ORIGINAL ARTICLE

STYLE (NCT03449173): A Phase 2 Trial of Sunitinib in Patients With Type B3 Thymoma or Thymic Carcinoma in Second and Further Lines

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ABSTRACT

Introduction: Thymic malignancies are rare tumors with few therapeutic options. The STYLE trial was aimed to evaluate activity and safety of sunitinib in advanced or recurrent type B3 thymoma (T) and thymic carcinoma (TC).

Methods: In this multicenter, Simon 2 stages, phase 2 trial, patients with pretreated T or TC were enrolled in two cohorts and assessed separately. Sunitinib was administered 50 mg daily for 4 weeks, followed by a 2-week rest period (schedule 4/2), until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). Progression-free survival, overall survival, disease control rate and safety were secondary endpoints.

Results: From March 2017 to January 2022, 12 patients with T and 32 patients with TC were enrolled. At stage 1, ORR was 0% (90% confidence interval [CI]: 0.0–22.1) in T and 16.7% (90% CI: 3.1–43.8) in TC, so the T cohort was closed. At stage 2, the primary endpoint was met for TC with ORR of 21.7% (90% CI: 9.0%–40.4%). In the intention-to-treat analysis, disease control rate was 91.7% (95% CI: 61.5%–99.8%) in Ts and 89.3% (95% CI: 71.8%–97.7%) in TCs. Median progression-free survival was 7.7 months (95% CI: 2.4–45.5) in Ts and 8.8 months (95% CI: 5.3–11.1) in TCs; median overall survival was 47.9 months (95% CI: 4.5–not reached) in Ts and 27.8 months (95% CI: 13.2–53.2) in TCs. Adverse events occurred in 91.7% Ts and 93.5% TCs. Grade 3 or greater treatment-related adverse events were reported in 25.0% Ts and 51.6% TCs.

Conclusions: This trial confirms the activity of sunitinib in patients with TC, supporting its use as a second-line treatment, albeit with potential toxicity that requires dose adjustment.

Keywords: Thymic carcinoma; B3 thymoma; Sunitinib; Second line

Introduction

Thymic epithelial tumors (TETs) are rare malignancies originating from the thymus and account for 50% of the anterior mediastinal tumors in adults.[1] According to the WHO histopathologic classification, they are categorized as thymoma (T)—further distinguished in types A, AB, B1, B2 and B3—and thymic carcinoma (TC).[2] Compared with Ts, TCs are extremely rare (incidence of <0.1 per million) and, due to the common blood and lymphatic spread, are frequently diagnosed in advanced stage.

Surgery represents the cornerstone of treatment for TETs in the early stage of disease. Cytoreductive chemotherapy may be delivered in case of locally advanced tumors, whereas radiotherapy has a role especially in the adjuvant setting in case of more aggressive histotype, extracapsular involvement, or residual disease.[3–6] Patients with metastatic or unresectable disease usually undergo systemic palliative treatments, and platinum-based chemotherapy represents the standard of care in the first-line setting.[7,8] To date, no standard salvage treatments are available for patients with progressive disease during or after first-line chemotherapy.[9–11]

Although the development of new drugs is hindered by disease rarity, recent advances in the knowledge of molecular alterations involved in TET pathogenesis led to the identification of new potential targets.[12–18] Several agents, such as insulin-like growth factor-1 receptor inhibitors, angiogenesis inhibitors, and tropomyosin receptor kinase A/cyclin-dependent kinase inhibitors, have been formally investigated with varying success

rates.[19–22] In a phase 2 trial, the mechanistic target of rapamycin inhibitor everolimus has shown a disease control rate (DCR) of 88% with a median progression-free survival (PFS) of 10.1 months in 51 pretreated patients.[23] Angiogenesis is another process that plays an important role in TETs as vascular endothelial growth factor (VEGF)-A, VEGF receptor 1 (VEGFR-1), and VEGFR-2 are overexpressed. Moreover, the microvessel density and VEGF expression levels were found to correlate with tumor invasion, aggressive histotype and clinical stage.[24–27] The platelet-derived growth factor (PDGF) and PDGF receptor alpha (PDGFRα) are also overexpressed in TETs and anecdotal reports have suggested that drugs targeting VEGF or PDGF (e.g., sorafenib) might be effective in these tumors.[28,29] Two multitarget antiangiogenic drugs, lenvatinib and regorafenib, have recently reported efficacy in TETs in two distinct phase 2 trials.[30,31] Finally, c-KIT mutations are reported in approximately 15% of TC, whereas they are very rare in T. The presence of c-KIT mutation has been described as a potential negative prognostic factor. Anecdotal responses to c-KIT inhibitors have been reported in chemotherapy-pretreated patients harboring an activating c-KIT mutation.[20,32,33]

