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Phase II trial of single agent amrubicin in patients with previously treated advanced thymic malignancies

Jessica A. Hellyer[a], Matthew A. Gubens[a,d], Kristen M. Cunanan[a], Sukhmani K. Padda[a], Matthew Burns[b], A. John Spittler[b], Jonathan W. Riess[a,c], Melanie San Pedro-Salcedo[a], Kavitha J. Ramchandran[a], Joel W. Neal[a], Heather A. Wakelee[a,*,1], Patrick J. Loehrer Sr[b,1]

[a] Stanford University School of Medicine and Stanford Cancer Institute, 875 Blake Wilbur Driver, Stanford, CA, USA
[b] Indiana University Melvin and Bren Simon Cancer Center, 535 Barnhill Dr. Indianapolis, IN, USA
[c] UC Davis Comprehensive Cancer Center, 2279 45thSt, Sacramento, CA, USA
[d] University of California San Francisco, 1450 3rdSt, San Francisco, CA, USA

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ABSTRACT

Objectives: There are limited treatment options for patients with thymic malignancies. Here we present data supporting treatment with single agent amrubicin, a third generation anthracycline and topoisomerase II inhibitor.

Materials and methods: This was a phase 2 open-label, single arm trial of amrubicin in patients with thymoma (T) or thymic carcinoma (TC), conducted at two academic institutions. Patients were included if they had received at least one prior chemotherapy regimen. The first 18 patients received amrubicin at 40 mg/m2 IV days 1–3 repeated every 3-weeks. Due to the high incidence of febrile neutropenia, dosing was subsequently amended to 35 mg/m2 for the final 15 patients.

Results: A total of 33 patients (14 T/19 TC) were enrolled from 2011 to 2014. Median number of prior therapies was 2. Best response included 6 partial responses, 21 stable disease, and 6 progressive disease (all TC). Objective response rate was 18% (90% exact binomial CI 8.2%–32.8%; T = 4/14 (29%), TC = 2/19 (11%)). Median progression-free survival was 7.7 months (T: 8.3 months; TC: 7.3) and median overall survival was 29.7 months (T: 54.1 months; TC: 18 months). There was a high rate of febrile neutropenia (7 patients) that occurred despite a reduction in amrubicin dose and one related death. Five patients had reduction in LVEF below 50% during the course of treatment resulting in treatment discontinuation in one patient.

Conclusion: Amrubicin shows promise as a single agent in heavily pre-treated patients with thymic malignancies. Notable side effects include febrile neutropenia and the use of growth factor support is essential. Further investigation of this agent is warranted.

1. Introduction

Thymoma (T) and thymic carcinoma (TC) are rare tumors of the mediastinum and optimal treatment regimens have not been elucidated. In part due to their rarity, much of our current data stem from retrospective analyses and there are few prospectively designed clinical trials to guide therapy.

The current standard of care for advanced thymoma and thymic carcinoma is a first-line platinum-based regimen based on small single-arm phase 2 studies. Cyclophosphamide/doxorubicin/cisplatin (CAP) is the NCCN preferred regimen for advanced thymoma [1]. Carboplatin/paclitaxel is recommended for advanced thymic carcinoma, but notably has only a 22% objective response rate in previously untreated patients [2]. In the progressive or relapsed setting, no standard regimen exists. Toxicity from chemotherapy such as neuropathy (from taxanes) or cardiomyopathy (from doxorubicin) is often dose limiting; therefore, the development of effective regimens with more tolerable side-effect profiles is warranted.

The anthracycline doxorubicin is a key component of treatment regimens for thymic malignancies and some studies suggest an

* Corresponding author at: Department of Medicine, Division of Oncology, Stanford Cancer Institute/Stanford University School of Medicine, 875 Blake Wilbur Drive, Stanford, CA, 94305, USA.
E-mail address: hwakelee@stanford.edu (H.A. Wakelee).
[1] Co-Senior Authors.

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enhanced response rate with anthracycline-containing regimens [3]. Amrubicin is a 3rd generation anthracycline and topoisomerase II inhibitor with significantly lower cardiac toxicity compared with doxorubicin [4,5]. Given the anthracycline-based mechanism of action and improved tolerability of amrubicin with regards to cardiotoxicity, we designed this prospective study to test the efficacy of single-agent amrubicin in patients with previously treated advanced thymoma and thymic carcinoma.

