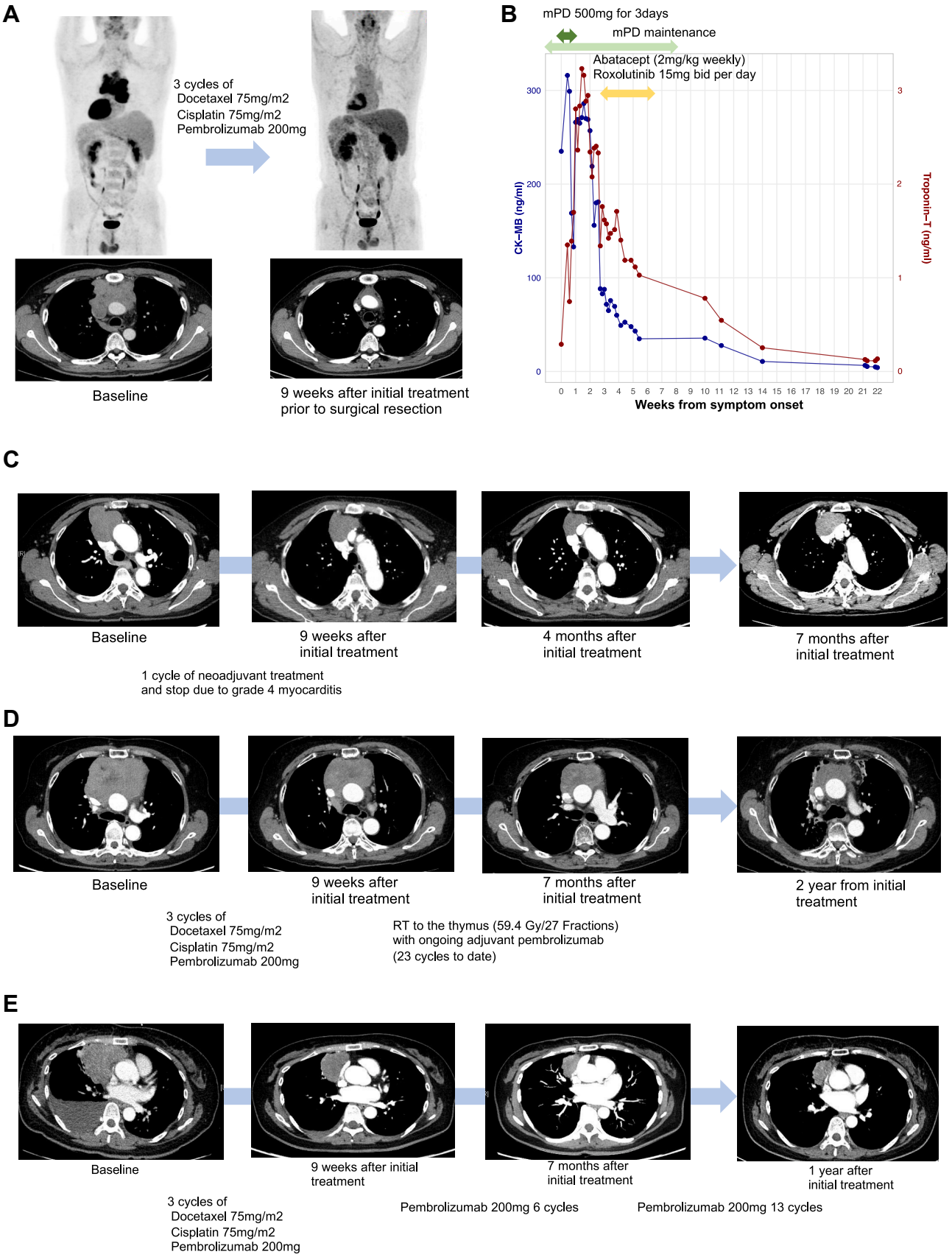

Figure 4. Representative and discussed cases. (*A*) Pre- and post-neoadjuvant treatment CT and PET/CT images of patient #13 with pathologic complete response. (*B*) Serial cardiac biomarker levels after symptom onset. (*C–E*) Serial imaging of tumor radiographic features in the course of treatment in patient #40 (*C*), patient #32 (*D*), and patient #31 (*E*). CT, computed tomography; PET, positron emission tomography.