Sunitinib is a potent, oral, multitargeted kinase inhibitor of VEGFR, KIT, and PDGFR and to date represents the target therapy with the highest objective response rate (ORR) reported in patients with TC pretreated with platinum-based chemotherapy. The single-arm, phase 2 trial conducted in the United States by Thomas et al.[34] enrolled 41 pretreated patients with advanced TETs, revealing sunitinib efficacy in patients with TC, with a 26% of partial response (PR) and 65% of stable disease. Disease control was achieved in 21 patients (91%) with TC and 13 (81%) with T. Median PFS was 7.2 months in patients with TC and 8.5 months in those with T. After a median follow-up of 17 months, median overall survival (OS) was 15.5 months for patients with T and not reached for patients with TC.[34]

On the basis of such promising results, we have designed a phase 2 study to evaluate the activity and safety of sunitinib in a European population of patients with advanced or recurrent type B3 T or TC previously treated with platinum-based chemotherapy.

Materials and Methods

Study Design and Patients

STYLE (NCT03449173) is a prospective, open-label, single-arm, phase 2 trial conducted at five Centers of the Italian Collaborative Group for the ThYmic MalignanciEs (TYME) network (Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; Humanitas Research Hospital, Rozzano; A.O.U. Ospedali Riuniti, Ancona; A.O.U. Pisana, Pisa; IRCCS Istituto Oncologico Veneto, Padova). Eligible patients were aged above or equal to 18 years, had a confirmed diagnosis of recurrent or metastatic B3 T (B2 T with areas of B3 T were eligible) or TC, had progression of disease after at least one previous platinum-based regimen, had measurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of less than or equal to 2. Patients with untreated brain metastases, uncontrolled or relevant cardiovascular disease, history of cerebrovascular accident, and recent deep vein thrombosis or pulmonary embolism were excluded from the study.

Taking into account the different biology and historically discrepant responses of T and TC, patients were enrolled in two separate cohorts according to histotype.

The protocol and all amendments were approved by the local ethical committees. The trial was conducted in accordance with the International Conference on Harmonization Guidelines on Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent before enrollment.

This study was registered in ClinicalTrials.gov (NCT03449173).

Treatment and Procedures

Sunitinib was administered orally at 50 mg once daily for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks and continued until progression disease (PD), unacceptable toxicity, or other discontinuation criteria were met. Two dose reductions, in 12.5 mg decrements, or a schedule change (2 wk of treatment followed by 1 wk rest) was allowed for safety reasons. The maximum allowed treatment interruption was 6 weeks. Tumor response was assessed according to RECIST 1.1 every 6 weeks for the first 6 months and then every 12 weeks ($\pm$ 7 d). Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical Analysis

The primary end point was ORR, defined as the proportion of patients who achieved complete response (CR) or PR according to RECIST 1.1 at any point. The primary endpoint was assessed in the per-protocol (PP) population, which included all registered patients who provided informed consent and without major violations of eligibility criteria. Patients who discontinued treatment in the first 2 months (i.e., 55 d) for any reason other than PD or experienced grade (G)4 toxicity in the same period were excluded from the PP

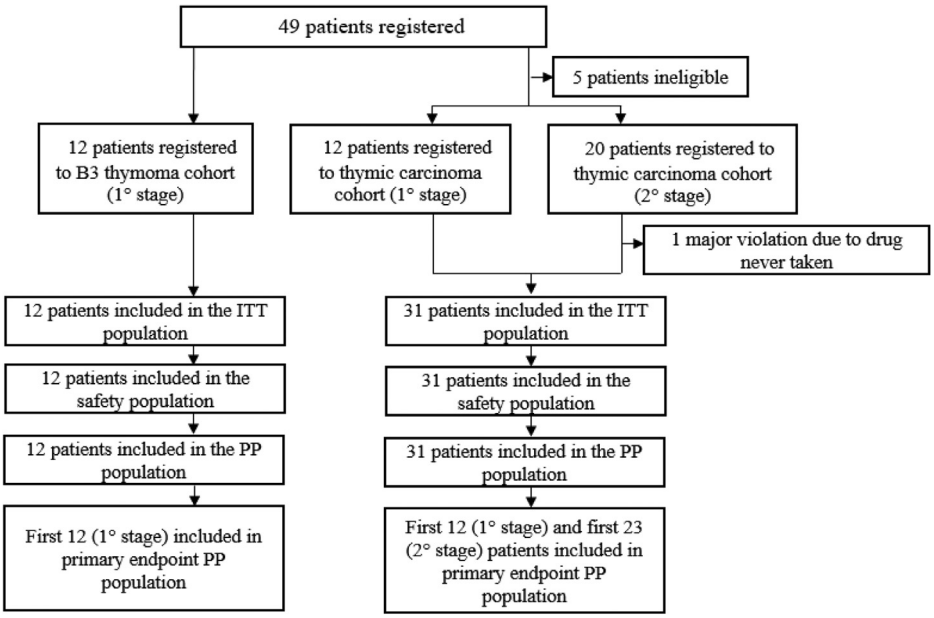

Figure 1. Study flowchart. ITT, intention-to-treat; PP, per-protocol.