2. Materials and methods

2.1. Patient selection

Patients were included if they had histologically confirmed, inoperable thymoma or thymic carcinoma and had progressed or relapsed after at least one prior chemotherapy regimen (no limit on number of prior regimens). Patients must have had an Eastern Cooperative Oncology Group performance status of 0–1, with adequate bone marrow function (leukocytes $\geq$ 3000/mm^3, absolute neutrophil count $\geq$1500/mm^3, platelets $\geq$100,000/mm^3 and hemoglobin $\geq$9 g/d), hepatic (serum bilirubin $<$ 1.5x institutional upper limit of normal (ULN), aspartate transaminase and alanine transaminase ratio $<$ 3 ULN), renal (serum creatinine $<$ 1.5x institutional ULN) and cardiac function (left ventricular ejection fraction $\geq$ 50%). Patients with symptomatic brain metastases or who had another active malignancy were excluded. All patients provided written informed consent. The local institutional review boards approved this study and the study was listed on clinicaltrials.gov (NCT01364727).

2.2. Study design

This was an open-label investigator-initiated single arm phase II trial with objective response rate (ORR) as the primary endpoint. The study was conducted at two academic institutions. The initial planned dose of amrubicin was 40 mg/m^2 IV over 5 min on days 1, 2 and 3 of a 21 day cycle (+/- 4 days). However, due to high rates of febrile neutropenia, after the enrollment of the first 18 patients, the protocol was amended to reduce the dose to 35 mg/m^2 IV D1–3 of a 21 day cycle and utilize growth factor support (GCSF). Computed tomography imaging was performed every two cycles and evaluated with RECIST v1.1 [6]. For cardiac monitoring, a transthoracic echocardiogram was performed at baseline and every 3 cycles. Complete blood counts, chemistry panels and physical exam were completed prior to each cycle. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.

The primary endpoint was the objective response rate, which was calculated from the confirmed best overall response (the number of partial and complete responders using RECIST version 1.1). Secondary objectives were progression free survival, disease control rate, duration of response, overall survival and evaluation of toxicity. Progression free survival was calculated from the date of therapy initiation to the date of progression, and patients were censored on the date of last follow up if they had not progressed. Disease control rate was assessed using proportion of patients who achieved a complete response, partial response or stable disease as confirmed using RECIST version 1.1. and was measured from date of first confirmed response until date of disease progression. Overall survival was measured from date of therapy initiation to the date of death. If lost to follow up, the patient was censored at the last date the patient was known to be alive. Patients alive at the last follow up date were censored.

2.3. Statistical design and analysis

This study employed a two-stage Simon optimal design. Patients with either a complete (CR) or partial response (PR) that was confirmed on subsequent scan were characterized as responders. For the primary analysis, the null hypothesis was set to be H_0: $ORR \leq 5\%$. The alternative hypothesis of a response rate of 20% was used to determine the expected treatment effect. The design was specified to have 90% power and a significance level of 10% (one-sided). During stage one, 12 patients were to be enrolled. If 1 or more patients responded (90% CI for 1 response: [0.4%, 33.9%]), accrual would continue to stage two. During stage two, 25 patients were to be enrolled. If 4 or more patients responded out of the total 37 patients, then the study will be considered successful (90% two stage CI for 4 responses: [4.0%, 25.3%]). With 37 patients, the optimal Simon two-stage design has 90% power at a 10% significance level to test the null hypothesis that the ORR $\leq$ 5%, assuming a target ORR of 20%.

The probability of stopping early was 0.07 and 0.54 if the true overall response rate is 5% and 20%, respectively.

Kaplan-Meier curves for progression free and overall survival were calculated. Comparison of survival curves was done using the log-rank (Mantel-Cox) test.

The study was funded by Celgene, including financial support to conduct the study and providing investigational drug. Celgene provided input on the study design and protocol but had no role in data collection, analysis or interpretation. All authors had full access to data in the study and final responsibility for approving the publication submission.

3. Results

The first 12 patients (6 T/6 TC) in stage one were enrolled at Stanford University starting in July 2011. Three out of the 12 enrolled patients (25%) achieved an objective response. This met criteria to enroll to stage two of the study. For stage two, the study was expanded to include Indiana University and an additional 21 patients (9 T/12 TC) were accrued. Enrollment was discontinued in April 2014 due to product strategic prioritization at Celgene, with a total of 33 patients treated on study.