ruxolitinib (15 mg daily) were administered for 1 month. Cardiac markers gradually improved, and symptoms resolved. Despite receiving only 1 cycle of neoadjuvant therapy, the primary tumor shrank from 59 mm to 48 mm, and the response was maintained for 7 months. After tumor regrowth, salvage surgery was performed, achieving R0 resection. Figure 4*D* and *E* presents a representative sequential clinical course of patients who did not undergo surgery. Patient #32 received neoadjuvant chemotherapy but was ultimately deemed inoperable. After a multidisciplinary team discussion involving thoracic surgery, radiation oncology, radiology, and medical oncology, the patient received definitive radiotherapy followed by consolidation pembrolizumab. The patient has maintained PR for more than 2 years (Fig. 4*D*). Patient #31 was also considered inoperable due to vascular invasion. As both surgery and radiotherapy were deemed inappropriate, pembrolizumab monotherapy was initiated and continued as maintenance treatment. After 23 cycles, the patient remains in a durable PR (Fig. 4*E*).

Discussion

In this prospective phase 2 trial, the addition of perioperative pembrolizumab to standard neoadjuvant chemotherapy demonstrated encouraging efficacy and safety in patients with locally advanced TETs. To the best of our knowledge, this is the first clinical trial evaluating the efficacy and safety of neoadjuvant immunotherapy combined with platinum-based chemotherapy in patients with TETs.

In this study, we observed an MPR of 32.5% and a pCR of 12.5% in the overall cohort. Although the predefined primary end point of a 50% MPR rate was not met, the thymic carcinoma subgroup achieved an MPR rate of 44.8%, approaching the predefined target. Given the rarity of the disease and the heterogeneity of thymoma and thymic carcinoma across studies, direct comparisons should be made with caution. Nevertheless, previous studies of neoadjuvant cytotoxic therapy have reported relatively low MPR rates of 23.8% to 27.3% and pCR rates of 0% to 14.3%,[8,22] suggesting a potential benefit of adding pembrolizumab to neoadjuvant therapy.

In addition, considering previously reported ORRs of 36.0% to 42.9% with taxane–carboplatin regimens and approximately 50% with CAP regimens (cyclophosphamide, doxorubicin, and cisplatin) in the metastatic setting[23–25] and 42.9% to 63.0% in the neoadjuvant setting,[7,8] the ORR to the neoadjuvant immunochemotherapy was 57.5% and the R0 resection rate was 50.0% observed in our study suggesting favorable tumor shrinkage and resectability. Given that thymic carcinoma is frequently diagnosed at an advanced stage,[5] limiting the feasibility of complete resection, this finding is noteworthy. Furthermore, although 30% of the patients (n = 12) were unavailable to receive surgery, the 1-year DFS rate for patients who received surgery (n = 28, 70%) reached 91.0%, highlighting the potential benefit of combining immunotherapy with conventional treatment to successfully control micrometastatic disease and improve long-term outcomes. Among the patients who did not undergo surgery, the median PFS was 21.8 months (95% CI: 8.4–NR), highlighting the additional long-term benefit of ICI used in a perioperative manner.

Currently, ICI is used as a standard treatment in the later-line setting with observed ORR ranging from 21.2% to 29.0%.[18–20] Despite the similar clinical efficacy of ICI in thymic carcinoma and thymoma, revealing ORR of 28.6% versus 19.2%,[19] adverse events were significantly different; severe immune-related adverse events led to more frequent treatment discontinuation in patients with thymoma.[18–20] In our study, we observed a similar trend of a higher proportion of patients with thymoma unable to undergo surgery due to toxicity-related treatment discontinuation (45.5% versus 10.3%, $p = 0.025$). The differential adverse event rates may reflect fundamental differences in tumor immunobiology: thymomas impair central immune tolerance more severely than thymic carcinomas, owing to disrupted thymic architecture and reduced autoimmune regulator expression.[26–29] At the same time, thymomas may aberrantly express and present self-like antigens, promoting the activation of autoreactive T cells. In the context of immune checkpoint inhibition, this excessive or ectopic self-antigen presentation can break peripheral tolerance and lead to severe systemic autoimmune toxicities.[26,30]