population. Patients with B3 T and TC were assessed in two different cohorts. Sample size was determined for each cohort by two identical Simon's two-stage study designs according to the minimax approach. In both cohorts, an ORR of 5% or less (p0) was defined as not of therapeutic interest and an ORR of 25% (p1) or more was defined as highly clinically relevant. Assuming a type I error probability of 5%, one sided, and a power of 85%, 23 patients were needed to be enrolled for each cohort. For the first stage, 12 patients were enrolled in each cohort. If one or more CR or PR were found, additional 11 patients would have been enrolled for the second stage (23 patients in total). At the final analysis, sunitinib would have been considered active if four of 23 patients had reached CR or PR.

Secondary endpoints were PFS, OS, DCR and safety. The secondary efficacy endpoints were evaluated in the intention-to-treat (ITT) population, defined as all patients registered in the study who provided informed consent and without major violations of eligibility criteria. PFS was defined as the time from the first experimental treatment administration to PD or death for any cause, whichever occurred first. Subjects alive and without PD at the time of the final analysis were censored at the date of the last follow-up. OS was defined as the time from the first experimental treatment administration to death for any cause. Subjects alive at the time of the final analysis were censored at the last date on which they were known to be alive. Survival curves were estimated by the Kaplan-Meier method, and their confidence intervals (CIs) were computed with the log-log method. DCR was defined as the proportion of patients who have achieved CR, PR, or stable disease. Duration of response (DOR) was defined as the time from the first evidence of PR or CR to PD.

The toxicity profile was evaluated in the safety population, defined as all patients registered in the study, who provided informed consent without major violations of eligibility criteria and received at least one dose of medication. For any AE type, the absolute and relative frequencies of events and the maximum G experienced by each subject were provided.

Continuous variables were expressed as mean, SD, first quartile (Q1), median, third quartile (Q3), ranges (minimum and maximum), and number of missing values. Categorical variables were expressed as frequency and proportion of each subject in each category. All analyses were done with SAS software, version 9.4 (SAS Institute).

Results

From March 2017 to January 2022, a total of 12 and 32 patients were enrolled in the T and TC cohort, respectively. All the patients were included in the ITT, safety and PP analyses, except for one patient in the TC cohort excluded due to major violation (Fig. 1). Patients' characteristics are summarized in Table 1.

B3 T Cohort

In the T cohort, median age was 53.6 years (Q1–Q3: 50.9–58.7); seven patients (58.3%) were male. ECOG PS was 0 in eight (66.7%) and 1 in four (33.3%) patients, respectively. Three patients (25.0%) were diagnosed with

Table 1. Clinical and Demographic Characteristics at Baseline

Patients' Characteristics	B3 Thymoma n = 12	Thymic Carcinoma n = 31
Age (y)		
Median (Q1-Q3)	53.6 (50.9-58.7)	53.7 (43.1-61.9)
Sex, n (%)		
Female	5 (41.7)	8 (25.8)
Male	7 (58.3)	23 (74.2)
ECOG performance status, n (%)		
0	8 (66.7)	25 (80.6)
1	4 (33.3)	5 (16.1)
2	0 (0.0)	1 (3.2)
Myasthenia gravis, n (%)		
Not present	9 (75.0)	31 (100.0)
Present	3 (25.0)	0 (0.0)
Liver metastases, n (%)	5 (41.7)	15 (48.4)
Bone metastases, n (%)	3 (25.0)	12 (38.7)
Lung metastases, n (%)	6 (50.0)	14 (45.2)
Brain metastases, n (%)	2 (16.7)	2 (6.5)
Lymph node metastases, n (%)	6 (50.0)	18 (58.1)
Pleura metastases, n (%)	8 (66.7)	13 (41.9)
Masaoka clinical staging at study entry, n (%)		
IIIA	0 (0.0)	1 (3.2)
IVA	2 (16.7)	7 (22.6)
IVB	10 (83.3)	23 (74.2)
Number of previous antitumor therapy lines, n (%)		
1	6 (50.0)	22 (71.0)
≥2	6 (50.0)	9 (29.0)
Most frequent previous antitumor therapies, n (%)		
CBDCA + TXL (carboplatin-paclitaxel)	4 (33.3)	15 (48.4)
ADOC (cisplatin-doxorubicin-vincristine-cyclophosphamide)	6 (50.0)	1 (3.2)
CAP (cisplatin-doxorubicin-cyclophosphamide)	2 (16.7)	4 (12.9)
Carboplatin-paclitaxel-ramucirumab	0 (0.0)	5 (16.1)
Milciclib	2 (16.7)	0 (0.0)
Previous radiotherapy, n (%)	7 (58.3)	19 (61.3)
Previous surgery, n (%)	11 (91.7)	11 (35.5)