3.1. Patient characteristics

Patient characteristics are listed in Table 1. There were 33 patients, 14 with thymoma (42%) and 19 with thymic carcinoma (58%), enrolled from July 2011 to April 2014. All patients had stage IV disease with WHO Type B2 (50%) and B3 (29%) being the most common histology in the thymoma cohort. The majority of patients were male (58%) and white (70%). The average age was 58 ($\pm$ 12 years). A majority of patients had received surgery (61%) or radiation (67%) earlier in their treatment course. All patients had at least one prior systemic therapy, with the median number of prior therapies of 2 (TC) and 2.5 (T), respectively.

3.2. Efficacy

Twenty-eight patients (85%) completed at least 4 cycles of therapy and 17 (52%) completed at least 10 cycles. The median number of cycles completed was 10 (interquartile range 6,15) and the range was 1-64. The reason for treatment discontinuation included disease progression (n = 22), adverse events (n = 5), patient withdrawal (n = 4) and treating physician decision (n = 2). The ORR was 6 out of 33 patients (18%; 90% exact binomial CI: (8.2%, 32.8%); T: n = 4 (29%); TC n = 2 (11%)) using the best overall response. Despite the study not reaching full enrollment, amrubicin displayed sufficient evidence of activity for further investigation. Of the 6 responders, 5 patients had a partial response (T: n = 3 (21%); TC: n = 2 (11%)) and 1 patient had a complete response (T, 7%). The median duration of response (n = 6) was 5.2 months (2.9,23.3). The disease control rate (DCR) was 91% (30 of 33 patients) using the best overall response (T: n = 14 (100%); TC: n = 16 (84%)). Of these 30 patients, 24 patients had stable disease (T: n = 10 (71%); TC: n = 14 (74%)). Kaplan-Meier curves for PFS of the entire cohort and stratified by histology are presented in Fig. 1. Median

Table 1
Patient and Tumor Characteristics. Abbreviations: ECOG; Eastern Cooperative Oncology Group. WHO; World Health Organization. NOS; not otherwise specified.

Characteristics	Thymoma (n = 14)	Thymic Carcinoma (n = 19)
Average age (years)	57	59
Sex		
Female	8 (57)	6 (32)
Male	6 (43)	13 (68)
Ethnicity		
Hispanic	0 (0)	1 (5)
Non-Hispanic	14 (100)	18 (95)
Race		
Asian	3 (21)	6 (32)
African-American	1 (7)	0 (0)
White	10 (71)	13 (68)
ECOG Performance Status		
0	7 (50)	8 (42)
1	7 (50)	11 (58)
WHO Histology		
Type A	0 (0)	0 (0)
Type AB	0 (0)	0 (0)
Type B1	0 (0)	0 (0)
Type B2	7 (50)	0 (0)
Type B3	4 (29)	0 (0)
Type C	0 (0)	19 (100)
NOS	3 (21)	0 (0)
Prior Therapy		
Surgery	10 (71)	6 (32)
Radiation	6 (43)	11 (58)
Prior Doxorubicin exposure		
Yes	12 (86)	6 (32)
No	2 (14)	13 (68)
Prior chemotherapy regimens		
1	3 (21)	6 (32)
2	4 (29)	8 (42)
3	3 (21)	1 (5)
4	1 (7)	2 (11)
> / = 5	3 (21)	2 (11)
Median	2.5	2

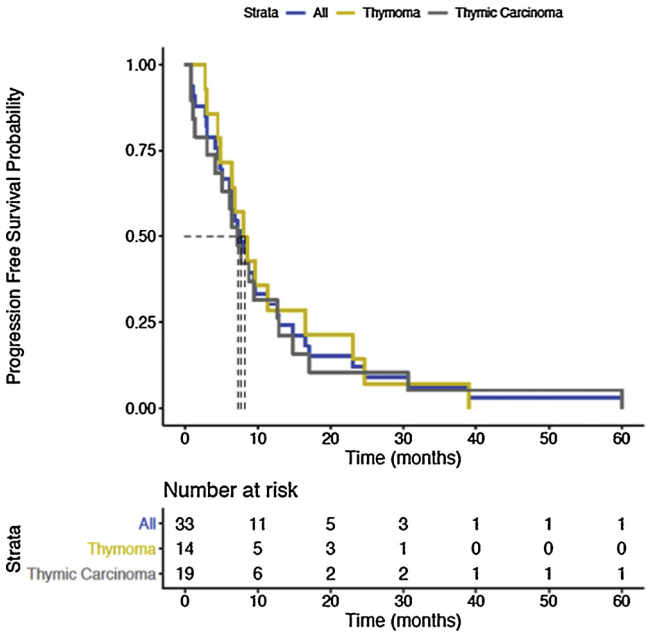

Fig. 1. Progression free survival for thymoma, thymic carcinoma and the entire cohort.