Importantly, six patients developed immune-related myocarditis and four achieved full recovery with high-dose corticosteroids and IVIG. In contrast, the remaining two patients—both with thymoma—developed fulminant myocarditis and died despite timely intervention. Those grade 5 events occurred during the early phase of the study. As experience accumulated, our approach to toxicity prevention and management evolved. We implemented routine cardiac enzyme monitoring, refined patient selection to include predominantly thymic carcinoma, and applied early intervention strategies, including corticosteroid pulse therapy and, in fulminant myocarditis, abatacept and ruxolitinib.[31] These adjustments have enabled more consistent and safer administration of perioperative ICI in TETs. Moreover, even patients who were unable to complete the full course of immunotherapy, or even curative-intent treatments such as surgery, experienced a prolonged response, which may be attributed to a

previously primed immune system. The observation that long-term efficacy was maintained even in patients who experienced adverse events underscores the importance of early detection and appropriate management of side effects. This highlights the need to consider strategies for safer use of ICIs.

This study has limitations, including its single-center, single-arm design; modest sample size; and relatively short follow-up for long-term survival outcomes. In addition, after the occurrence of an early fatal myocarditis event in patients with thymoma, subsequent enrollment was restricted to patients with thymic carcinoma. This safety-driven adjustment resulted in a cohort skewed toward thymic carcinoma, which should be considered when interpreting histology-specific findings. Moreover, initial histologic classification relied on biopsy specimens, which carry an inherent risk of sampling error and may not always capture the full histologic complexity required for accurate WHO subtyping. Nonetheless, a substantial proportion of patients who would have otherwise been precluded from surgery were able to undergo surgical resection, resulting in a meaningful resection rate and response rate, highlighting the potential clinical benefit of this approach.

In conclusion, although this trial did not meet its predefined primary end point, perioperative chemo-immunotherapy with pembrolizumab was feasible and demonstrated promising MPR and R0 resection rates, along with favorable long-term DFS in patients with potentially resectable stages III to IV thymic carcinoma. Conversely, the potential for fatal immune-related toxicity in thymoma underscores the need for caution. Randomized clinical trials are warranted to validate these findings and guide treatment strategies.

CRediT Authorship Contribution Statement

Yeong Hak Bang: Formal analysis, Writing - original draft, Writing - review and editing.

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Boram Lee: Writing - review and editing.

Yoon-La Choi: Writing - review and editing.

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Hyunsu Kim: Writing - review and editing.

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Hong Kwan Kim: Enrollment and clinical care, Writing - review and editing.

Yong Soo Choi: Enrollment and clinical care, Writing - review and editing.

Seong Yong Park: Enrollment and clinical care, Writing - review and editing.

Sehhoon Park: Study design, Enrollment and clinical care, Formal analysis, Original draft, Writing - review and editing. All authors had full access to all data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Disclosure

Dr. Jung reports having advisory roles at Yuhan, Guardant, and AIMEDBIO and received research funding from Yuhan. Dr. Jin Seok Ahn received honoraria from Pfizer, Roche, BC World Pharmaceutical, Yuhan, Hanmi, Novartis, JW Pharmaceutical, Amgen, Boehringer Ingelheim, Menarini, Kyowa Kirin, AstraZeneca, Bayer, Lilly, Takeda, Boryung, and Samyang and has advisory roles at Bayer, Yooyoung Pharmaceutical Co., Ltd., Pharmbio Korea, Guardant Health, Yuhan, ImmuneOncia, Therapex, Daiichi Sankyo Korea, and Roche. Dr. Myung-Ju Ahn received honoraria from AstraZeneca, Lilly, Merck Sharp & Dohme, Takeda, Amgen, Merck Serono, and Yuhan; reports advisory roles at AstraZeneca, Lilly, Merck Sharp & Dohme, Takeda, Alpha Pharmaceutical, Amgen, Merck Serono, Pfizer, Yuhan, and Arcus Ventures; and received research funding from Yuhan. Dr. Se-Hoon Lee received honoraria from AstraZeneca/MedImmune, Roche, Merck, Lilly, and Amgen; has advisory roles at AstraZeneca, Roche, Merck, Pfizer, Lilly, Bristol Myers Squibb/Ono, Takeda, Janssen, and IMBdx; and received research funding from Merck, AstraZeneca, and Lunit. The remaining authors declare no conflict of interest.

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had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Data Sharing

The study protocol is available in the Supplementary material. A data-sharing plan was not included in the trial protocol, and data sharing will be conditional on approval of the Institutional Review Board of Samsung Medical Center. A data access agreement will be required for access.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2025.08.011.

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