Note: Only antitumor therapies received by at least 10% of patients in one cohort were considered as most frequent.
ECOG, Eastern Cooperative Oncology Group; Q1-Q3, first to third quartiles.

myasthenia gravis. Half of the patients received sunitinib as second-line therapy, three (25.0%) as third-line therapy and three (25.0%) as fourth-line therapy. Surgery on the primary tumor was performed in 11 patients (91.7%). At the final analysis, one patient (8.3%) was still on treatment. Median treatment duration was 5.4 months (Q1–Q3: 2.9–17.2). Of the 11 patients who had discontinued treatment, six (54.5%) discontinued due to radiological PD, two (18.2%) for AE, two (18.2%) for death, and one (9.1%) for non-compliance. More than half of the patients (seven patients, 58.3%) shifted to the alternated schedule; dose reduction occurred in eight patients (66.7%) with four (33.3%) requiring two dose reductions (Supplementary Table 1). The main reason for dose adjustments was AE occurrence.

At the first stage, 11 patients (91.7%) had stable disease and one patient (8.3%) had PD as best response (see the waterfall plot for best response at Fig. 2). Therefore, ORR was 0% (90% CI: 0.0%–22.1%) and DCR was 91.7% (95% CI: 61.5%–99.8%) (Table 2). Because no response was observed, the cohort was closed for accrual.

After a median follow-up of 55.5 months, 11 patients (91.7%) progressed or died. Median PFS was 7.7 months (95% CI: 2.4–45.5). During the study, eight patients (66.7%) died and median OS was 47.9 months (95% CI: 4.5–not reached) (Fig. 3*A* and *B*).

Overall, 76 AEs were reported, 52 (68.4%) grade (G) 1, 19 (25.0%) G2, four (5.3%) G3, and one (1.3%) G4. Three patients (25.0%) experienced at least one AE G3 or greater. The most common AEs of any grade were: fatigue (58.3%), hypertension (41.7%) and oral mucositis (41.7%). In Table 3, the AEs related to the study treatment with a 10% prevalence cutoff are found (see Supplementary Table 2 for more details). One patient experienced a gastrointestinal perforation and another experienced a Guillain-Barré syndrome both related to sunitinib, which led to permanent treatment