progression free survival was 7.7 months (90% CI 6.2,12.7) in the entire cohort (T: 8.3 months (6.4, 24.7); TC: 7.3 months (5.1,14.8)). Kaplan-Meier curves for OS of the entire cohort and stratified by histology are

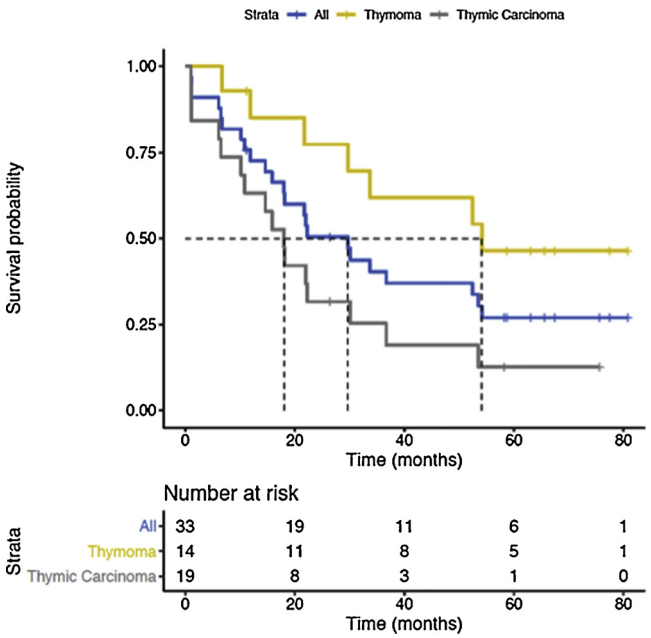

Fig. 2. Overall survival for thymoma, thymic carcinoma and the entire cohort.

presented in Fig. 2. Median overall survival was 29.7 months (90% CI 18, 54.1) in the entire cohort (T: 54.1 months (29.7, NR); TC: 18 months (10.8, 53.5)). Finally, we wanted to evaluate if the receipt of prior doxorubicin chemotherapy had an impact on the efficacy of amrubicin. There were 18 patients who received prior doxorubicin and 15 patients who had not. There was no difference in PFS (7.4 vs 7.7 months, p = 0.76) or OS (p = 0.33) between patients who had prior doxorubicin and patients who had not received prior doxorubicin (Supplemental Figs. 1–2), though the analysis is complicated by the fact that the prior doxorubicin group were predominantly thymoma patients (12/18) and the no prior doxorubicin group predominantly had TC histology (13/15).

3.3. Safety

Common grade 1–2 adverse events regardless of relatedness to drug are shown in Table 2 and included fatigue (N = 24), mucositis (N = 18), dyspnea (N = 17), musculoskeletal pain (N = 17) and nausea (N = 16). There was a high rate of grade 3–4 febrile neutropenia (N = 3) which led to an amended starting dose of 35 mg/m^2 days 1–3 of 21-day cycles after 14 patients and use of growth factor support. Despite this, 3 additional patients went on to develop grade 3–4 febrile neutropenia. There was one fatality on trial due to grade 5 febrile neutropenia at the higher 40 mg/m2 dose. Other grade 3–4 possibly related adverse events are listed in Table 3 and included fatigue (N = 7), anemia (N = 5), epigastric abdominal pain (N = 2), thrombocytopenia (N = 2) and pleural effusion (N = 3). There were 5 cases of clinically asymptomatic LVEF reduction below 50% on serial echocardiograms, 4 of which occurred at the 35 mg/m^2 dose. Reduction in LVEF was noted in 3 patients at the end of at cycle 3, while the additional 2 patients occurred at cycle 7 and 36, respectively. One patient with persistent reduction in LVEF starting around cycle 36 of therapy (LVEF 36%) was taken off of study; two patients had persistent mild reduction in LVEF at the end of study (41 and 45%) and two patients had resolution of LVEF reduction without intervention (EF 52 and 54% at end of study). Three of these patients, including the one patient taken off of study for low LVEF, had received prior doxorubicin. In addition, one patient with thymoma developed acute myeloid leukemia (AML) after being on treatment for 36 months and this was thought to be possibly related to amrubicin toxicity. The patient was taken off of trial

Table 2
Grade 1–2 Treatment-Related Adverse Events.