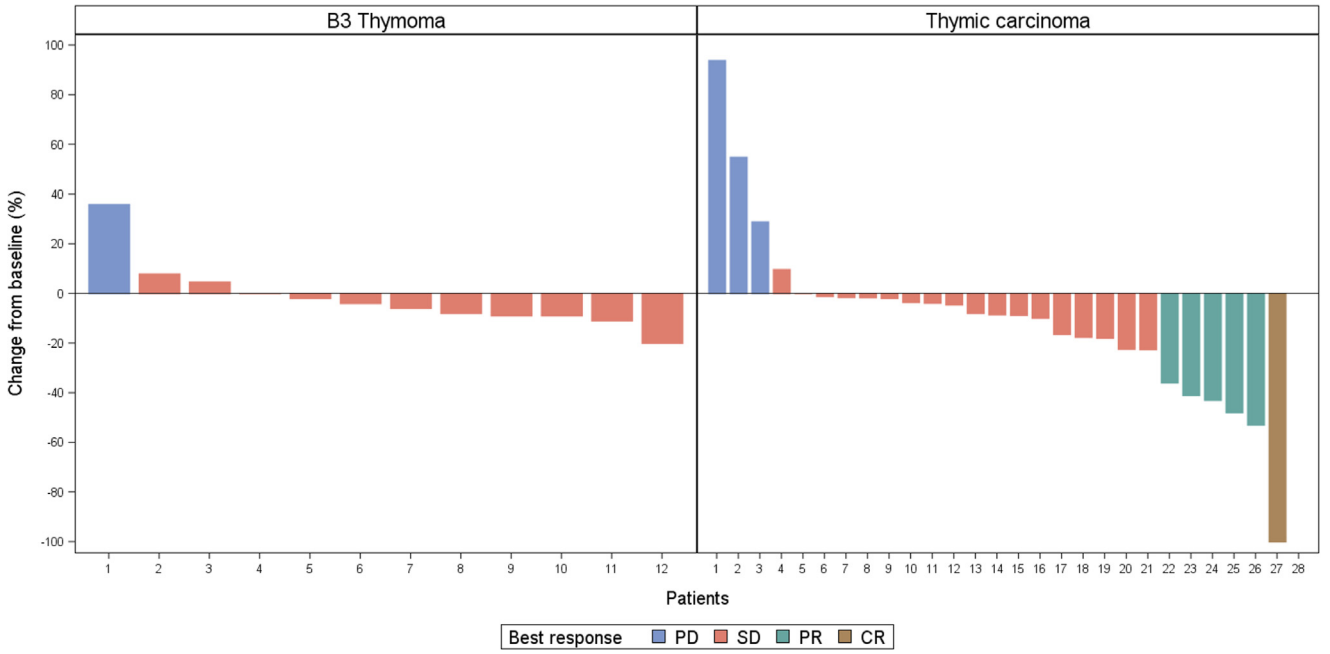

Figure 2. Waterfall plot for best response. CR, complete response; ITT, intention-to-treat; PD, progression disease; PR, partial response; SD, stable disease.

discontinuation (serious AEs [SAEs] are reported in Supplementary Table 3).

TC Cohort

In the TC cohort, median age was 53.7 years (Q1–Q3: 43.1–61.9); 23 patients (74.2%) were male. ECOG PS was 0 in 25 (80.6%), 1 in five (16.1%) and 2 in one (3.2%) patients, respectively. Sunitinib was the second, third, fourth, and fifth line of therapy in 22 (71.0%), six (19.4%), two (6.5%), and one (3.2%) patients, respectively. Surgery on the primary tumor was performed in 11 patients (35.5%). Regarding histotype, squamous cell carcinoma was the most common subtype, but four basaloid carcinomas, two thymic neuroendocrine neoplasms, two epidermoid, and one lymphoepithelial carcinoma subtypes were identified. c-KIT status was known for 10 of 31 patients, of which six harbored a c-KIT mutation.

At the final analysis, five patients (16.1%) were still on treatment. Median treatment duration was 9.1 months (Q1–Q3: 4.6–11.3). Of the 26 patients who discontinued treatment, 17 (65.4%) discontinued due to radiological PD, three (11.5%) clinical PD, two (7.7%) AE, two (7.7%) death, and two (7.7%) non-compliance. Sunitinib dose adjustments were required in almost half of the patients, with 14 patients (45.2%) switching to the alternated schedule. Dose reductions were reported in 13 patients (41.9%), of which three (9.7%) needed a further dose reduction (Supplementary Table 1).

At the first stage, of the 12 enrolled patients, two (16.7%) achieved a PR, eight (66.7%) a stable disease, and two (16.7%) PD as best response. Therefore, ORR was 16.7% (90% CI: 3.1%–43.8%) (Table 2). According to protocol design, additional 11 patients were enrolled for the second stage.

At the second stage, the primary end point was met. Of the first 23 patients assessable for the primary end point, CR and PR were observed in one patient (4.3%) and four patients (17.4%), respectively. Furthermore, 15 patients (65.2%) had stable disease and three patients (13%) PD. ORR was 21.7% (90% CI: 9.0%–40.4%) (Table 2).

Regarding all the 31 patients included in the ITT population, three were not assessable for response as radiological evaluation had not yet been performed at the time of data cutoff. Of the 28 assessable patients, one (3.6%) had CR, five (17.9%) PR, 19 (67.9%) stable disease, and three (10.7%) PD (see the waterfall plot for best response at Fig. 2). ORR was 21.4% (95% CI: 8.3%–41.0%), DCR was 89.3% (95% CI: 71.8%–97.7%), and median DOR was 20.8 months (95% CI: 3.5–40.4). After a median follow-up of 29.8 months, 26 patients (83.9%) progressed and 16 patients (51.6%) died. Median PFS was 8.8 months (95% CI: 5.3–11.1), whereas median OS was 27.8 months (95% CI: 13.2–53.2) (Fig. 3*C* and *D*). Among the six known patients with a c-KIT mutation, the best response was stable disease in five patients and PR in the remaining one. Interestingly, the patient who achieved a CR as best response was a case of metastatic basaloid carcinoma with pleural and nodal metastases. c-KIT status was unknown. The patient was treated with

Table 2. Efficacy Analyses

Efficacy Analysis	B3 Thymoma	Thymic Carcinoma
Stage I		
Number of patients, n (%)	12	12
Best response, n (%)		
PR	0 (0.0)	2 (16.7)
SD	11 (91.7)	8 (66.7)
PD	1 (8.3)	2 (16.7)
ORR (CR + PR), n (%)	0 (0.0)	2 (16.7)
[90% CI]	[0.0-22.1]	[3.1-43.8]
Stage II		
Number of patients, n	-	23
Best response, n (%)		
CR	-	1 (4.3)
PR	-	4 (17.4)
SD	-	15 (65.2)
PD	-	3 (13.0)
Objective response rate (CR + PR), n (%)	-	5 (21.7)
[90% CI]	-	[9.0-40.4]
ITT population		
Number of patients, n	12	31
Best response, n (%)		
CR	0 (0.0)	1 (3.6)
PR	0 (0.0)	5 (17.9)
SD	11 (91.7)	19 (67.9)
PD	1 (8.3)	3 (10.7)
Not evaluated[a]	0	3
Objective response rate (CR + PR), n (%)	0 (0.0)	6 (21.4)
[95% CI]	[0.0-26.5]	[8.3-41.0]
DCR (CR + PR + SD), n (%)	11 (91.7)	25 (89.3)
[95% CI]	[61.5-99.8]	[71.8-97.7]
DOR in patients with CR or PR		
DOR event, n (%)	-	5 (83.3)
Type of DOR event, n (%)		
Progression	-	4 (80.0)
Death without progression	-	1 (20.0)
Censored, n (%)	-	1 (16.7)
Kaplan-Meier estimate for DOR (mo)		
First quartile	-	5.3
Median [95% CI]	-	20.8 [3.5-40.4]
Third quartile	-	23.4

Note: Primary endpoint (ORR), secondary endpoint (DCR, DOR).
[a]Patients who did not receive at least one radiological evaluation after the study entry.
CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; ITT, intention-to-treat; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

standard first-line platinum-based chemotherapy and subsequent sunitinib, with an early disease response.

Overall, 193 AEs were reported. In detail, 116 (60.1%) G1, 50 (25.9%) G2, and 27 (14.0%) G3. Furthermore, 16 patients (51.6%) experienced at least one AE with grade greater than or equal to 3. Most common AEs of any grade were: platelet count decreased (48.4%), neutrophil count decreased (45.2%) and fatigue (38.7%). In Table 3 the AEs related to the study treatment with a 10% prevalence cutoff are reported (see Supplementary Table 2 for more details). Three SAEs occurred in two patients: one patient experienced dyspnea and one patient anemia and tumor pain. Two of three were related to sunitinib (dyspnea and anemia). A SAE related to sunitinib (dyspnea) led to permanent discontinuation of the treatment (SAEs are reported in Supplementary Table 3).

Discussion

In the phase 2 STYLE trial, sunitinib was found to have an activity in patients with TC refractory to standard first-line chemotherapy, with an ORR of 21.4%, a DCR of 89.3% and a median PFS of 8.8 months in the ITT population. The accrual in B3 T cohort was stopped at first-stage analysis for futility, despite an encouraging