Grade 1-2 Treatment-Emergent Adverse Events (non-lab), regardless of relatedness to drug affecting ≥ 10% patients	
Adverse Event	% (n)
Fatigue	73 (24)
Mucositis and/or Oral Pain	55 (18)
Dyspnea	52 (17)
Musculoskeletal pain	52 (17)
Nausea	48 (16)
Anemia	45 (15)
Constipation	45 (15)
Cough	45 (15)
Alopecia	42 (14)
Anorexia	39 (13)
Gastroesophageal reflux disease	33 (11)
Edema, any location (face/ limbs/ neck)	27 (9)
Infection	27 (9)
Rash	27 (9)
Abdominal pain/discomfort	24 (8)
Anxiety	24 (8)
Fever	24 (8)
Skin and subcutaneous tissue disorders – Other	24 (8)
Diarrhea	21 (7)
Gastrointestinal disorders - other	21 (7)
Headache	21 (7)
Pain	21 (7)
Thrombocytopenia	21 (7)
Upper respiratory infection	21 (7)
Vomiting	21 (7)
Non-cardiac chest pain	18 (6)
Insomnia	15 (5)
Reduction in Ejection Fraction	15 (5)
Hypertension	12 (4)
Hypomagnesaemia	12 (4)
Muscle cramps	12 (4)
Neutropenia	12 (4)
Palpitations	12 (4)
Sinus Tachycardia	12 (4)
Sinusitis and/or sinus infection	12 (4)
Urinary tract infection	12 (4)

Table 3
Grade 3–4 Treatment-Related Adverse Events.

Grade 3-4 Treatment-Emergent Adverse Events (all), regardless of relatedness to drug	
Adverse Event	% (n)
Abdominal pain (epigastric)	6 (2)
Anemia	15 (5)
Anorectal infection (perirectal abscess)	3 (1)
Atrial Fibrillation	3 (1)
Cerebral Edema	3 (1)
Confusion	3 (1)
Dyspnea	3 (1)
Fatigue	21 (7)
Febrile neutropenia	21 (7)
Hypertension	3 (1)
Hypokalemia	3 (1)
Hyponatremia	3 (1)
Hypoxia	3 (1)
Infections	6 (2)
Lethargy	3 (1)
Mucositis	3 (1)
Musculoskeletal pain (back)	3 (1)
Neutrophil count decreased	12 (4)
Non-cardiac chest pain	3 (1)
Palmar-plantar erythrodysesthesia syndrome	6 (2)
Pancytopenia	6 (2)
Platelet count decreased	3 (1)
Pleural effusion	9 (3)
Pneumonitis	3 (1)
Portal vein thrombosis	3 (1)
Sepsis	6 (2)
Syncope	6 (2)
Thromboembolic event	3 (1)
Urinary tract infection	6 (2)
White blood cell decreased	3 (1)

and treated for AML with consolidation decitabine which led to a brief remission of AML. The AML relapsed a few months later and was treated palliatively. Most other AEs were low grade and occurred in the first cycle (data not shown), which led to the prolonged use of the drug as a 'maintenance therapy' in several patients.

4. Discussion

Amrubicin at a dose of 35 mg/m^2 was found to be a promising single agent in a population of pretreated patients with advanced thymoma or thymic carcinoma. This study met its pre-specified endpoint of 4 or more responders. Across 33 patients treated, the overall response rate was 18% (T 29%, TC 11%) and the disease control rate was 91% (T 100%, TC 84%). For patients who responded, the response was relatively durable with a median duration of response of 6.9 months in patients with thymoma and 7.4 months in patients with thymic carcinoma.

Following initiation of this trial there were several case reports published from Japan of single-agent amrubicin as a salvage regimen in advanced thymoma/thymic carcinoma. In one case, a patient with advanced invasive thymoma had a partial response to third-line amrubicin [7]. In a cohort of six patients with refractory thymic carcinoma, amrubicin in combination with a platinum agent led to a partial response in two patients [8]. A retrospective analysis of single-agent amrubicin in nine patients with heavily pretreated thymic carcinoma resulted in a response rate of 44% and median progression free survival of 4.9 months [9].

Amrubicin was also examined in combination with carboplatin in a single-center phase II trial of advanced stage thymoma (n = 18) and thymic carcinoma (n = 33) patients. Response rates were 17% (T) and 30% (TC), with disease control rates of 89% and 85%, respectively. Amrubicin was generally well-tolerated with the exception of febrile neutropenia and no cardiac toxicity was reported [10].