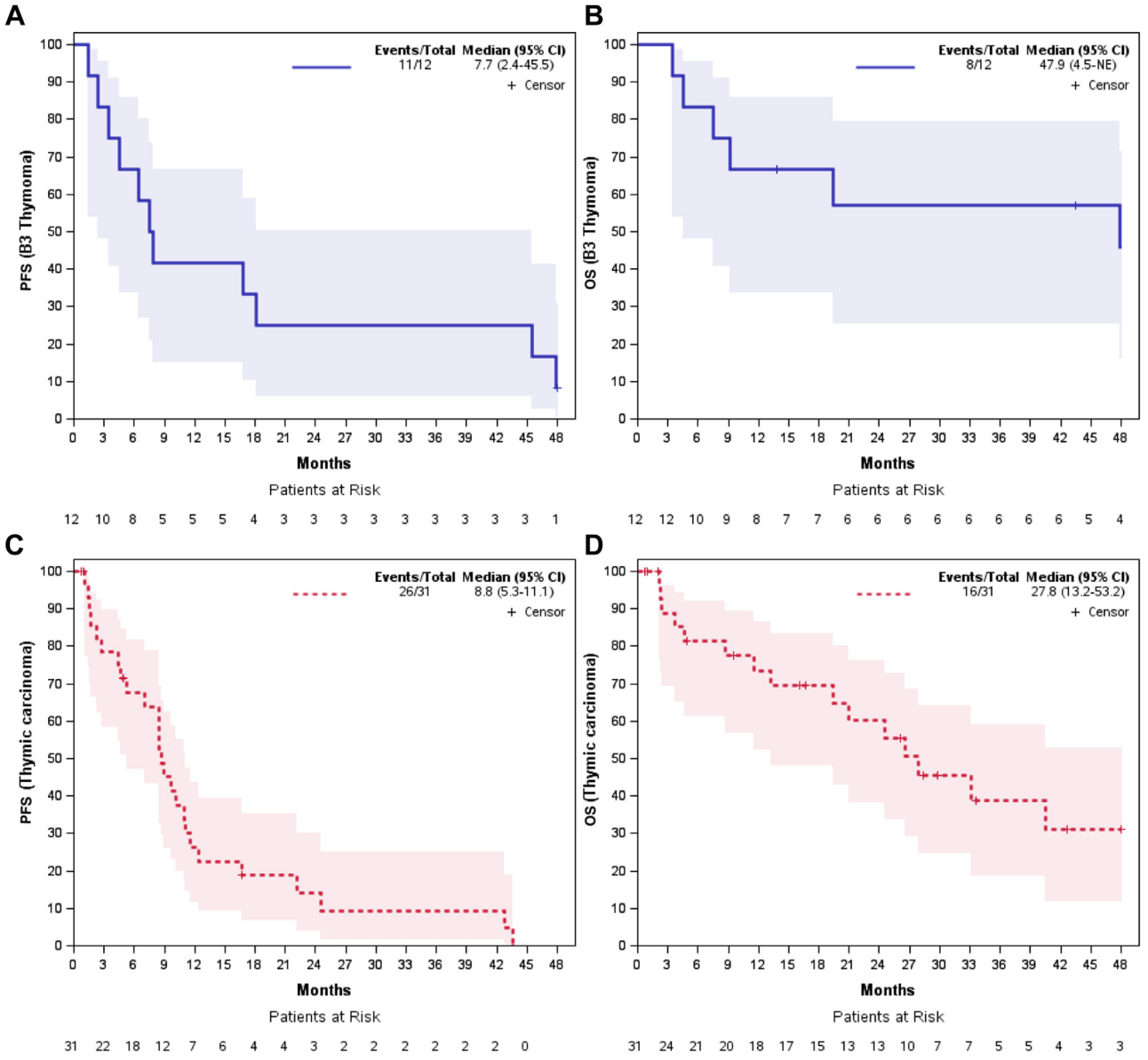

Figure 3. Kaplan-Meier estimate for PFS and OS. (*A*) Kaplan-Meier estimate for PFS in B3 thymoma cohort. (*B*) Kaplan-Meier estimate for OS in B3 thymoma cohort. (*C*) Kaplan-Meier estimate for PFS in thymic carcinoma cohort. (*D*) Kaplan-Meier estimate for OS in thymic carcinoma cohort. CI, confidence interval; OS, overall survival; PFS, progression-free survival.

DCR of 91.7% and a median PFS of 7.7 months of not clear value due to the intrinsic better prognosis of T compared with TC. To ensure the number of assessable patients needed for the primary analysis, defined as patients who completed two months of treatment and underwent the first radiological evaluation, nine additional patients to the preplanned 23 were enrolled in the TC cohort.

Type B3 Ts and TCs are rare malignancies characterized by negative prognosis due to their aggressiveness, resistance to chemotherapy and high likelihood to give distant metastases. Because of their rarity, no randomized trial has been performed to date. Platinum-based chemotherapy represents the standard first-line treatment and there are no standard salvage options after failure of the first-line therapy.

Different targeted agents have been investigated in this setting. Angiogenesis is thought to play an important role in the genesis of TETs, especially in TC. In the REMORA phase 2 trial, the activity of lenvatinib, an orally multitargeted kinase inhibitor for VEGFR, FGFR, and c-KIT, was assessed in 42 patients with advanced TC who progressed after at least one platinum-based chemotherapy.[30] The ORR was 38%, DCR 95% and the median PFS 9.3 months. Interestingly, a considerable proportion of patients (30 of 42,

Table 3. Adverse Events Related to the Study Treatment (10% Prevalence Cutoff)

	B3 Thymoma (n = 12) and Thymic Carcinoma (n = 31), N = 43		
Adverse Event	Any Grade	G3	G4
Overall	40 (93.0)	18 (41.9)	1 (2.3)
Fatigue	19 (44.2)	2 (4.7)	0 (0.0)
Platelet count decreased	19 (44.2)	1 (2.3)	0 (0.0)
Neutrophil count decreased	18 (41.9)	4 (9.3)	0 (0.0)
Hypertension	15 (34.9)	6 (14.0)	0 (0.0)
Mucositis, oral	15 (34.9)	0 (0.0)	0 (0.0)
Diarrhea	12 (27.9)	1 (2.3)	0 (0.0)
Anemia	11 (25.6)	2 (4.7)	0 (0.0)
Dysgeusia	10 (23.3)	0 (0.0)	0 (0.0)
Nausea	9 (20.9)	0 (0.0)	0 (0.0)
Blood bilirubin increased	6 (14.0)	1 (2.3)	0 (0.0)
Hypothyroidism	6 (14.0)	0 (0.0)	0 (0.0)
Liver function test alterations	6 (14.0)	1 (2.3)	0 (0.0)
Abdominal pain	5 (11.6)	0 (0.0)	0 (0.0)
Gastroesophageal reflux disease	5 (11.6)	0 (0.0)	0 (0.0)

Note: All values are n (%).
G, grade.

71%) had squamous carcinoma and 14 of 30 (47%) had PR. In the RESOUND phase 2 trial, regorafenib, a potent inhibitor of angiogenic and stromal receptor tyrosine kinases VEGFR1, VEGFR2, and VEGFR3, was found to have a DCR of 78.9% with a median PFS of 9.6 months in 19 patients in the same setting.[31] These findings suggested that both lenvatinib and regorafenib may have a potential activity in the treatment of TC. In a phase 2 trial, sunitinib as second-line therapy achieved an overall response rate of 26% with a median PFS of 7.2 months in 23 patients with TC, but limited activity was reported in the T cohort with an ORR of 6% (one of 16 patients).[34] In contrary, in the retrospective analysis of the French group RYTHMIC on eight T and 20 TC, sunitinib obtained an ORR in 29% T and 20% TC, respectively. The retrospective nature of the trial and the limited number of T (one B1, four B2, and three B3) may contribute to explain such discrepancy. The TC cohort DCR was 55%, whereas the T cohort DCR was 85.7%.[35]

In this context, STYLE trial further supports the activity of the multitarget tyrosine kinase inhibitor sunitinib in pretreated TC. Our results are consistent with those of the previous studies reported, confirming that sunitinib is a viable treatment with a high ORR in patients with TC pretreated with platinum-containing polychemotherapy and therefore could represent a valid option in this setting. According to all the achieved results, efficacy of sunitinib in T remains uncertain.

As regards safety, toxicities were consistent with available data, with 91.7% of patients in T and 93.8% in TC experiencing at least one AE. The most common AEs of any grade were fatigue, hypertension, neutrophil count decreased, platelet count decreased, mucositis and diarrhea. Owing to AEs, schedule changes (58.3% in the T and 45.2% in the TC cohorts) and dose adjustments (66.7% and 41.9% in T and TC, respectively) were required.

Recently, a retrospective study evaluated efficacy and safety of sunitinib administered continuously at the dose of 37.5 mg daily on 20 consecutive patients (12 TC, six B3, and two B2 T), revealing an ORR of 31.6% (95% CI: 12.5%–56.5%) in the overall population with a manageable toxicity profile.[36] Considering these data, an alternative dosing regimen should be further explored to improve patient compliance to the treatment and possibly outcomes.

The STYLE trial has some limitations. First of all the lack of a control group to perform a direct comparison. Nevertheless, no standard second-line treatment currently exists and identifying a valid drug regimen comparator is not trivial. Furthermore, the rarity of the disease makes randomized trials very hard to conduct.

A second limitation is represented by the number of previous lines and the different regimens received by the enrolled patients. This reflects the variability of therapeutic management after progression to first-line treatment in the clinical practice. Recently, Petat et al.,[37] analyzing the RYTHMIC French database on the real-life management of TC, described a huge variability in the choice of second-line options, including platinum-based doublet chemotherapy, sunitinib or single-agent chemotherapies. Nevertheless, despite many patients were heavily pretreated with two or more previous lines in the STYLE trial (approximately 30% and 50% in the TC and T cohorts, respectively), sunitinib confirmed its activity in TCs. The third limitation derives from the long

time spent for completing the accrual. This was partially expected due to the rarity of the disease. The coronavirus disease 2019 pandemic, however, further hurdled the enrollment, limiting patients' access to the Italian referral centers involved in the study.[38]

Nevertheless, the STYLE trial, together with previously reported data, supports the use of multitarget antiangiogenic drugs in patients with TC. The lack of response in the T population and the potential influence on DCR of the natural history and the less aggressive behavior of T compared with TC make sunitinib role in patients with T unclear.

To further investigate the efficacy of antiangiogenetic drugs in thymic malignancies is actually ongoing in Italy the phase 2 RELEVENT trial that evaluates activity and safety of the combination of ramucirumab and chemotherapy as first-line treatment in patients with metastatic TC or B3 T with areas of carcinoma.[39]

The use of other response criteria, such as Choi criteria, or other type of imaging technique, such as RGD-PET (Arg-Gly-Asp positron emission tomography), could be useful to better evaluate treatment efficacy in both cohorts. Therefore, the identification of specific biomarkers to better select patients could help clinicians to identify the subgroup of patients with TETs who may most benefit from angiogenetic therapies.

In conclusion, the multicentric, prospective, phase 2 STYLE trial confirms the efficacy of sunitinib in pretreated advanced TC, with manageable toxicity profile. These data support sunitinib as a second-line option in TC and suggest caution about the related toxicity, thus considering the possibility of early switch to a lower dose schedule.

CRediT Authorship Contribution Statement

Claudia Proto: Conceptualization, Methodology, Validation, Writing—original draft preparation.

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Giuseppe Lo Russo: Investigation, Methodology, Writing—reviewing and editing.

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Giulia Galli: Conceptualization, Investigation, Visualization.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and all patients signed informed

consent for scientific research purposes. The protocol was submitted to the Ethics Committee of the participating centers.

Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Data are contained within the article.

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.2023.04.009.

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