The response to amrubicin is similar to other chemotherapeutics used in the advanced setting for thymic malignancies. For example, in a phase II study of single-agent pemetrexed in advanced thymoma and thymic carcinoma, the response rate was 19% with a median progression-free survival of 10.6 months (12.1 months T, 2.9 months TC) [11]. In a separate study, single-agent ifosfamide in a cohort of 15 patients with advanced thymoma had an overall response rate of 46% with a duration of response of over 66 months [12]. The combination of gemcitabine and capecitabine was examined in a phase II trial of 30 patients (22 T, 8 TC) and showed an ORR of 40% with a median progression-free survival of 11 months [13].

Although there was much enthusiasm for targeted therapies, overall response rates in these phase II trials are similar to established chemotherapy regimens and to that seen with amrubicin in our study. For example, in a study of 41 patients (25 TC and 16 T) treated with sunitinib, the ORR was 26% in TC and 6% in T with disease control rates of 88% and 81%, respectively. Cardiotoxicity was observed even with this targeted therapy, with five (13%) patients having a decrease in left ventricular ejection fraction, 3 (8%) of which were grade 3. Rate of discontinuation for adverse events due to sunitinib was 21% [14]. Everolimus was examined in a cohort of previously treated thymoma (N = 32) and thymic carcinoma (N = 19) patients. The ORR was 16% for TC and 9% for T with disease control rates of 94% and 78%, respectively. The rate of discontinuation for adverse events was 18% (9 patients) and there were 3 (6%) deaths due to pneumonitis [15]. Finally, the checkpoint inhibitor pembrolizumab was recently examined in two separate phase II trials of advanced, pretreated thymoma and thymic carcinoma. In the study by Giaccone et al which examined 41 thymic carcinoma patients, response rate was 22.5% but the rate of severe immune related adverse events was 15% [16]. In the second trial

by Cho et al, both thymoma and thymic carcinoma patients were enrolled, though enrollment of the thymoma cohort halted early due to prohibitively high rates of immune related adverse events (71%). Response rates in this trial were similar at 19% [17]. Although response rates with pembrolizumab were promising, the high rates of immune related adverse events have raised significant concerns [18] and these agents must be used cautiously in this population. Overall, the activity and adverse event profile (rate of discontinuation due to AE 15%) of single-agent amrubicin appears comparable to that of other chemotherapy and targeted agents used in advanced thymic tumors.

Our experience with amrubicin and safety analysis from this study demonstrate that single-agent amrubicin at a dose of 35 mg/m^2 days 1–3 of a 21-day cycle showed preliminary efficacy. Although few prospective studies have been conducted in thymic carcinoma, the response to single agent amrubicin is competitive with any prospective single agent (or combination) therapy published to date. The high rate of febrile neutropenia in our study (21%), despite dose reduction, is cause for caution and strongly supports the prophylactic use of growth factor. Serial echocardiograms were performed with a clinically significant decrease in LVEF in one patient after 36 cycles of amrubicin, necessitating termination of therapy. Four additional patients had small reductions in LVEF (40–50%) noted on echocardiogram without clinically significant cardiac toxicity. Overall, the low burden of cumulative toxicities allowed for ongoing “maintenance” treatment in this protocol in several patients.

The limitations of this study included the small sample size and non-randomized design, although the level of evidence from this study is on par with other studies that support therapies currently used in advanced thymoma and thymic carcinoma. In addition, amrubicin is currently only available in Japan, which limits the potential widespread use of the agent. At the same time, the strength of this study is its prospective, multi-institution design as many studies in advanced thymic malignancies are limited to single institution retrospective series.

In conclusion, single-agent amrubicin has clinical activity and manageable toxicity profile in patients with advanced, heavily pretreated thymoma and thymic carcinoma.

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Heather A. Wakelee: Honoraria: Novartis, AstraZeneca. Advisory board participation (compensated): AstraZeneca, Xcovery.

Advisory board (NOT compensated): Merck, Takeda, Genentech/Roche.

Declaration of Competing Interest

Sukhmani K. Padda: Grant/Research support (paid to institution): Epicent Rx, Forty Seven Inc, Bayer. Consulting: AstraZeneca, AbbVie, G1 Therapeutics, Janssen Pharmaceuticals.

Matthew Burns: Employment: Lilly.

Jonathan W. Riess: Advisory Board: Boehringer Ingelheim, Spectrum, Loxo Oncology. Consulting: Celgene. Research to Institution: Merck, Novartis, Boehringer Ingelheim, AstraZeneca.

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Appendix A. Supplementary data

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